J Antimicrob Chemother 2024; **79**: 2554–2560
https://doi.org/10.1093/jac/dkae255 Advance Access publication 2 August 2024

Journal of Antimicrobial Chemotherapy

Fluoroquinolones and the risk for incidental seizures: a comparative retrospective study

Itai Gueta [1,2,3]*, Hagith Yonath[2,3,4,5], Ronen Fluss[5], Bernice Oberman[5], Amit Oppenheim[2,3], David Ozeri[2,3], Yitshak Kreiss[3,5] and Ronen Loebstein[1,3]

[1]*Institute of Clinical Pharmacology and Toxicology, Sheba Medical Center, Tel Hashomer, Israel;* [2]*Internal Medicine A, Sheba Medical Center, Tel Hashomer, Israel;* [3]*Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel;* [4]*Danek Gertner Institute of Human Genetics, Sheba Medical Center, Tel Hashomer, Israel;* [5]*Biostatistics Unit, Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Tel Hashomer, Israel*

*Corresponding author. E-mail: guetai@tlvmc.gov.il

Received 5 March 2024; accepted 6 July 2024

Background: Over the years, reports have associated fluoroquinolones (FQ) with seizures. The incidence and whether FQ compared to non-epileptogenic antibiotic are associated with increased risk of seizures has yet to be examined.

Methods: A retrospective observational study of hospitalized patients treated with FQ (ofloxacin, ciprofloxacin, levofloxacin, moxifloxacin) or macrolides (MA: azithromycin or roxithromycin) between January 2009 and January 2021 in a large tertiary academic medical centre. The outcome was the occurrence of a seizure during treatment. The Naranjo scale was used to assess causality between FQ treatment and seizures. Comparative analysis was conducted using propensity score matching to correct for possible bias due to non-random selection, followed by inverse probability weighting (IPW) to estimate the difference in seizure risk between FQ and MA.

Results: Overall, 52 722 patients were treated with FQ during a total of 178 982 days. Mean age was 65 (±19) years and 47% were females. Thirty-three patients (0.06%) experienced a seizure, yielding an incidence of 1:5422 treatment days. Causality was deemed probable and possible among 9/33 and 24/33, respectively. The MA group composed of 8522 patients treated during 17 954 treatment days. Mean age was 65 (±21) years, 49% were females. Six (0.07%) patients experienced each a single seizure. IPW estimated OR for seizures among the FQ versus MA group was 1.44 (95%CI 0.59–3.5, $P=0.42$).

Discussion: The incidence of FQ associated seizures among hospitalized patients is low and the risk did not significantly exceed that under macrolides. Our results provide evidence for clinicians and decision-makers when balancing fluoroquinolones risks and benefits.

Introduction

Fluoroquinolones (FQ), a class of broad-spectrum antibiotics, are commonly used to treat various infections both in the community and among hospitalized patients. While these agents are generally considered well tolerated, rare complications (e.g. tendonitis, tendon rupture, aortic dissection and peripheral neuropathy) have raised concerns about the risk-to-benefit ratio for indications such as acute bacterial sinusitis or uncomplicated urinary tract infection.[1,2]

Over the years, several case-reports have associated FQ use with the occurrence of seizures.[3–6] Moreover, *in vitro* studies have demonstrated their ability to inhibit GABA binding to its receptor, further suggesting causality.[7,8] Nevertheless, a self-controlled study comparing seizures incidence before and following FQ initiation among more than 6000 individuals did not observe an increased seizure risk.[9]

FQ are highly effective antibiotic class with many advantageous pharmacokinetic properties. Data on seizure incidence and risk factors are limited and comparative studies are lacking. Therefore, the objective of the current study was to examine the incidence of seizures associated with exposure to fluoroquinolones among hospitalized patients and to compare it to an antibiotic not known to be associated with seizures.

Methods

Ethics

The study was approved by the Chaim Sheba Medical Center ethical review board (8056-21-SMC). The IRB waived the requirement for informed consent for this study.

Study design, cohort and outcome definition

A retrospective observational study comprised all hospitalized patients at the Chaim Sheba Medical Center, a large tertiary academic hospital, who were treated with either a fluoroquinolone (FQ: ofloxacin, ciprofloxacin, levofloxacin or moxifloxacin) or a macrolide (MA: azithromycin, roxithromycin) between January 2009 and January 2021. These two macrolides were selected as a control group given that they are not associated with seizure and do not have any significant pharmacokinetic drug–drug interactions. Inclusion criteria were age ≥18 years and no history of documented adverse drug event to either antibiotic (either FQ or MA). Patients were followed from the time of antibiotic initiation until either the occurrence of a seizure (while on antibiotic therapy) or hospital discharge. Seizures were identified by ICD-10 codes (Table S1, available as Supplementary data at *JAC* Online) and their temporal relation to the antibiotic exposure was verified by manual review of each medical record; only seizures occurring while on FQ or MA therapy were considered as an outcome. Patients were excluded if they were not hospitalized (e.g. antibiotic given in emergency room and then discharge) or when seizure occurred prior to antibiotic initiation during the same hospitalization. The study was approved by the Chaim Sheba Medical Center ethical review board.

Data extraction and covariate definition

Data collected for each patient included baseline demographics and comorbidities: history of seizures or epilepsy, stroke or brain injury during the preceding 30 days, dementia, CNS infection or encephalitis diagnosed during the preceding 90 days, diagnosis of drug or alcohol use disorder within the previous 1 year, medications known to be associated with seizures [benzodiazepines, barbiturates, antiseizure medications (ASM)] and relevant blood value ±24 hours from antibiotic initiation (lowest glucose, lowest sodium, highest creatinine, highest urea). We also collected data on medications known to induce seizures that were administered following FQ or MA initiation (beta-lactams, antipsychotics, lithium, tricyclic antidepressants, isoniazid, calcinurin inhibitors, azathioprine, etc.). Data were retrieved using MDClone, a query tool that provides comprehensive patient-level data of wide-ranging variables in a defined time frame around an index event (mdclone.com).

Data analysis

Descriptive data are presented as mean ± standard deviation (SD) or median with interquartile range as appropriate for continuous variables and proportions for categorical variables, respectively. Causality was assessed by calculating Naranjo score for each FQ associated seizure. For the comparative analysis, seizure risk was evaluated among all cases exposed to FQ compared to MA between January 2009 and January 2021. To correct for possible bias due to non-random selection of patients to each antibiotic, we used propensity scores (PS). The PSs are the estimated probabilities of each patient to be treated by FQ given his/her sets of covariates. We used a logistic regression to estimate the PS including the risk factors (RF) described in the 'Study design, cohort and outcome definition' section. We did not include medications that were administered following FQ or MA initiation as they could introduce bias, but only in the final outcome model as a sensitivity analysis. We used the inverse probability weighting (IPW) method to estimate the difference in risk of seizures between the two treatment groups. A patient's weight was defined as the inverse of his PS score if he was in the FQ group and the inverse of 1-PS otherwise. A weighted logistic regression was applied including only the group as a predictor for seizure. To avoid noisy PS, rare RF were grouped together based on their seizure risk.[10–14] Analyses were done with the R software.[15] Missing values of blood tests (14%, Table S2) were imputed using the mice procedure in R.[16] As a sensitivity analysis we also examined multiple imputations analysis.

Results

Characteristics of patients treated with FQ

Overall, 52 772 hospitalized patients during 178 932 days were treated with a FQ between 2009 and 2021 (Figure 1). Mean age was 64.8 (±19.4) years and 47.2% were females. Past seizures or epilepsy, recent stroke and recent brain trauma were present among 1214 (2.3%), 2927 (5.5%) and 550 (1%), respectively. Of the different FQs, 33 823 (64%) patients were treated with ofloxacin, 11 294 (21.4%) with ciprofloxacin, 7646 (14.5%) with levofloxacin and nine (0.02%) with moxifloxacin. Thirty-three (0.06%) patients experienced a seizure following a median of 3 days of treatment (IQR 2–4), yielding an incidence of 1:5422 treatment days. As shown in Table 1, these patients were more likely (P value <0.05) to have a history of past seizures, recent stroke or brain trauma, recent CNS infection or encephalopathy, anoxic brain injury, exposure to ASM and higher urea concentration.

Causality between FQ exposure and seizures was determined by Naranjo scale as probable (score 5–8) in 9/33 (27%) cases and possible (score 1–4) in 24/33 (73%) cases (Table 2). The case with the highest score (7) was a seizure in a 60 year-old diabetic male treated empirically with per-os ofloxacin and amoxicillin/clavulanic acid indicated for suspected urinary tract infection and

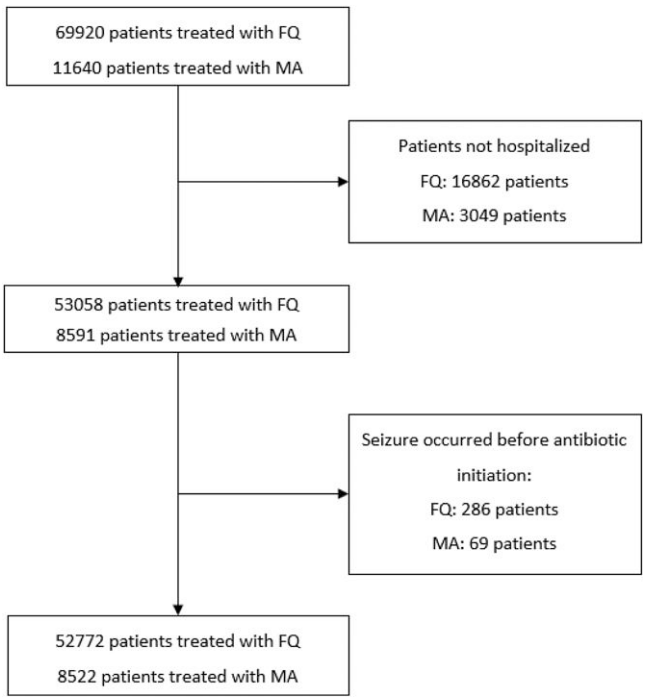

Figure 1. Inclusion and exclusion flow diagram.

Table 1. Baselines characteristics of patients treated with FQ

	Quinolones		Macrolides	
	No seizure	Seizure	No seizure	Seizure
N	52 739	33	8516	6
Age, years (SD)	64.7 (±19)	66.1 (±22)	65.3 (±20)	32.6 (±20)
Females (%)	24 918 (47%)	16 (48%)	4193 (49.2%)	4 (66.7%)
Past seizures or epilepsy (%)	1205 (2.3%)	9 (27%)	353 (4.1%)	4 (66.7%)
Dementia (%)	2353 (4.5%)	1 (3%)	358 (4.2%)	0
Recent stroke or brain trauma ≤30 days (%)	3209 (6.1%)	5 (15%)	266 (3.1%)	0
CNS infection or encephalopathy ≤90 days (%)	194 (0.4%)	1 (3%)	24 (0.3%)	0
Diagnosis of brain neoplasm (%)	1040 (2%)	5 (15%)	201 (2.4%)	0
Anoxic brain injury (%)	108 (0.2%)	1 (3%)	11 (0.1)	0
Drug or alcohol use disorder within previous 1 year (%)	280 (0.5%)	0	44 (0.5%)	0
Antiseizure medications (%)	6574 (12.5%)	10 (30%)	1059 (12.4%)	4 (66.7%)
Laboratory values				
Sodium, mEq/L (SD)	137 (5)	134 (6)	136 (±1)	138 (±2)
Glucose, mg/dl (SD)	116 (47)	113 (56)	116 (±45)	100 (±36)
Creatinine, mg/dl (SD)	1.2 (1)	1.6 (1.4)	1.2 (±1)	0.7 (±0.3)
Urea, mg/dl (SD)	52 (41)	91 (69)	54 (±40)	35 (±15)

diabetic foot infection; treatment with ciprofloxacin 2 months later was associated with status epilepticus. Lower Naranjo scores (i.e. possible causality) were mainly due to the presence of clinically significant acute comorbidities acting as an alternative aetiology for seizure (e.g. stroke, hyperammonaemia, acute renal failure, etc.).

Comparative group characteristics and propensity score analysis

The MA groups composed of 8522 hospitalized patients with a total of 17 954 treatment days. Mean age was 65 (±20.5) years and 49% were females (Table 1). Azithromycin was administered to 73% of them. Six (0.07%) patients experienced each a single seizure following a median of one treatment day (IQR 1–3), resulting in seizure incidence of 1:2991 treatment days. Of the entire MA cohort, 4.1% had history of epilepsy or seizures, 4.2% were diagnosed with dementia, 3.6% were diagnosed with recent stroke and 2.4% had an intracranial neoplasm. We applied the logistic regression including the RF as covariates to obtain PS and calculated patient's weights as explained before. The distributions (density) of the PS in each treatment group are almost identical as shown in Figure S1, indicating a similarity in their RF distributions. Table S2 demonstrates how well the weights balance the RF distribution between the two groups; all RF except for one were well balanced (SMD less than 0.1) even without weighting and after weighting all SMD were lower or equal to 0.01. The IPW estimated OR for seizures among FQ versus MA group was 1.44 (95%CI 0.59–3.5, $P=0.42$). Sensitivity analysis in which multiple imputations for the blood tests variables were applied showed an average OR of 1.4 with a neglectable difference (SD =0.002) between imputations. Adjusting the weighted logistic regression for each of the antibiotics administered after FQ or MA initiation did not significantly alter the results (Table 3) except for when controlling for beta-lactams (95%CI 0.77–4.8).

Discussion

In this large-scale retrospective controlled study accounting for all potential confounders known to affect the occurrence of seizures, we demonstrate that among hospitalized patients treated with FQ, the absolute risk for seizures was very small (0.06%) and did not significantly exceed that of MA (azithromycin or roxithromycin) that are not known to be associated with seizures.

While FQ are considered well tolerated, their use along the years has been hampered by emerging reports of different side effects.[17] Recently, such reports (and related warnings) have challenged the balance between their effectiveness and potential risks, often resulting in restricted prescribing and even avoidance.[18,19] Reports associating their use with Achilles tendonitis and rupture have resulted in a substantial decreased prescription rate.[20,21] Similarly, reports about causal relationship between FQ and seizures has led to refraining from their use in patients with conditions that predispose to convulsions.[22]

To the best of our knowledge, our study is by far the largest to address the questionable association between exposure to FQ and seizures. Given the very small number of cases who developed seizures, we validated each of them for causality using the Naranjo scale: none of the cases was found to have definite causality, while 9/33 (27%) were deemed probable and the rest possible. These results corroborate the findings of a previous large-scale self-controlled trial in which >6000 subjects prescribed FQ did not demonstrate increased seizure rates.[9] It is important to note that opposed to outpatient database studies that rely on drug prescriptions and patient/physician reports, our study on hospitalized patients verifies actual medications administration with more accurate reports as to the primary outcome and all other potential confounders.

The results of our study together with those of the other large retrospective study are supported biologically by the fact that ciprofloxacin and ofloxacin (both account for most FQ administrations) were demonstrated to be weak inhibitors of the $GABA_A$ receptor,

Table 2. Patients with seizures associated with fluoroquinolone treatment

Number	Age, gender	Antibiotic	Regimen	Time to seizure (days)	Risk factors	Co-medications[a]	Naranjo score	Comment
1	60, M	PO. Ofloxacin	200 mg bid	2	None	Amoxicillin-Clavulanic acid	7	Treatment with ciprofloxacin 2 months later was associated with status epilepticus
2	23, M	PO. Ofloxacin	400 mg bid	5	None	None	6	
3	76, F	IV. Ciprofloxacin	400 mg bid	3	Severe dementia	None	6	
4	72, F	PO. Ofloxacin	200 mg bid	3	Mild dementia	None	6	
5	79, M	PO. Ofloxacin	400 mg bid	2	Dementia	None	6	
6	82, M	PO. Ofloxacin	400 mg qd	2	None	Ceftriaxone	6	Urosepsis and ceftriaxone
7	92, F	PO. Ofloxacin	200 mg bid	1	Dementia	None	6	
8	87, F	PO. Levofloxacin	250 mg qd	3	Acute on chronic renal failure	None	5	Re-challenge was not associated with seizure
9	96, F	IV. ciprofloxacin	400 mg bid	1	None	None	5	Re-challenge was not associated with seizure
10	71, M	PO. Ofloxacin	400 mg bid	7	None	Cyclosporine	3	Following bone marrow transplantation. Cyclosporine serum concentration of 286 mg/dl. Suspected maxillary sinus aspergillosis
11	32, F	IV. Ciprofloxacin	400 mg bid	7	Epilepsy	Levetiracetam, Valproic acid, Phenytoin, clonazepam	3	
12	77, M	PO. Levofloxacin	750 mg qd	6	Acute renal failure	None	3	Urea concentration 272 mg/dL
13	86, F	PO. Ofloxacin	400 mg bid	6	Recent ischaemic stroke	None	3	Subacute stroke in right MCA territory
14	59, F	PO. Ofloxacin	200 mg qd	5	Acute renal failure	Imipenem	3	
15	75, F	PO. Ofloxacin	200 mg bid	4	Meningioma, s/p radiation therapy, acute renal failure	None	3	
16	66, M	PO. Ofloxacin	200 mg bid	4	None	Mycophenolate (MMF)	3	Allogenic bone marrow transplantation. A seizure 2 days following ofloxacin initiation. No sign of CNS infection per LP, head CT and MRI. MMF continued
17	36, F	PO. Ofloxacin	400 mg bid	3	CP (no seizure history)	Clonazepam	3	Re-challenge a year later was not associated with seizure
18	52, F	PO. Ciprofloxacin	500 mg bid	2	S/P Subarachnoid haemorrhage	None	3	

Continued

Table 2. *Continued*

Number	Age, gender	Antibiotic	Regimen	Time to seizure (days)	Risk factors	Co-medications[a]	Naranjo score	Comment
19	67, M	PO. Ofloxacin		2	Colorectal carcinoma with brain metastasis	None	3	
20	28, F	PO. Ofloxacin	400 mg qd	2	CP, epilepsy	Ceftriaxone	3	
21	92, F	PO. Ofloxacin	400 mg bid	1	Seizures, dementia	None	3	
22	34, M	PO. Ofloxacin	400 mg bid	1	Epilepsy, anaplastic astroglioma grade III	Dexamethasone, levetiracetam	3	
23	83, M	PO. Ofloxacin	200 mg bid	1	Hyperammonemia	None	3	
24	78, F	PO. Ofloxacin	200 mg bid	1	Dementia, epilepsy, intracranial bleeding	Phenytoin, valproic acid, ceftriaxone	3	
25	70, M	PO. Ciprofloxacin	200 mg bid	6	Recent ischaemic stroke	None	2	
26	35, M	PO. Ofloxacin	400 mg bid	5	Epilepsy	None	2	
27	94, M	PO. Ofloxacin	400 mg bid	3	Subacute stroke	None	2	
28	71, M	PO. Levofloxacin	500 mg qd	3	S/P cardiogenic shock and successful resuscitation	None	2	
29	84, M	PO. Ofloxacin	200 mg bid	3	Severe dementia	Ceftriaxone	2	
30	97, F	IV. Ciprofloxacin	500 mg bid	3	Severe dementia	None	2	
31	41, M	PO. Ofloxacin	200 mg bid	2	None	Cefazolin	2	Re-challenge was not associated with seizure
32	51, F	PO. Ciprofloxacin	500 mg bid	1	Epilepsy, acute stroke	None	2	
33	32, M	IV. Ciprofloxacin	400 mg bid	1	Glioblastoma	Dexamethasone, levetiracetam, ceftriaxone	2	

[a]Medications known to be associated with seizures (benzodiazepines, barbiturates, ASM) or induce seizures (beta-lactams, antipsychotics, lithium, isoniazid etc.)

Table 3. Odds ratio estimates for seizures between FQ and MA group after controlling for agents administered after FQ or MA initiation

	OR	95% CI	*P* value
Beta lactam	1.93	0.77–4.80	0.16
CNS medications[a]	1.41	0.58–3.42	0.45
Immunosuppressant agents[b]/isoniazid	1.4	0.59–3.47	0.43

[a]Antipsychotics, buspirone, lithium, tricyclic antidepressants.
[b]Azathioprine, calcineurin inhibitors.

although their *in vitro* concentrations required for GABA receptor inhibition are at least 10 times higher than those achieved *in vivo* under therapeutic doses.[7,8,23] In that context, it may by arguable that specific CNS conditions such as hypoxic brain injury, CNS infections or CNS malignancies may alter FQ disposition leading to increased penetration and thus higher concentrations of these agents in the CNS.[24] In the current cohort, the case with the highest Naranjo score was a male patient with history of ischaemic heart disease, heart failure with reduced ejection fracture, hypertension, chronic kidney disease (eGFR 48 mL/min/1.73 m^2) and uncontrolled type II diabetes: comorbidities with significant cardiovascular risk, but none commonly associated with seizures. A head CT conducted during the hospitalization showed signs of chronic ischaemic changes, as commonly observed among patients at high cardiovascular risk but no acute or other major brain pathology. Causality was also suggested by the re-challenge with levofloxacin 2 months later, following which status epilepticus occurred. Cases with seizures on re-challenge were previously reported but along with the presence of baseline brain pathology.[1]

Several limitations of our study deserve attention: the observational retrospective nature of the study prevents adjustment of all potential confounders. Similarly, seizures that were not recorded as ICD10 code might have been missed. Data were extracted solely

from the institutional medical records and thus, RF not documented during the current or prior hospitalization have not been captured and thus not accounted for. Nevertheless, given the large sample size of each group we believe that this potential bias is probably balanced between the two study groups and therefore of little significance. Second, confounding bias characterized by a low prevalence of past seizures and brain trauma among the patients in the FQ group may represent a lower baseline risk for seizures in this group that cannot be ruled out. However, this potential bias was dealt with by performing propensity score analyses that balanced between the groups with that respect. The Naranjo scale was not used for the MA group to assess causality given the lack of data associating either azithromycin or roxithromycin with the occurrence of seizures among adult population. Therefore, applying tools to assess causality in this group is probably of no value. Finally, we grouped together different CNS neoplasms that may harbour different seizure risks. Because this was done similarly in both treatment groups, we believe that the overall significance of this potential bias is small, if at all.

In conclusion, our large-scale study accounting for all known potential confounders provides evidence that FQ administration among hospitalized patients is not associated with increased risk for seizures compared to MA antibiotics. Our results provide evidence for clinicians and decision-makers on balancing the risk and benefits of fluoroquinolones.

Acknowledgements

None.

Funding

The study was carried out as part of our routine work.

Transparency declarations

I.G. and R.L. declare that they recieved fees for consultations provided to MDClone.

Author contributions

I.G. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Conception, design, acquisition: I.G. Data analysis: I.G., B.O., R.L. and R.F. Interpretation of data: all authors. Drafting the work: I.G. and R.L. Critical revisions for important intellectual content: all authors. All authors approved the final manuscript version.

Supplementary data

Figure S1 and Tables S1 and S2 are available as Supplementary data at *JAC* Online.

References

1 US Food and Drug Administrations. FDA drug safety communication: FDA warns about increased risk of ruptures or tears in the aorta blood vessels with fluoroquinolone antibiotics in certain patients 2018. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics

2 US Food and Drug Administrations. FDA drug safety communication: FDA requires label changes to wan of risk for possibly permanent nerve damage from antibacterial fluoroquinolone drugs taken by mouth or by injection 2013. https://www.fda.gov/media/86575/download

3 Kushner JM, Peckman HJ, Synder CR. Seizures associated with fluoroquinolones. *Ann Pharmacother* 2001; **35**: 1194–8. https://doi.org/10.1345/aph.10359

4 Bird SB, Orr PG, Mazzola JL *et al*. Levofloxacin-related seizure activity in a patient with Alzheimer's disease: assessment of potential risk factors. *J Clin Psychopharmacol* 2005; **25**: 287–8. https://doi.org/10.1097/01.jcp.0000162811.15066.8e

5 Tomé AM, Filipe A. Quinlones: review of psychiatric and neurological adverse reactions. *Drug Saf* 2011; **34**: 465–88. https://doi.org/10.2165/11587280-000000000-00000

6 Sutter R, Rüegg S, Tschudin-Sutter S. Seizures as adverse events of antibiotic drugs: a systematic review. *Neurology* 2015; **85**: 1332–41. https://doi.org/10.1212/WNL.0000000000002023

7 Halliwell RF, Davey PG, Lambert JJ. Antagonism of GABAA receptors by 4-quinolones. *J Antimicrob Chemother* 1993; **31**: 457–62. https://doi.org/10.1093/jac/31.4.457

8 Halliwell RF, Davey PG, Lambert JJ. The effects of quinolones and NSAIDs on GABA-evoked currents recorded from rat dorsal root ganglion neurons. *J Antimicrob Chemother* 1991; **27**: 209–18. https://doi.org/10.1093/jac/27.2.209

9 Chui CS, Chan EW, Wong AY *et al*. Association between oral flouroquinolones and seizures: a self-controlled case series study. *Neurology* 2016; **86**: 1708–15. https://doi.org/10.1212/WNL.0000000000002633

10 Bladin CF, Alexandrov AV, Bellavance A *et al*. Seizures after stroke. *Arch Neurol* 2000; **57**: 1617–22. https://doi.org/10.1001/archneur.57.11.1617

11 Zhao B, Shen LX, Ou YN *et al*. Risk of seizures and subclinical epileptiform activity in patients with dementia: a systematic review and meta-analysis. *Ageing Res Rev* 2021; **72**: 101478. https://doi.org/10.1016/j.arr.2021.101478

12 Huntoon K, Musrave N, Shaikhouni A *et al*. Frequency of seizures in patients with metastatic brain tumors. *Neurol Sci* 2023; **44**: 2501–7. https://doi.org/10.1007/s10072-023-06695-y

13 Stritzelberger J, Gesmann A, Fuhrmann I *et al*. Time-dependent risk factors for epileptic seizures in glioblastoma patients: a retrospective analysis of 520 cases. *Epilepsia* 2023; **64**: 1853–61. https://doi.org/10.1111/epi.17658

14 Woo YN, Kim K, Ko DS *et al*. Alcohol consumption on unprovoked seizure and epilepsy: an updated meta-analysis. *Drug Alcohol Depend* 2022; **232**: 109305. https://doi.org/10.1016/j.drugalcdep.2022.109305

15 R Core Team. R: a language and environment for statistical computing. R foundation for Statistical Computing, Vienna, Austria, 2019. https://www.R-project.org.

16 van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw* 2011; **45**: 1–67. https://doi.org/10.18637/jss.v045.i03

17 Owens RC Jr, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis* 2005; **41**Suppl 2: S144–57. https://doi.org/10.1086/428055

18 Tanne JH. FDA adds "black box" warning label to fluoroquinolone antibiotics. *BMJ* 2008; **337**: a816. https://doi.org/10.1136/bmj.a816

19 Rusu A, Munteanu A-C, Arbanasi E-M *et al*. Overview of side-effects of antibacterial fluoroquinolones: new drugs versus old drugs, a step

forward in the safety profile? *Pharmaceutics* 2023; **15**: 804. https://doi.org/10.3390/pharmaceutics15030804

20 Sankar A, Swanson K, Zhou J *et al*. Association of fluoroquinolones prescribing rates with black box warnings from the US food and drug administration. *JAMA Netw Open* 2021; **4**: e2136662. https://doi.org/10.1001/jamanetworkopen.2021.36662

21 Yarrington E, Anderson DJ, Ashley ED *et al*. Impact of FDA black box warning on fluoroquinolone and alternative antibiotic use in southeastern US hospitals. *Infect Control Hosp Epidemiol* 2019; **40**: 1297–300. https://doi.org/10.1017/ice.2019.247

22 European Medicines Agency. Public hearing on quinolone and fluoroquinolone medicines, EMA/225564/2018, 2018. https://www.ema.europa.eu/en/documents/other/public-hearing-quinolone-and-fluoroquinolone-written-interventions_en.pdf

23 Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clin Microbiol Rev* 2010; **23**: 858–83. https://doi.org/10.1128/CMR.00007-10

24 Famularo G, Pizzicannella M, Gasbarrone L. Levofloxacin and seizures: what risk for elderly adults? *J Am Geriatr Soc* 2014; **62**: 2018–9. https://doi.org/10.1111/jgs.13039