Society of Medical Education & Research

2024, Volume 4, Issue 1, Page No: 147-157
ISSN: 3108-4850

Annals of Pharmacy Education, Safety, and Public Health Advocacy

A Retrospective Pharmacovigilance Evaluation of Safety Profiles of Fluoroquinolones versus Other Antibiotic Classes in Reported Adverse Drug Reactions

Sofía Martínez[1]*, Carlos Gómez[1], Lucia Navarro[2]

[1]Department of Pharmacovigilance and Drug Safety, Faculty of Pharmacy, Polytechnic University of Madrid, Madrid, Spain.
[2]Department of Clinical Pharmacology and Pharmacoepidemiology, Faculty of Pharmacy, University of Barcelona, Barcelona, Spain.

***E-mail** ✉ sofia.martinez@upm.es

Abstract

Fluoroquinolones (FQs) are widely used antimicrobial agents known for their strong efficacy against a broad range of infections. Despite their extensive use and generally acceptable tolerance profile, safety concerns remain. This study aimed to evaluate the incidence, severity, and outcomes of fluoroquinolone (FQ)-related adverse drug reactions (ADRs) using reports from a regional spontaneous ADR reporting system. A retrospective cross-sectional observational design was employed, including all patients with documented ADRs associated with fluoroquinolones or other antibiotics (ABs) reported to the Regional Pharmacovigilance Center (PVC) database from January 2019 to December 2022. Data were obtained from the Saudi ADR reporting system of the PVC, which aligns with the MedWatch ADR reporting format of the U.S. Food and Drug Administration (FDA). A total of 605 antibiotic-related ADR reports were analyzed. Fluoroquinolones accounted for the highest proportion of reported ADRs (177; 29.3%), followed by penicillins (100; 23.4%) and cephalosporins (90; 21%). No statistically significant difference was observed in FQ-related ADRs between males (104; 58%) and females (OR: 1.17, 95% CI: 0.82–1.67, P = 0.386). However, individuals aged 40 years or older had a significantly higher incidence of FQ-related ADRs (OR: 1.56, 95% CI = 1.09–2.22, P = 0.015). Most FQ-associated ADRs were of moderate severity (157; 88.7%), required medical intervention (83; 46.9%), and resolved following treatment (154; 87%). In addition, patients exposed to FQs were approximately four times more likely to develop neurological adverse events (OR: 4.15, 95 % CI = 2.48–6.93, P < 0.001). Fluoroquinolones had a higher frequency of ADRs than other antibiotic classes. Continuous monitoring of antibiotic safety is essential to enhance awareness among healthcare professionals and the public regarding appropriate antibiotic use and to restrict fluoroquinolone use to infections where alternative treatments are ineffective.

Keywords: Pharmacovigilance, Fluoroquinolones (FQs), Adverse drug reactions (ADRs), Antibiotics (ABs)

Introduction

Adverse drug reactions (ADRs) are described as unintended and undesirable responses that occur following the use of a medicinal product for diagnosis, prevention, or treatment, where a reasonable causal relationship exists between the drug exposure and the adverse outcome [1, 2]. Serious ADRs represent a major public health concern as they may lead to life-threatening conditions or death [3]. In addition, severe reactions such as hepatic or renal failure have been responsible for market withdrawal of certain pharmaceutical products [4, 5].

Despite their importance, preventing ADRs remains difficult due to limited awareness and understanding of their mechanisms, as well as the inherently unpredictable nature of some reactions. This contributes to higher drug development costs and higher clinical trial attrition rates [1, 2]. Consequently, obtaining comprehensive and

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Received: 22 March 2024; **Accepted:** 18 July 2024

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How to cite this article: Martínez S, Gómez C, Navarro L. A Retrospective Pharmacovigilance Evaluation of Safety Profiles of Fluoroquinolones versus Other Antibiotic Classes in Reported Adverse Drug Reactions. Ann Pharm Educ Saf Public Health Advocacy. 2024;4(1):147-57. https://doi.org/10.51847/EQKr5LD7OU

reliable ADR-related data is essential for improving patient safety and minimizing risks for pharmaceutical industries [6]. Identifying underlying pharmacological mechanisms and recognizing populations at higher risk are key strategies for managing and mitigating ADRs [1, 2].

Fluoroquinolones (FQs) are widely prescribed antimicrobial agents considered effective and generally well tolerated against a broad range of bacterial infections, due to their extensive activity against both Gram-positive and Gram-negative organisms [7-9]. They also possess favorable pharmacokinetic characteristics, including high oral absorption and wide tissue distribution, and exert their antibacterial effect by inhibiting DNA topoisomerase enzymes essential for bacterial DNA replication and transcription processes [8-10]. Furthermore, they exhibit minimal inhibitory effects on human enzymes and are generally regarded as having a strong safety profile [10].

FQs are commonly used to treat infections such as urinary tract infections (UTIs), pneumonia, and tuberculosis (TB) [11]. However, inappropriate antibiotic (AB) use has contributed to rising antimicrobial resistance and increased incidence of ADRs, leading to higher healthcare costs, prolonged hospitalization, and increased mortality rates [7, 12, 13]. Although FQs are largely well tolerated, safety concerns have persisted [11]. Most reported ADRs are mild and reversible, with discontinuation required in fewer than 2% of patients [11]. Nevertheless, FQs have also been associated with serious adverse outcomes, including recurrent *Clostridium difficile* infection (CDI), cardiovascular toxicity, musculoskeletal disorders, renal and hepatic impairment, and central nervous system (CNS)-related effects [7, 8, 10, 11, 14]. The rate of FQ-related ADRs leading to emergency department visits has been estimated at 9.2 per 10,000 prescriptions, which is higher than that reported for other antibiotics such as macrolides and cephalosporins [15].

Concerns regarding fluoroquinolone safety have led to increased regulatory scrutiny, including boxed warnings issued by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency [7, 11]. The FDA has repeatedly highlighted risks associated with FQs, particularly long-lasting and severe ADRs affecting the nervous, musculoskeletal, and joint systems [7, 11]. Despite these regulatory warnings and accumulating evidence, inappropriate prescribing of FQs remains common in many healthcare settings [16, 17]. Therefore, their use should be limited to situations where the therapeutic benefits outweigh potential risks and no safer alternatives are available [7, 11, 18]. In addition, the economic burden associated with serious FQ-related ADRs is likely underestimated [18]. Evidence also suggests that boxed warnings have had limited influence on prescribing behavior, largely because healthcare professionals lack sufficient awareness [16, 17].

The Saudi Food and Drug Authority (SFDA) [19] has implemented pharmacovigilance systems that monitor ADRs reported for marketed products through the National Pharmacovigilance Center. These systems collect spontaneous ADR reports submitted by healthcare professionals and consumers nationwide [19]. Several studies have examined ADR reporting trends in Saudi Arabia [20-22]; however, to the best of our knowledge, no study has specifically focused on fluoroquinolone-related ADR patterns in the Saudi context. Accordingly, this study was designed to evaluate the rates, severity, seriousness, outcomes, and types of FQ-related ADRs reported to a regional spontaneous ADR database, and to compare them with those of other antibiotics.

Materials and Methods

Study design

This study employed a retrospective cross-sectional pharmacovigilance approach, including all reported ADRs associated with fluoroquinolones and other antibiotics submitted to the Tabuk Regional Pharmacovigilance Center (PVC) database.

Data source

The Tabuk Regional PVC database collects electronically submitted ADR reports from hospitals within the Tabuk region of Saudi Arabia. The system is modeled on the Saudi Food and Drug Authority (SFDA) ADR reporting form [23, 24], which is comparable to the US FDA MedWatch reporting system [4, 25]. Each report included detailed patient and event information such as age, sex, description of the reaction, seriousness, onset and resolution times, duration of suspected drug use, recovery status, and clinical outcomes. Additionally, the Naranjo algorithm was applied to evaluate the causality assessment of the reported ADRs [26].

Study population

The study included all patients with documented ADRs linked to fluoroquinolones or other antibiotics recorded

in the PVC database between January 2019 and December 2022. Reports involving non-antibiotic medications and those related to topical antibiotic use were excluded. The study workflow and analysis framework are presented in **Figure 1.**

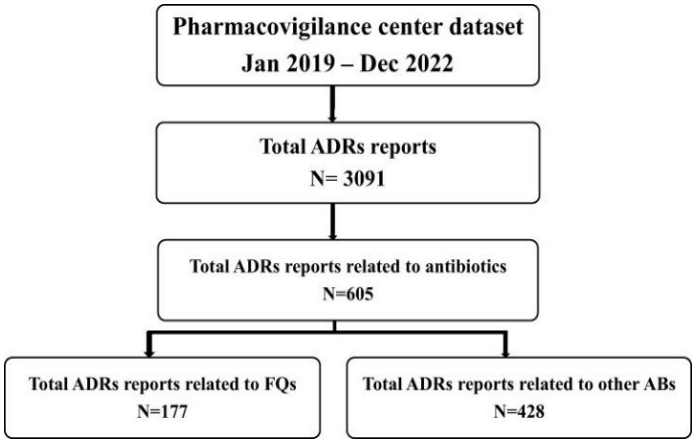


Figure 1. Diagram illustrating the selection and processing of adverse drug reaction reports retrieved from the regional pharmacovigilance database.

Study outcomes

The main endpoint of this research was the reporting rate of fluoroquinolone (FQ)-associated ADRs submitted to the PVC, compared with other antibiotics (ABs). Additional endpoints included assessment of ADR severity, seriousness, clinical outcomes, and classification of reaction types.

Definitions

Fluoroquinolone antibiotics in this study refer to systemic agents including ciprofloxacin, moxifloxacin, and levofloxacin. Other antibiotics (ABs) comprise all systemically administered antimicrobial agents, including penicillins, cephalosporins, carbapenems, aminoglycosides, glycopeptides, macrolides, and sulfonamides.

Based on the Saudi Food and Drug Authority (SFDA) ADR reporting guidelines [27], severity is defined as the level of intensity of the reaction, categorized as mild, moderate, severe, or fatal. In contrast, seriousness refers to regulatory and clinical criteria triggered by the event, such as hospitalization, prolonged hospitalization, the need for medical intervention, life-threatening conditions, or death. Outcome refers to the patient's condition after discontinuation of the suspected drug, including whether recovery occurred. Causality evaluation was conducted using the Naranjo algorithm [26].

Statistical analysis

Descriptive statistics, including counts and percentages, were used to summarize categorical variables, including demographic characteristics, ADR severity, seriousness, and outcomes. Univariate logistic regression analyses were performed to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for factors potentially associated with fluoroquinolone-related ADRs, and to compare severity and outcomes between FQs and other ABs. The likelihood of ADR occurrence among patients exposed to FQs was assessed relative to those receiving other antibiotics. Statistical significance was defined as a p-value below 0.05. For variables with multiple categories showing significant results, a post-hoc Bonferroni correction was applied to identify specific group differences (0.05 divided by the number of comparisons). Data analysis was conducted using SPSS software version 22 (SPSS Inc.).

Results and Discussion

A total of 3,091 ADR reports were recorded in the PVC during the study period. Among these, 605 (19.6%) were linked to systemic antibiotic use. Fluoroquinolones represented the most frequently reported antibiotic class associated with ADRs (177; 29.3%), while the remaining 428 cases (70.7%) were attributed to other antibiotic classes (**Table 1**). Among non-FQ antibiotics, penicillins

accounted for the highest number of reports (100; 23.4%), followed by cephalosporins (90; 21%).

Male patients experienced slightly more FQ-related ADRs compared with females (104; 58.8%), although this difference was not statistically significant (P = 0.386). Distribution of ADRs across age groups is shown in **Table 1**, with the 31–40-year age group showing the highest frequency of fluoroquinolone-associated ADRs (47; 26.6%).

Table 1. Comparative profile of ADRs associated with fluoroquinolones and other antibiotics.

Variables	Other antibiotics (n (%))	Fluoroquinolones (FQ) (n (%))	Total (n (%))	Odds of ADRs (95% CI)	P-value
Overall ADRs	428 (70.7)	177 (29.3)	605 (100)	—	—
Sex					
Female*	193 (45)	73 (41.2)	266 (44)	1.17 (0.82–1.67)	0.386
Male	235 (55)	104 (58.8)	339 (56)	—	—
Age (years)					
0–10	75 (17.5)	0 (0)	75 (12.4)	—	—
11–20	8 (1.9)	2 (1.1)	10 (1.7)	—	—
21–30	75 (17.5)	23 (13.0)	98 (16.2)	—	—
31–40	63 (14.7)	47 (26.6)	110 (18.2)	—	—
41–50	81 (18.9)	40 (22.6)	121 (20.0)	1.56 (1.09–2.22)**	0.015
51–60	58 (13.6)	33 (18.6)	91 (15.0)	—	—
61–70	29 (6.8)	23 (13.0)	52 (8.6)	—	—
71–80	30 (7.0)	9 (5.1)	39 (6.4)	—	—
> 80	9 (1.4)	0 (0.0)	9 (1.0)	—	—
Route of administration					
IV*	220 (51.4)	51 (28.8)	271 (44.8)	—	—
Oral	208 (48.6)	126 (71.2)	334 (55.2)	2.63 (1.82–3.85)	<0.001
Severity					
Mild*	10 (2.3)	11 (6.2)	21 (3.5)	—	—
Moderate	410 (95.8)	157 (88.7)	567 (93.7)	0.35 (0.15–0.84)	0.018
Severe	6 (1.4)	9 (5.1)	15 (2.5)	1.02 (0.28–3.68)	0.970
Lethal	2 (0.5)	0 (0.0)	2 (0.3)	—	—
Seriousness					
Hospitalization*	24 (5.6)	31 (17.5)	55 (9.1)	0.28 (0.15–0.50)	<0.001
Prolonged hospitalization	187 (43.7)	61 (34.5)	248 (41.0)	—	—
Medical intervention required	211 (49.3)	83 (46.9)	294 (48.6)	—	—
Life-threatening	4 (0.9)	2 (1.1)	6 (1.0)	—	—
Death	2 (0.5)	0 (0.0)	2 (0.3)	—	—
Outcomes					
Recovered*	364 (85.0)	154 (87.0)	518 (85.6)	1.37 (0.64–2.94)	0.422
Not recovered	19 (4.4)	11 (6.2)	30 (5.0)	—	—
Fatal	2 (0.5)	0 (0.0)	2 (0.3)	—	—
Unknown	43 (10.0)	12 (6.8)	55 (9.1)	—	—
Causality					
Definite*	254/351 (59.3)	98/139 (55.4)	352 (58.2)	1.09 (0.71–1.69)	0.679
Possible	51 (12.0)	23 (13.0)	74 (12.2)	—	—
Probable	46 (10.8)	18 (10.2)	64 (10.6)	—	—
Missing	77 (17.9)	38 (21.4)	115 (19.0)	—	—
Type of events					
Cardiovascular	50 (11.7)	24 (13.6)	74 (12.2)	—	—
Dermatological	114 (26.6)	29 (16.4)	143 (23.6)	—	—
Renal	20 (4.7)	5 (2.8)	25 (4.1)	—	—

Hepatic	52 (12.1)	15 (8.5)	67 (11.1)	—	—
Endocrine	1 (0.2)	3 (1.7)	4 (0.7)	—	—
Gastrointestinal	91 (21.3)	26 (14.7)	117 (19.3)	—	—
Hematological	23 (5.4)	10 (5.6)	33 (5.5)	—	—
Immunological	5 (1.2)	0 (0.0)	5 (0.8)	—	—
Neurological	29 (6.8)	41 (23.2)	70 (11.6)	—	—
Respiratory	9 (2.1)	5 (2.8)	14 (2.3)	—	—
Musculoskeletal	11 (2.6)	8 (4.5)	19 (3.1)	—	—
Electrolyte disturbance	4 (0.9)	2 (1.1)	6 (1.0)	—	—
Others	19 (4.4)	9 (5.1)	28 (4.6)	—	—

Notes: *Reference category for odds ratio calculation; **Age reference ≤40 years; statistical significance set at $p < 0.05$.

Patients older than 40 years showed a substantially higher risk of developing adverse drug reactions (ADRs) linked to fluoroquinolones (FQs) compared with younger individuals (≤ 40 years) when benchmarked against other antibiotics (OR: 1.56, 95% CI: 1.09–2.22, P = 0.015). Furthermore, oral delivery of FQs was associated with a greater likelihood of triggering ADRs than the intravenous (IV) route (OR: 2.63, 95% CI: 1.82–3.85, P = 0.015). Details on the ADRs reported by specific event category appear in Supplementary **Table 1**.

Table 2 presents the breakdown of ADR reports according to individual antibiotics and the categories of events involved. Across the entire set of ADR reports, ciprofloxacin accounted for the highest share (100 reports; 16%), followed by amoxicillin-clavulanic acid (63 reports; 10.4%) and levofloxacin (50 reports; 8.3%). The patterns of FQ-associated ADRs in relation to various factors are illustrated in **Figures 2a and 2b**.

Table 2. Types of ADR events per individual antibiotic therapy

Antibiotics	Total ADRs n (%)*	Frequently Reported Types of Events					
		Cardiovascular events (n (%))*	Gastrointestinal events (n (%))*	Hematological events (n (%))*	Hepatic events (n (%))*	Dermatological events (n (%))*	Neurological events (n (%))*
Fluoroquinolones							
Ciprofloxacin	100 (16.5)	11 (1.8)	16 (2.6)	10 (1.7)	8 (1.3)	20 (3.3)	19 (3.1)
Levofloxacin	50 (8.3)	9 (1.5)	3 (0.5)	0 (0)	6 (1)	9 (1.5)	14 (2.3)
Moxifloxacin	27 (4.5)	4 (0.7)	7 (1.2)	0 (0)	1 (0.2)	0 (0)	8 (1.3)
Other antibiotics							
Amoxicillin	21 (3.5)	4 (0.7)	7 (1.2)	0 (0)	0 (0)	4 (0.7)	4 (0.7)
Amoxicillin-clavulanic	63 (10.4)	5 (0.8)	22 (3.6)	1 (0.2)	9 (1.5)	12 (2)	2 (0.3)
Ampicillin	4 (0.7)	1 (0.2)	0 (0)	0 (0)	0 (0)	3 (0.5)	0 (0)
Cloxacillin	2 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.3)	0 (0)
Piperacillin-tazobactam	8 (1.3)	2 (0.3)	0 (0)	3 (0.5)	1 (0.2)	1 (0.2)	0 (0)
Ceftriaxone	28 (4.6)	3 (0.5)	4 (0.7)	2 (0.3)	1 (0.2)	11 (1.8)	1 (0.2)
Cefazolin	17 (2.8)	1 (0.2)	2 (0.3)	0 (0)	0 (0)	4 (0.7)	6 (1)
Cefuroxime	19 (3.1)	0 (0)	5 (0.8)	2 (0.3)	6 (1)	4 (0.7)	0 (0)
Cefotaxime	9 (1.5)	1 (0.2)	0 (0)	2 (0.3)	3 (0.5)	3 (0.5)	0 (0)
Ceftazidime	3 (0.5)	0 (0)	1 (0.2)	0 (0)	1 (0.2)	1 (0.2)	0 (0)
Azithromycin	47 (7.8)	12 (2)	15 (2.5)	0 (0)	6 (1)	11(1.8)	0 (0)
Clindamycin	12 (2)	3 (0.5)	1 (0.2)	0 (0)	0 (0)	3 (0.5)	0 (0)
Doxycycline	16 (2.6)	2 (0.3)	8 (1.3)	0 (0)	0 (0)	4 (0.7)	0 (0)
Vancomycin	41 (6.8)	5 (0.8)	3 (0.5)	3 (0.5)	1 (0.2)	21 (3.5)	1 (0.2)
Amikacin	8 (1.3)	2 (0.3)	0 (0)	0 (0)	2 (0.3)	3 (0.5)	0 (0)

Gentamicin	5 (0.8)	0 (0)	2 (0.3)	0 (0)	0 (0)	2 (0.3)	0 (0)
Clarithromycin	10 (1.7)	2 (0.3)	4 (0.7)	0 (0)	1 (0.2)	0 (0)	1 (0.2)

Note: *Percentage was calculated per the total number of ADRs (605).

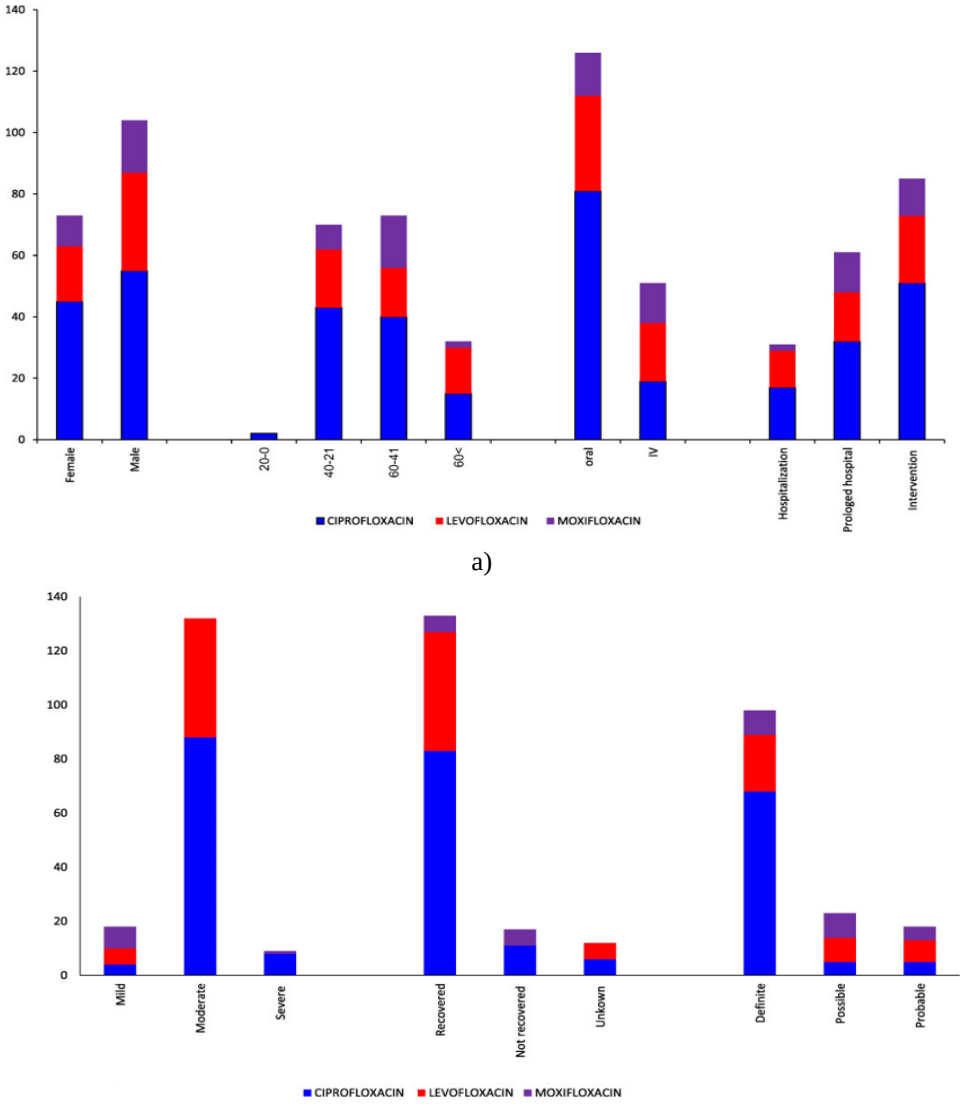


Figure 2. (a) illustrates the distribution of adverse drug reactions (ADRs) associated with individual fluoroquinolones (FQs) across patient demographic characteristics and levels of seriousness. In contrast, Figure (b) presents their distribution according to severity grading, clinical outcomes, and Naranjo causality scores.

In comparison with other antibiotic (AB) classes, most ADRs linked to FQs were classified as moderate in severity (157; 88.7%), whereas severe reactions were uncommon (9; 5.1%). Among the severe cases, eight occurred in patients treated with ciprofloxacin (**Figure 1**). No fatal outcomes were attributed to FQs, whereas two deaths (0.5%) were reported in association with cephalosporin antibiotics (**Table 1**).

In terms of seriousness classification, only two FQ-related ADRs (1.1%) were considered life-threatening, both involving bone marrow suppression and agranulocytosis. Additionally, 83 patients (46.9%) required therapeutic intervention, while the remaining cases resulted in hospitalization, either an initial admission or an extended stay. Overall, FQs were associated with a significantly lower likelihood of

causing serious ADRs that necessitated prolonged hospitalization or were life-threatening compared with other antibiotics (OR: 0.28, 95% CI: 0.15–0.50, P < 0.001). Within the other AB group, two in-hospital deaths occurred, both following anaphylactic reactions to intravenous cefazolin, whereas no deaths were recorded among FQ-related ADRs, as presented in **Table 1**. Post-hoc analyses indicated that differences in life-threatening ADRs between FQs and other antibiotics were not statistically significant, and no meaningful differences in mild or severe ADRs were observed between the two groups.

Regarding patient outcomes, most FQ-associated ADRs resolved completely (154; 87%), while a small proportion (11; 6.2%) remained unresolved at follow-up; no deaths were recorded in the FQ group (**Table 1**). There was no statistically significant difference in the rate of unresolved outcomes between FQs and other antibiotics (OR: 1.37, 95% CI: 0.64–2.94, P = 0.42). Causality assessment using the Naranjo scale showed that 98 cases (55.4%) of FQ-related ADRs were classified as definite (**Table 1**).

As summarized in **Table 1**, neurological manifestations were the most frequently reported ADRs associated with FQs (41; 23.2%), followed by dermatological (29; 16.4%) and gastrointestinal (26; 14.7%) events. In contrast, among other antibiotics, dermatological reactions were most common (143; 26.6%), followed by gastrointestinal (117; 21.3%) and cardiovascular (74; 11.7%) effects.

As presented in **Table 3**, individuals receiving fluoroquinolone therapy had approximately a fourfold increased likelihood of developing notable neurological adverse reactions compared with those treated with other antibiotics (OR: 4.15; 95% CI: 2.48–6.93; P < 0.001). In contrast, fluoroquinolones were associated with a significantly reduced risk of dermatological adverse events relative to other antibiotic groups. No statistically significant differences were observed between the two groups regarding cardiovascular, gastrointestinal, or hepatic adverse drug reactions.

Table 3. Odds Ratio and 95% confidence interval for FQs ADR events vs other antibiotics

ADRs events	P value	OR (95% CI)
Neurological events	< 0.001	4.15 (2.48–6.93)
Dermatological events	0.008	0.54 (0.34–0.85)
Cardiovascular Events	0.522	1.19 (0.70–1.99)
Gastrointestinal events	0.064	0.64 (0.96–1.03)
Hepatic events	0.192	0.67 (0.38–1.22)

As presented in Supplementary **Table 2**, the ophthalmic adverse drug reactions (ADRs) linked to fluoroquinolones (FQs) (n = 7) were classified within the "Other" category instead of being grouped under neurological disorders. Although certain ocular manifestations, such as diplopia, may be associated with extraocular muscle tendinopathy, these events were not explicitly categorized as neurological outcomes.

Spontaneous ADR reporting remains highly valuable in clinical research, as it helps identify previously unrecognized drug-related safety issues and supports the early detection of safety signals [28]. The present study provides important evidence on antibiotic-associated ADRs and emphasizes the need for careful prescribing of FQs, given their broad spectrum of associated adverse effects. Our findings indicated that a considerable proportion of suspected antibiotic-related ADRs were attributable to FQs, accounting for 29.3% of all reported reactions. Among all antibiotics, ciprofloxacin emerged as the most frequently implicated agent (16.5%).

These results align with a recent cross-sectional study from Saudi Arabia that reviewed antibiotic-related ADR reports over one year [22]. That study also identified FQs among the top ten drug classes associated with ADRs (14.9%), with ciprofloxacin being the most frequently reported agent [22]. Studies examining antimicrobial prescribing patterns across outpatient, inpatient, and emergency settings in regional hospitals have shown that third-generation cephalosporins (such as ceftriaxone and ceftazidime), aminoglycosides (such as gentamicin), and macrolides (such as azithromycin) are among the most commonly used antibiotics [29-32]. Considering overall prescribing trends, our results suggest that ADRs linked to fluoroquinolones may have a relatively greater clinical impact.

Regarding sex distribution, no statistically significant association was observed between FQ-related ADRs and patient gender. Nevertheless, the existing literature suggests that sex-based differences in clinically important ADRs may result from physiological and pharmacokinetic factors that affect drug metabolism and distribution in males and females [33]. Some studies further indicate that hormonal, chromosomal, and pharmacokinetic factors may contribute to a higher incidence of ADRs in women compared with men [10, 33, 34].

Age has also been recognized as an important determinant of ADR risk. Older individuals are generally more susceptible due to age-related changes in pharmacokinetics and pharmacodynamics, a higher burden of comorbidities, polypharmacy, and frailty [35]. In this study, patients aged 40 years or older were significantly more likely to experience FQ-related ADRs than those aged 40 years or younger. However, this association should be interpreted cautiously, as it may partly reflect higher prescribing frequency in this age group rather than increased biological vulnerability. Additional studies incorporating prescription exposure data are required to clarify this relationship. Notably, no FQ-related ADRs were recorded in pediatric patients, likely due to the restricted use of this antibiotic class in children because of safety concerns [36], reflecting appropriate prescribing practices. Pediatric pharmacovigilance data indicate that antibiotics and vaccines are the most commonly reported causes of ADRs in children [37].

Regarding severity, most ADRs associated with both FQs and other antibiotics were classified as moderate, requiring medical intervention or extended hospitalization, after which patients recovered with appropriate treatment. These findings are consistent with earlier research conducted in Malaysia [38]. Only a small number of cases were severe, including two life-threatening events, and no fatalities were recorded. The life-threatening reactions were attributed to ciprofloxacin-induced agranulocytosis and bone marrow suppression. Literature reports suggest that bone marrow suppression may resolve after discontinuation of ciprofloxacin; however, in rare cases, irreversible suppression leading to severe thrombocytopenia and hemorrhage has been documented [39, 40].

The present study also demonstrated that FQ exposure was associated with a higher frequency of neurological adverse events, followed by dermatological and gastrointestinal reactions. Fluoroquinolones have previously been linked to peripheral neuropathy as well as central nervous system toxicities, including confusion, encephalopathy, and psychotic symptoms [41, 42]. A systematic review and meta-analysis of 39 randomized controlled trials comparing oral FQs with other antimicrobials in primary care settings also found significantly higher neurological and gastrointestinal ADR rates in the FQ group. At the same time, dermatological reactions were not significantly different [43].

In contrast, a recent Italian pharmacovigilance study on quinolone-related spontaneous reports found that third-generation FQs (levofloxacin and moxifloxacin) were more strongly associated with musculoskeletal adverse events, followed by neurological and psychiatric effects. That study also noted a higher incidence of musculoskeletal reactions among patients aged 60 years or older receiving FQs [44]. In our dataset, ciprofloxacin showed higher frequencies of dermatological, neurological, and gastrointestinal ADRs compared with levofloxacin and moxifloxacin. This difference may be explained by the widespread use of ciprofloxacin, due to its lower cost and greater availability, resulting in greater exposure. Studies from Saudi Arabia have similarly reported that ciprofloxacin is the most commonly prescribed quinolone in multiple formulations, including oral, liquid, injectable, and ophthalmic preparations [16, 45, 46]. These studies also highlighted gaps in healthcare professionals' knowledge regarding appropriate indications for FQs and a relatively high rate of inappropriate outpatient prescribing [16, 45, 46].

Reducing FQ-associated ADRs requires both public education on the risks of misuse and improved awareness among healthcare providers regarding rational antibiotic prescribing. Continuous ADR monitoring is essential for identifying risk factors, preventing recurrence, and enhancing patient safety. Antimicrobial stewardship programs play a crucial role in reducing unnecessary antibiotic use, improving prescribing practices, and lowering both ADR incidence and antimicrobial resistance. Interventions targeting FQ prescribing have been shown to reduce inpatient and discharge prescriptions, thereby decreasing ADR occurrence [47, 48]. However, no FQ-related ADRs were observed in prescriptions issued at discharge in our study. Clinicians should carefully balance risks and benefits when prescribing FQs, particularly for conditions such as

uncomplicated urinary tract infections, for which safer alternatives may exist [49].

A major strength of this study is the use of data from a regional pharmacovigilance center, where ADR reports are not routinely accessible to the public, and the findings are consistent with international evidence. Nonetheless, several limitations should be acknowledged. The dataset was derived from the Tabuk Regional Pharmacovigilance Center, representing a single region of Saudi Arabia. Although it included a substantial number of reports from hospitals and primary care facilities, generalizability to other regions and populations may be limited. In addition, as a retrospective study based on spontaneous reporting by healthcare professionals and patients, underreporting of known ADRs is likely, leading to possible underestimation. The dataset also lacked information on drug–drug interactions, which may have contributed to some observed reactions. Missing data regarding hospitalization duration, comorbid conditions, and polypharmacy further limited comprehensive causality assessment and data quality evaluation.

Conclusion

Overall, fluoroquinolones accounted for the highest proportion of ADRs among other antibiotics in this pharmacovigilance dataset, particularly among individuals aged 40 years or older. Neurological adverse effects were the most frequently observed, highlighting the need for cautious prescribing and careful risk–benefit assessment when using FQs, or restricting their use to cases where alternative antibiotics are not suitable. These findings emphasize the importance of vigilant monitoring and rational use of fluoroquinolones to reduce associated risks.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Patton K, Borshoff DC. Adverse drug reactions. Anaesthesia. 2018;73(Suppl 1):76-84.
2. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255-9.
3. Montastruc JL, Lafaurie M, de Canecaude C, Bagheri H, Durrieu G, Montastruc F. Fatal adverse drug reactions: a worldwide perspective in the World Health Organization pharmacovigilance database. Br J Clin Pharmacol. 2021;87(11):4334-40.
4. MedWatch: the FDA safety information and adverse event reporting program [Internet]. FDA; [cited 2024 Jan 3]. Available from: https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program
5. Gallo K, Goede A, Eckert OA, Gohlke BO, Preissner R. Withdrawn 2.0—update on withdrawn drugs with pharmacovigilance data. Nucleic Acids Res. 2023;51(D1):D1202-D1206.
6. Khalil H, Huang C. Adverse drug reactions in primary care: a scoping review. BMC Health Serv Res. 2020;20(1):5.
7. Baggio D, Ananda-Rajah MR. Fluoroquinolone antibiotics and adverse events. Aust Prescr. 2021;44(5):161.
8. Millanao AR, Mora AY, Villagra NA, Bucarey SA, Hidalgo AA. Biological effects of quinolones: a family of broad-spectrum antimicrobial agents. Molecules. 2021;26(23):7152.
9. Chan T, Bunce PE. Fluoroquinolone antimicrobial drugs. CMAJ. 2017;189(17):E638.
10. Tomé AM, Filipe A. Quinolones: review of psychiatric and neurological adverse reactions. Drug Saf. 2011;34(6):465-88.
11. Fluoroquinolone Antimicrobial Drugs Information [Internet]. FDA; [cited 2024 Jan 3]. Available from: https://www.fda.gov/drugs/information-drug-class/fluoroquinolone-antimicrobial-drugs-information
12. Werner NL, Hecker MT, Sethi AK, Donskey CJ. Unnecessary use of fluoroquinolone antibiotics in hospitalized patients. BMC Infect Dis. 2011;11(1):187.
13. Donskey CJ. Fluoroquinolone restriction to control fluoroquinolone-resistant Clostridium difficile. Lancet Infect Dis. 2017;17(4):353-4.
14. Hayashi PH, Chalasani NP. Liver injury in the elderly due to fluoroquinolones: should these drugs be avoided? CMAJ. 2012;184(14):1555-6.

15. Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. Clin Infect Dis. 2008;47(6):735-43.
16. Mallhi TH, Alanazi AS, Khan YH, Alotaibi NH, Alzarea AI, Alotaibi AS. Assessment of knowledge regarding safety profile, use, and boxed warnings of fluoroquinolones among healthcare professionals in Saudi Arabia: a potential implication for drug regulatory authorities. Front Med. 2022;9:816320.
17. Buehrle DJ, Wagener MM, Clancy CJ. Outpatient fluoroquinolone prescription fills in the United States, 2014 to 2020: assessing the impact of Food and Drug Administration safety warnings. Antimicrob Agents Chemother. 2021;65(7):e0013221.
18. Kuula LSM, Backman JT, Blom ML. Healthcare costs and mortality associated with serious fluoroquinolone-related adverse reactions. Pharmacol Res Perspect. 2022;10(2):e00935.
19. Drug safety initiatives [Internet]. Saudi Food and Drug Authority; [cited 2024 Jan 3]. Available from: https://www.sfda.gov.sa/en/drug-safety-initiatives
20. Bin Yousef N, Yenugadhati N, Alqahtani N, Aljohani A, Almutairi M, Alharbi S. Patterns of adverse drug reactions (ADRs) in Saudi Arabia. Saudi Pharm J. 2022;30(1):8-13.
21. Alayed N, Alkhalifah B, Alharbi M, Alwohaibi N, Farooqui M. Adverse drug reaction (ADR) as a cause of hospitalization at a government hospital in Saudi Arabia: a prospective observational study. Curr Drug Saf. 2019;14(3):192-8.
22. Alenzi KA, Alanazi NS, Almalki M, Alomrani H, Alatawi FO. The evaluation of adverse drug reactions in Saudi Arabia: a retrospective observational study. Saudi Pharm J. 2022;30(6):735-41.
23. Saudi Vigilance. Adverse Drug Reactions (ADRs) Reporting Form [Internet]. Saudi Food and Drug Authority; [cited 2024 Jan 3]. Available from: https://ade.sfda.gov.sa/Request/AdeRequest
24. Report Form - Tiaquz [Internet]. Saudi Food and Drug Authority; [cited 2024 Jan 3]. Available from: https://ade.sfda.gov.sa/Request/AdeRequest
25. Craigle VM. The FDA safety information and adverse event reporting program. J Med Libr Assoc. 2007;95(2):224-5.
26. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45.
27. Guidance on Adverse Drug Events Reporting for Healthcare Professionals [Internet]. Saudi Food and Drug Authority; [cited 2023 Dec 31]. Available from: https://www.sfda.gov.sa/en/regulations?tags=2
28. Pal SN, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes: complementing spontaneous reporting systems. Drug Saf. 2013;36(2):75-81.
29. Alomi YA, Almasoudi AH, Alghamdi GA, Abboud NA. Antimicrobial drug consumption in emergency services at North West (Tabuk) Region hospitals, Saudi Arabia. Pharmacol Toxicol Biomed Reports. 2019;5(3):108-12.
30. Almasoudi AH, Alomi YA, Alghamdi GA, Alshahrani RS. Analysis of antimicrobial medications consumption in inpatient units at North West (Tabuk) Region hospitals, Saudi Arabia. Pharmacol Toxicol Biomed Reports. 2019;5(3):130-4.
31. Almasoudi AH, Alomi YA, Alghamdi GA. Antimicrobial drug consumption in ambulatory care settings, Tabuk Region, Saudi Arabia. Pharmacol Toxicol Biomed Reports. 2019;5(3):97-101.
32. Al Matar M, Enani M, Binsaleh G, Riaz S, Al Thaqafi A, Al Hamdan A. Point prevalence survey of antibiotic use in 26 Saudi hospitals in 2016. J Infect Public Health. 2019;12(1):77-82.
33. Moyer AM, Matey ET, Miller VM. Individualized medicine: sex, hormones, genetics, and adverse drug reactions. Pharmacol Res Perspect. 2019;7(6):e00541.
34. Zucker I, Prendergast BJ. Sex differences in pharmacokinetics predict adverse drug reactions in women. Biol Sex Differ. 2020;11(1):32.
35. Zazzara MB, Palmer K, Vetrano DL, Carfì A, Graziano O. Adverse drug reactions in older adults: a narrative review of the literature. Eur Geriatr Med. 2021;12(3):463-73.
36. Patel K, Goldman JL. Safety concerns surrounding quinolone use in children. J Clin Pharmacol. 2016;56(9):1060.
37. Bouquet É, Star K, Jonville-Béra AP, Durrieu G. Pharmacovigilance in pediatrics. Therapie. 2018;73(2):171-80.

38. Arulappen AL, Danial M, Sulaiman SAS. Evaluation of reported adverse drug reactions in antibiotic usage: a retrospective study from a tertiary care hospital, Malaysia. Front Pharmacol. 2018;9:838.
39. Chaudhry M, Tarneja N, Gundale A, Roa D, Levey R. Bone marrow suppression: a side effect of ciprofloxacin therapy. Am J Ther. 2010;17(5):e167-8.
40. Dutta TK, Badhe BA. Ciprofloxacin-induced bone marrow depression. Postgrad Med J. 1999;75(887):571-3.
41. Zareifopoulos N, Panayiotakopoulos G. Neuropsychiatric effects of antimicrobial agents. Clin Drug Investig. 2017;37(5):423-37.
42. Wierzbiński P, Hubska J, Henzler M, Kucharski B, Bieś R, Krzystanek M. Depressive and other adverse CNS effects of fluoroquinolones. Pharmaceuticals. 2023;16(8):1105.
43. Tandan M, Cormican M, Vellinga A. Adverse events of fluoroquinolones vs. other antimicrobials prescribed in primary care: a systematic review and meta-analysis of randomized controlled trials. Int J Antimicrob Agents. 2018;52(5):529-40.
44. Scavone C, Mascolo A, Ruggiero R, Sportiello L, Rafaniello C, Rossi F. Quinolones-induced musculoskeletal, neurological, and psychiatric ADRs: a pharmacovigilance study based on data from the Italian spontaneous reporting system. Front Pharmacol. 2020;11:563.
45. Ali MD, Patel M, Banu N, Ahmad A, Hassan YA. Drug utilization pattern and cost-effectiveness analysis of five most common antibiotics used in Saudi Arabia. J Pharm Heal Serv Res. 2021;12(2):242-6.
46. Ahmed NJ. Pattern of ciprofloxacin prescribing at outpatient setting in Al-Kharj. J Pharm Res Int. 2020;32(18):62-6.
47. Suzuki H, Perencevich EN, Alexander B, Cai M, Hasegawa S, Goto M. Inpatient fluoroquinolone stewardship improves the quantity and quality of fluoroquinolone prescribing at hospital discharge: a retrospective analysis among 122 Veterans Health Administration hospitals. Clin Infect Dis. 2020;71(5):1232-9.
48. Vaughn VM, Gandhi T, Conlon A, Chopra V, Malani AN, Flanders SA. The association of antibiotic stewardship with fluoroquinolone prescribing in Michigan hospitals: a multi-hospital cohort study. Clin Infect Dis. 2019;69(8):1269-77.
49. Mathews B, Thalody AA, Miraj SS, Kunhikatta V, Rao M, Saravu K. Adverse effects of fluoroquinolones: a retrospective cohort study in a South Indian tertiary healthcare facility. Antibiotics. 2019;8(3):104.