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Association Between Oral Fluoroquinolones and Neuropsychiatric Events: Self-Controlled Case Series With Active Comparator Design

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ABSTRACT

Purpose: The evidence of the neuropsychiatric effects associated with fluoroquinolones is mainly supported by case reports. Population-based evidence remains largely limited. We aimed to investigate the association between the use of fluoroquinolones and hospitalization or Accident & Emergency department visits for acute neuropsychiatric events using a self-controlled case series (SCCS) and active comparator to reduce confounding.

Methods: We conducted a SCCS with a recently described active comparator design using all public outpatient clinics, hospitalization, and Accident and Emergency department records from the Clinical Data Analysis and Reporting System, Hong Kong from 2001 to 2013. Among 166 325 people with an oral fluoroquinolone prescription, 4287 people who had an incident neuropsychiatric event were included. We then estimated the incidence rate ratio (IRR) of acute neuropsychiatric events during periods before and after fluoroquinolone prescription, versus baseline. We repeated the analysis for amoxicillin/clavulanic acid users as an active comparator. We then estimated the comparator-adjusted estimates by dividing the IRR for fluoroquinolone by the IRR for amoxicillin/clavulanic acid. The primary outcome was neuropsychiatric events. Secondary outcomes were psychotic events and cognitive impairment.

Results: An increased risk of neuropsychiatric events was observed in the current use of fluoroquinolone [IRR: 2.11 (95% confidence interval (CI): 1.58–2.83)] and 1–7 days after the end of fluoroquinolone prescription [IRR: 1.90 (95% CI: 1.30–2.75)] versus baseline. No increased risk was observed in other risk periods versus baseline. Similar patterns were observed in the current use of amoxicillin/clavulanic acid [IRR: 1.92 (95% CI: 1.19–3.11)] and 1–7 days after the end of fluoroquinolone prescription [IRR: 1.81 (95% CI: 1.11–2.97)] versus baseline. Similar results were found for secondary outcomes. Using the active comparator design,

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comparator-adjusted estimates were 1.10 (95% CI: 0.63–1.93) in current use of fluoroquinolones and 1.05 (95% CI: 0.57–1.95) in 1–7 days postexposure to fluoroquinolones versus baseline.

Conclusions: Although our study showed a higher incidence of neuropsychiatric events in the current use of fluoroquinolones and 7 days after the end of fluoroquinolones prescriptions compared with baseline, a similar temporal pattern was also found for amoxicillin/clavulanic acid users. Using amoxicillin/clavulanic acid as the active comparator, we found no difference in the risk of neuropsychiatric events associated with fluoroquinolone compared with baseline. Therefore, the risk of neuropsychiatric events may not need to influence the decision to prescribe either fluoroquinolones or amoxicillin/clavulanic acid based on the evidence in this study.

1 | Introduction

Fluoroquinolones are among the most common antibiotics prescribed in the treatment for respiratory and urinary tract infections [1]. However, their neuropsychiatric safety profile is still uncertain. In 2016, The US Food and Drug Administration approved the label changes of fluoroquinolones concerning its risk of serious side effects including confusion, hallucinations, and suicidal thoughts after reviewing the adverse event reports and case reports [2]. In 2019, there was advice from the UK Medicines and Healthcare Products Regulatory Agency/the Commission on Human Medicines about stopping fluoroquinolone treatment at the first signs of a serious adverse reaction including central nervous system effects, as precautions [3].

While the evidence concerning neuropsychiatric events associated with fluoroquinolones is primarily based on safety signals, clinical evidence of their central nervous system toxicity using population-based data is largely limited. In contrast to the biological plausibility that fluoroquinolones could lead to seizure, a self-controlled case series (SCCS) study using both population-based Hong Kong and UK routinely collected data showed no evidence of an association between fluoroquinolones and seizures [4]. Notably, a recent cohort study using a national commercial US health insurance claims database also showed no evidence of an increased risk of suicidality in people prescribed fluoroquinolones compared with people prescribed azithromycin or trimethoprim-sulfamethoxazole [5]. Although suicidality is a severe neuropsychiatric outcome, other neuropsychiatric events including psychosis and cognitive impairment associated with the use of fluoroquinolones, which are of significant clinical importance, are still under-investigated using population-based and routinely collected clinical data. Further, treatment decisions should be made based on the risks and benefits of different treatment options. Given the limited number of effective existing antibiotics, it is critical to compare the neuropsychiatric safety of fluoroquinolones with its alternative, specifically amoxicillin/clavulanic acid as the first-line treatment.

Therefore, we aimed to investigate the association between fluoroquinolones and neuropsychiatric events using population-based clinical data in Hong Kong. In this study, we used SCCS to eliminate time-invariant confounding by comparing rates of outcomes in different periods within the level of that particular individual. We further adjusted the estimates for fluoroquinolones using amoxicillin/clavulanic acid, which had similar indications shown in the clinical guidelines in Hong Kong [6], as the active comparator design in the SCCS. By doing this, the neuropsychiatric safety profiles of fluoroquinolones and amoxicillin/clavulanic acid can also be compared for further clinical implications.

2 | Methods

2.1 | Data Source

In this study, we used the routinely collected clinical data from the Clinical Data Analysis and Reporting System. The Clinical Data Analysis and Reporting System is an electronic health record database developed by the Hospital Authority in Hong Kong. All Hong Kong residents have access to public healthcare services provided by the Hospital Authority. Public healthcare services are highly subsidized by the Hong Kong government and are available to Hong Kong citizens at a low cost. Hospital Authority is the main public healthcare provider in Hong Kong which manages all the public hospitals, outpatient general, and specialist clinics in Hong Kong [7]. The patient data are collected and entered into the Clinical Management System by healthcare professionals. Data available, including demographics, laboratory results, prescription details, and records from in-patient, outpatient, and accident and emergency departments, are then transferred to the Clinical Data Analysis and Reporting System for audit and research purposes. The patient records are de-identified to ensure privacy and confidentiality. It was used to investigate the association between clarithromycin and neuropsychiatric events [8] and other drug safety studies associated with gastroenterological, cardiovascular, antimicrobial, and psychotropic medications and COVID-19 vaccines [9–12].

2.2 | Study Design

We conducted an SCCS with the active comparator design to investigate the association between fluoroquinolones and neuropsychiatric events. The SCCS design is a within-individual comparison study design that requires cases only for the analysis [13]. By comparing the rate of outcome occurrence during the predefined risk periods and baseline periods, time-invariant confounding such as gender and genetics are inherently eliminated in the analysis. The SCCS performs best for acute events, such as neuropsychiatric events, and transient exposure, such as antibiotics like fluoroquinolones and amoxicillin/clavulanic acid.

We further performed an SCCS with the recently described active comparator design to reduce confounding by indication

Summary

- A higher incidence rate of neuropsychiatric events was observed with the current use and 1–7 days postexposure to fluoroquinolone compared to baseline in SCCS.
- However, using amoxicillin/clavulanic acid as an active comparator, there was no difference in the risk of fluoroquinolone-related neuropsychiatric events compared with the baseline.
- The risk of neuropsychiatric events may not need to influence the decision to prescribe either fluoroquinolones or amoxicillin/clavulanic acid.

and compare the neuropsychiatric risk between antibiotics using amoxicillin/clavulanic acid as the active comparator. This active comparator design in SCCS has been recently developed to reduce confounding by indication by comparing the relative incidence of outcomes between antibiotics [14]. An empirical example was demonstrated by investigating the association between penicillin and venous thromboembolism, using roxithromycin, as an active comparator. We selected amoxicillin/clavulanic acid as it shares similar indications (e.g., respiratory tract infections) as fluoroquinolones [6, 15] and has a relatively good neuropsychiatric safety profile, which is the recommended selection criteria for an active comparator [16, 17]. In Hong Kong, the indications for the two drugs are similar, including the treatment of respiratory tract infections, with amoxicillin/clavulanic acid as the preferred treatment and fluoroquinolones as an alternative [6], suggesting that the clinical use of the two drugs in Hong Kong is comparable. The neuropsychiatric safety profile of amoxicillin/clavulanic acid was assessed by reviewing current literature. We found minimal evidence of the risk of neuropsychiatric events associated with amoxicillin/clavulanic acid despite its long use history (Supporting Information S1).

2.3 | Participants

We identified people aged ≥ 18 years at the beginning of their observation period and had at least one oral prescription of fluoroquinolones or amoxicillin/clavulanic acid from the outpatient setting during the study period (1 January 2001–31 December 2013). As no drug alerts for quinolones about severe neurotoxicity have been issued during this study period [2, 18], clinicians were unlikely to avoid prescribing fluoroquinolones after a neuropsychiatric event during the study period. It is therefore unlikely to violate the assumption of the SCCS study design that events do not influence subsequent exposures [19]. People who also had an incident diagnosis of an acute neuropsychiatric event during the study period were included. Those with unidentified, missing gender or birthdate were excluded. Due to the limitation of computation power and resources, we randomly selected a subset of people who had amoxicillin/clavulanic acid to match a similar proportion of FQ prescriptions during the study period, using an approximate sampling rate of 0.125 in the database. The inclusion and exclusion criteria and definitions of risk periods and observation periods in the analysis for amoxicillin/clavulanic acid were the same as those in the analysis for fluoroquinolones.

2.4 | Exposure

The start date of exposure to fluoroquinolones or amoxicillin/clavulanic acid was derived from the dispensing date. We calculated the treatment duration by dividing the dispensing quantity by the drug frequency and dosage if the prescription duration was not available. If there was any missing data, we imputed the duration with the study population median for that antibiotic drug. When the gap between prescriptions was 7 days or less, we assumed the treatment to have been continued.

2.5 | Outcome

The primary outcome of interest was the first recorded neuropsychiatric event. The secondary outcomes included the first recorded psychotic events and cognitive impairment, respectively. All outcomes of interest were principal diagnoses of in-patient or accident and emergency admission, identified by the International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9-CM) codes. We compiled a list of codes to identify neuropsychiatric events that were considered acute and potentially drug-induced in the case reports [20–28]. These codes indicate symptoms of psychosis, cognitive impairment, bipolar disorder, and sleep disturbance. While the primary outcome consisted of all the codes listed as the composite outcome, the diagnosis codes for secondary outcomes, which were categorized into psychotic or cognitive diagnoses based on the descriptions, were subsets of the composite outcome. The codes were then independently validated by two psychiatrists (EHML and WCC). The epidemiologists and psychiatrists confirmed the list of diagnostic codes with consensus (Table S1).

2.6 | Statistical Analysis

The observation period started on the latest of the study start date or the date when the patient started to use services provided by the Hospital Authority in the databases and ended at the earliest of the study end date or date of death. Risk periods were predefined as 8–14 days before the start of prescription (8–14 days pre-exposure), 1–7 days before the start of the prescription (1–7 days pre-exposure), current use, 1–7 days after the end of the prescription (1–7 days postexposure) and 8–28 days after the end of the prescription (8–28 days postexposure) (Figure S1). All other periods were classified as baseline periods. 7 days is the recommended prescribing duration for quinolones, and similar risk periods have been defined in previous literature [4]. The pre-exposure periods were included to examine whether the occurrence of the acute neuropsychiatric event would temporarily affect the probability of being prescribed fluoroquinolones or amoxicillin/clavulanic acid. Similar analyzes have also been applied in previous literature [29]. The postexposure periods were included

to examine the possibility of delayed effects of the neuropsychiatric event after the end of the prescription. We estimated the incidence rate ratio (IRR) with a 95% confidence interval (CI) using the conditional Poisson regression, comparing the rate of the outcome in the prespecified risk periods with that in baseline periods. We further adjusted for the effects of age using 1 year bands. We also examined the assumption that the event of interest should not affect the observation period regarding the potential for censoring around death (Supporting Information 2).

After estimating the IRRs for fluoroquinolones and amoxicillin/clavulanic acid separately in the SCCS, we applied the active comparator method using the simple ratio approach [14]. We calculated the comparator-adjusted IRRs by dividing (the IRRs for fluoroquinolones) by (the IRRs for amoxicillin/clavulanic acid) for each risk period, followed by computing the 95% CI using the Wald test-based method (Supporting Method 1).

Microsoft Excel, SAS 9.3 (SAS Inc., United States) and R 4.1.3 (R Foundation for Statistical Computing, Vienna, and Austria) were used for data management and analyzes.

2.7 | Sensitivity Analysis

It is possible that clinicians may have recorded the neuropsychiatric event on the prescription date at the time of hospital admission. In this scenario, the event may have occurred prior to the fluoroquinolones prescription but not associated with the exposure. This may induce bias by overestimating the rate of neuropsychiatric events during the current fluoroquinolones period in the SCCS analysis. Therefore, a sensitivity analysis was conducted for the neuropsychiatric events by taking the first day of prescription as a separate risk period. This approach has been performed and described in a previous study [30]. Second, we removed overlapped cohorts of fluoroquinolones and amoxicillin/clavulanic acid users for neuropsychiatric events to test any potential effect of drug switching, as another sensitivity analysis.

3 | Results

A total of 291 751 oral fluoroquinolone prescriptions in 166 325 people were identified. Among them, 4287 patients were included in the analysis for fluoroquinolones (Figure S2). Their mean age (standard deviation [SD]) at the date of the event was 66 (18) years for neuropsychiatric events and psychotic events respectively, and 73 (15) years for cognitive impairment. Men accounted for approximately 46% for neuropsychiatric events and psychotic events respectively and 52% for cognitive impairment in the study cohort. Table 1 presents the demographics and follow-up time in each risk period and baseline in each analysis. The median prescription duration was 7 days. Levofloxacin (46%) and ciprofloxacin (41%) were the most commonly prescribed fluoroquinolones in the study period (Table S2).

Among 4287 people, we observed an increased risk of neuropsychiatric events associated with fluoroquinolones with an IRR of 2.11 (95% CI 1.58–2.83) during current use (Figure 1). A 1.9-fold increased IRR was also observed in the 1–7 days postexposure but not in other risk periods, versus baseline. There were 2437 and 870 people who had a prescription of fluoroquinolones and the first diagnosis of cognitive impairments and psychotic events respectively. A similar temporal pattern was observed for cognitive impairment as the primary outcome of neuropsychiatric events. For psychotic events, we observed an increased risk during 1–7 days postexposure with an IRR of 2.57 (95% CI 1.32–4.98). An IRR of 1.43 (95% CI 0.73–2.79) for psychotic events was also found in the current use of fluoroquinolones, versus baseline.

A total of 286 337 amoxicillin/clavulanic acid prescriptions were identified in 165 148 randomly selected subset of amoxicillin/clavulanic acid users. Of these, 2449 patients were included in the amoxicillin/clavulanic acid analysis. Their mean age (SD) at the date of the event was 60 (20) years for neuropsychiatric events, 58 (20) for psychotic events, and 71 (17) years for cognitive impairment (Table 1). Men accounted for 47% for neuropsychiatric events, 49% for psychotic events, and 54% for cognitive impairment of the study cohort. Similarly, we observed an increased risk of neuropsychiatric events associated with amoxicillin/clavulanic acid with an IRR of 1.92 (95% CI 1.19–3.11) during current use among 2449 people (Figure 1). A 1.8-fold increased IRR was also observed in the 1–7 days postexposure but not in other risk periods (Figure 1), versus baseline. There were 1022 and 383 people who had a prescription of amoxicillin/clavulanic acid and the first diagnosis of cognitive impairments and psychotic events respectively. A similar temporal pattern was observed for cognitive impairment as the primary outcome of neuropsychiatric events. For psychotic events, we observed an increased risk during 1–7 days postexposure with an IRR of 2.86 (95% CI 1.06–7.75) versus baseline. Notably, the number of events for psychotic outcomes in people prescribed amoxicillin/clavulanic acid was very low in each risk period.

Using the active comparator design comparing the IRRs in the analyzes for fluoroquinolones and amoxicillin/clavulanic acid, we observed no difference in comparator-adjusted estimates of neuropsychiatric events for fluoroquinolones in current use versus baseline (IRR: 1.10, 95% CI: 0.63–1.93) and in 1–7 days postexposure versus baseline (IRR: 1.05, 95% CI: 0.57–1.95) (Figure 1). Similar results were found for secondary outcomes.

Sensitivity analyzes of separating the first day of prescription and that of removing overlapped cohorts of fluoroquinolones and amoxicillin/clavulanic acid users did not result in significant change compared with the primary analysis (Tables S3 and S4).

4 | Discussion

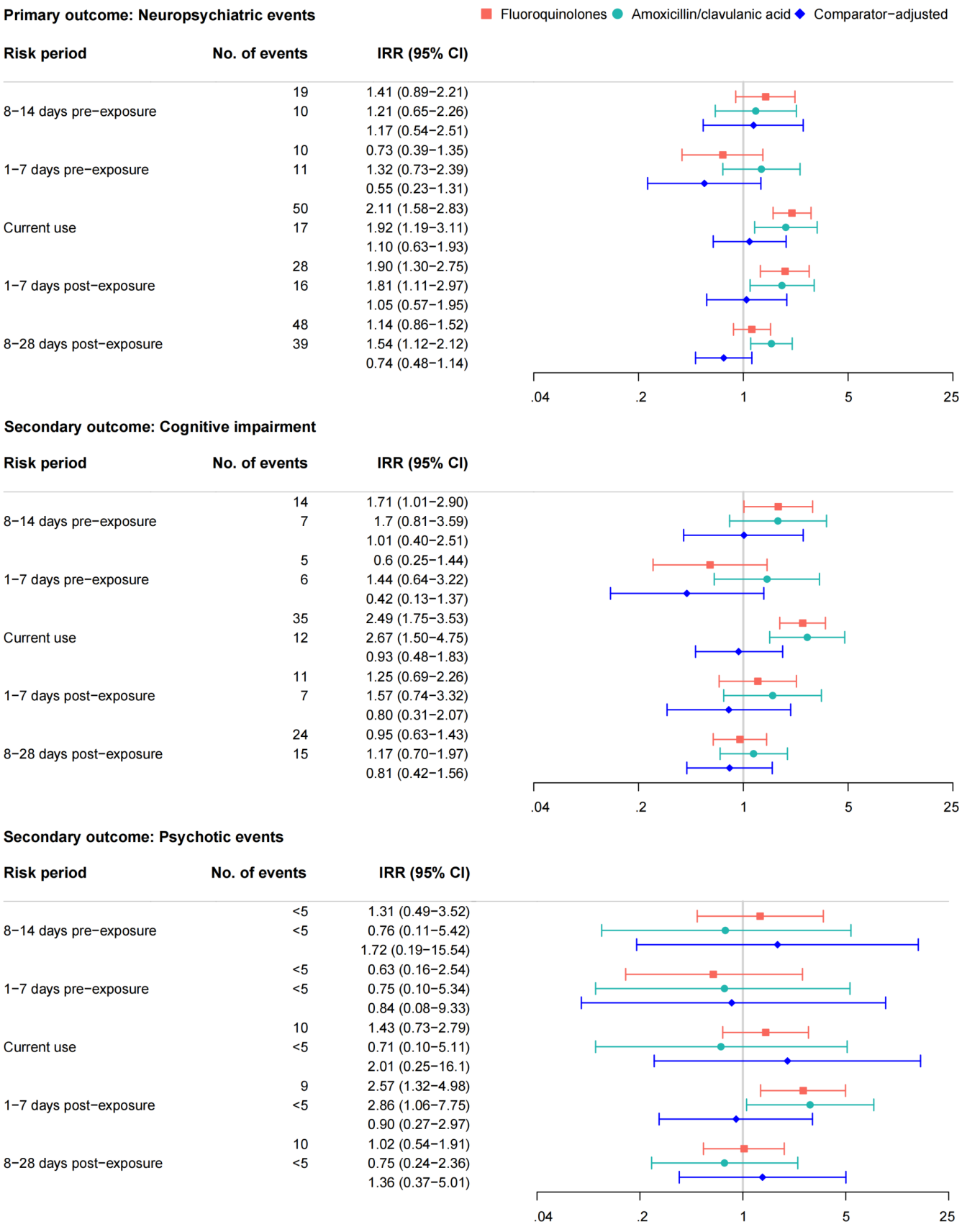
4.1 | Summary

Based on routinely collected clinical data, our study showed a higher incidence of neuropsychiatric events associated with fluoroquinolones in the current use of fluoroquinolones and 1–7 days postexposure periods relative to baseline in the SCCS. A similar temporal pattern was also found for amoxicillin/clavulanic acid. Using the recently described active comparator method in SCCS, we showed that there was no difference in risk

TABLE 1 | Characteristics of included people.

	Fluoroquinolone			Amoxicillin/clavulanic acid		
	Individuals with neuropsychiatric events (*n* = 4287)	**Individuals with cognitive impairment (*n* = 2437)**	**Individuals with psychotic events (*n* = 870)**	**Individuals with neuropsychiatric events (*n* = 2449)**	**Individuals with cognitive impairment (*n* = 1022)**	**individuals with psychotic events (*n* = 383)**
Sex *n* (%)						
Male	2025 (47.24)	1269 (52.07)	402 (46.21)	1157 (47.24)	554 (54.21)	188 (49.09)
Female	2262 (52.76)	1168 (47.93)	468 (53.79)	1292 (52.76)	468 (45.79)	195 (50.91)
Age at event date (year)						
Mean (Standard deviation)	66.71 (17.88)	73.19 (14.93)	66.07 (17.56)	59.67 (20.41)	70.98 (16.95)	57.84 (20.49)
Common comorbidities at cohort entry *n* (%)						
Chronic obstructive pulmonary disease	212 (4.95)	121 (4.97)	53 (6.09)	88 (3.59)	43 (4.21)	15 (3.92)
Ischemic heart disease	271 (6.32)	184 (7.55)	61 (7.01)	105 (4.29)	62 (6.07)	19 (4.96)
Diabetes	390 (9.10)	257 (10.55)	95 (10.92)	127 (5.19)	74 (7.24)	24 (6.27)
Ischemic stroke	176 (4.11)	125 (5.13)	35 (4.02)	66 (2.69)	42 (4.11)	10 (2.61)
Heart failure	591 (13.79)	403 (16.54)	141 (16.21)	189 (7.72)	115 (11.25)	36 (9.4)
Hypertension	107 (2.5)	80 (3.28)	28 (3.22)	37 (1.51)	22 (2.15)	7 (1.83)
Follow-up (person-year)						
8–14 days pre-exposure	121.42	67.94	25.07	86.60	36.75	12.84
1–7 days pre-exposure	123.39	69.10	25.45	87.60	37.25	12.99
Current use	223.27	126.97	56.41	91.59	39.48	13.43
1–7 days postexposure	132.36	72.94	28.34	92.35	39.59	13.66
8–28 days postexposure	378.42	209.08	79.93	266.44	113.83	39.38
Baseline[a]	46160.02	25856.18	8931.77	28664.13	11411.93	4457.63

Note: Current use = prescription duration of fluoroquinolone or amoxicillin/clavulanic acid.
[a]Baseline = nonrisk period.



Notes: We used amoxicillin/clavulanic to be the comparator. IRR = Incidence rate ratio. CI = Confidence interval. Current use = prescription duration of fluoroquinolone or amoxicillin/clavulanic acid.

FIGURE 1 | Results of SCCS studies.

of neuropsychiatric events associated with fluoroquinolones in the current use of fluoroquinolones and 1–7 days postexposure to fluoroquinolones relative to baseline comparing that with amoxicillin/clavulanic acid, as the comparator-adjusted estimates were close to null.

4.2 | Findings in Context

To our knowledge, there is limited evidence using routine clinical data on the neuropsychiatric safety profile of fluoroquinolones. The relationship between neuropsychiatric toxicity including psychosis, delirium, and other related events and fluoroquinolones was mainly supported by case reports [20–28, 31–40] and adverse drug reaction reporting systems [41]. Another study showed that 23 out of 631 people were found to meet criteria based on Naranjo's score for fluoroquinolones-associated delirium or psychosis [42]. Our study outcome did not encompass peripheral neuropathy, as its biological mechanism pertains to the peripheral nervous system that would be different from the central nervous system dysfunctions under investigation. Furthermore, many studies have quantified the risks of peripheral neuropathy associated with oral fluoroquinolones [43, 44]. Notably, urinary tract infections could lead to acute neuropsychiatric events [45]. However, as the current studies by design do not have comparison groups (i.e., unexposed group/active comparator) in the analysis, these studies were not able to disentangle the effect of confounding by indication (i.e., underlying infection) versus that of fluoroquinolones. In our study, we chose amoxicillin/clavulanic acid as the active comparator in this comparative safety research as it is a first-line treatment of respiratory tract infection [6, 15] and has a relatively safe profile for neuropsychiatric effects as neuropsychiatric adverse reactions of amoxicillin/clavulanic acid were rarely reported. Although we were not able to confirm whether fluoroquinolones and amoxicillin/clavulanic acid included in our study were used for the same indications, as in other studies [14, 46–48] we could reduce confounding by indication by selecting such drugs with similar indications stated in the clinical guideline as active comparators. From our literature search, we only found very few case reports and one study using spontaneous reports indicated an increased risk of psychosis associated with amoxicillin/clavulanic acid compared to minocycline [49]. However, due to the beneficial effects of minocycline on negative symptoms in people with psychosis [50], minocycline would not be an ideal reference group to compare the risk of neuropsychiatric events with amoxicillin clavulanate. This led to an uncertainty about whether the observed risk in this study compared with minocycline represents a true positive signal for neuropsychiatric events associated with amoxicillin/clavulanic acid. The small increased IRR of amoxicillin/clavulanic acid observed in this study could be partially explained by the underlying infection. Although we could not rule out any possibility of a small increased risk of neuropsychiatric events associated with amoxicillin/clavulanic acid, we can still conclude that there is no difference in the risk of neuropsychiatric events for fluoroquinolones, compared with amoxicillin/clavulanic acid, which is of significant clinical implications.

Other observational studies showed no evidence of a higher risk of neuropsychiatric events (using suicidality as an outcome) associated with fluoroquinolones using cohort [5] and case–control study design [51] respectively.

4.3 | Clinical Impact

Due to the growing antibiotic resistance, the safety profiles of the limited number of effective existing antibiotics need to be carefully evaluated to inform optimal prescribing choices. This study is of clinical importance with respect to the recommendation of the US Food and Drug Administration to further study potential psychiatric adverse events associated with fluoroquinolones in the postmarketing setting [52]. The findings of this study serve as important clinical evidence for prescribers to compare the neuropsychiatric safety profiles of fluoroquinolones and their alternatives. Importantly, there is no difference in the neuropsychiatric adverse effects between fluoroquinolones and amoxicillin/clavulanic acid, one of the most prescribed antibiotics [53], suggesting that when choosing antibiotics for treatment such as respiratory tract infections, the neuropsychiatric effect is not an additional concern for prescribing either fluoroquinolones or amoxicillin/clavulanic acid.

4.4 | Strengths and Limitations

This is the first population-based study investigating the association between fluoroquinolones and neuropsychiatric events using SCCS. We used this study design to inherently control for residual confounders that could not be accounted for in the classic epidemiological study designs. Importantly, we also applied the active comparator design to account for the time-varying confounding (i.e., the underlying infection) using amoxicillin/clavulanic acid. This study demonstrated the importance of choosing the appropriate analyzes to evaluate medication safety using healthcare databases. The active comparator design in SCCS can be used to study drug safety to mitigate confounding by indication as well as compare risks between drugs in future studies. Second, unlike the administrative databases, our data were directly retrieved from the electronic records of hospitals, ambulatory clinics, and emergency rooms; all diagnoses were made by clinicians and entered by trained clinicians for clinical management.

Similar to other observational studies using large healthcare databases, this study is also subject to limitations. Adherence to medications is not reflected in our data, which could lead to misclassification bias of exposure. To minimize such bias, we assumed continuous exposure for treatment gaps between prescriptions of ≤ 7 days. In addition, the data from the private healthcare sector is not available in the Clinical Data Analysis and Reporting System. However, we included patients who visited the public healthcare sector at least twice in our analysis because they had to use the public healthcare services at least once for the start of the observation period and had the outcome occurred during the observation period to be included in the SCCS. Given the low consultation fee and drug cost, our included cohorts were more likely to use public healthcare services. Moreover, we did not have data on indications, which prevented us from directly controlling for antibiotic indications by restricting or stratifying the population based on

these indications. However, we chose antibiotics with similar indications as active comparators to reduce confounding by indication. Lastly, although the study design we used aims to control for time-invariant confounding and confounding by indication, comparing incidence rate ratios between two populations using active comparators might not entirely remove residual confounding due to health differences between the two populations.

5 | Conclusions

Although the use of fluoroquinolones was associated with an increased risk of neuropsychiatric events, a similar increased risk was also observed in people prescribed amoxicillin/clavulanic acid. A recently described active comparator design in SCCS showed that there is no evidence to indicate a higher risk of neuropsychiatric events following the use of fluoroquinolones. Therefore, the risk of neuropsychiatric events may not need to influence the decision to prescribe either fluoroquinolones or amoxicillin/clavulanic acid based on the evidence in this study. Future studies are required to confirm the findings.

5.1 | Plain Language Summary

The evidence of the neuropsychiatric effects associated with fluoroquinolones is mainly supported by case reports and spontaneous reports. Clinical evidence from population-based clinical data remains largely limited. In this SCCS with the recently described active comparator design of 166 325 fluoroquinolones users, a higher incidence rate of neuropsychiatric events was observed with the current use and 1–7 days post-exposure to fluoroquinolone compared to baseline in SCCS. However, using amoxicillin/clavulanic acid as an active comparator, there was no difference in the risk of fluoroquinolone-related neuropsychiatric events compared with baseline. The risk of neuropsychiatric events does not need to influence the decision to prescribe either fluoroquinolones or amoxicillin/clavulanic acid.

Author Contributions

C.S.L.C. is the guarantor. C.S.L.C., I.C.K.W., A.Y.S.W., E.H.M.L., W.C.C., E.Y.H.C., and E.W.C. had the original idea for this study and contributed to the development of the idea and the study design. C.S.L.C., F.M. and N.T.T. reviewed the literature. Y.Z., F.M., C.S.L.C., and A.Y.S.W. undertook the analyses. Y.Z., F.M., C.S.L.C., and A.Y.S.W. wrote the first draft of the paper. All authors contributed to the interpretation of the analyses, reviewing and editing of the manuscript, as well as approving the final manuscript.

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Ethics Statement

This study obtained ethics approval from the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (IRB reference number: UW 23–215).

Consent

This study used only de-identified patient-level data, and therefore individual informed consent was not required.

Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi_disclosure.pdf] and declare the following: C.S.L.C. has received: grants from the Food and Health Bureau of the Hong Kong Government, Hong Kong Research Grant Council, Hong Kong Innovation and Technology Commission, MSD, Pfizer, IQVIA, and Amgen; nonexecutive director of Adance Data Analytics for Medical Science (ADAMS) Limited (HK); and personal fees from Primevigilance, outside the submitted work. EWYC reports grants from the Research Grants Council (RGC, Hong Kong), Research Fund Secretariat of the Food and Health Bureau, National Natural Science Fund of China, Wellcome Trust, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen, Takeda, and Narcotics Division of the Security Bureau of HKSAR, and an honorarium from the Hospital Authority, outside the submitted work. I.C.K.W. reports grants from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK and Novartis, the Hong Kong Research Grant Council, the Hong Kong Health and Medical Research Fund in Hong Kong, the National Institute for Health Research in England, European Commission, National Health and Medical Research Council in Australia, consulting fees from IQVIA and World Health Organization, payment for expert testimony for Appeal Court of Hong Kong and is a nonexecutive director of Jacobson Medical in Hong Kong, ADAMS Limited (HK), Asia Medicine REgulatory Affairs (AMERA) Services Limited, OCUS Innovation LImited (HK, Ireland, and UK) and Therakind in England, outside of the submitted work; no other relationships or activities that could appear to have influenced the submitted work. A.Y.S.W. holds a fellowship (FS/19/19/34175) from the British Heart Foundation. Funders had no role in the study design, collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Data Availability Statement

Computing code and study protocol are available from the corresponding author upon request to reproduce the results. The study data cannot be made available for external access.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.