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Letter to the Editor

Fluoroquinolone-associated suicide

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Suicide is a huge global health problem and is the tenth leading cause of death in the United States. Several case reports have raised concerns that exposure to fluoroquinolones (FQs) may increase the risk of suicidal behavior. Though FQs, including levofloxacin, ciprofloxacin, and moxifloxacin have been available for the last 3 decades, there has been a significant paradigm shift about their safety in the last five years (Supplementary Table 1). Recently, European Medicines Agency has started undertaking a detailed investigation on long-term side effects primarily affecting neurological and musculoskeletal system [1]. In 2013, FQ labeling for levofloxacin, ciprofloxacin, and moxifloxacin, respectively had been revised to indicate that suicide represented "isolated" reports, events that were "reported in < 1% of treated patients," and "very rarely reported adverse events". In 2015, a new syndrome termed "FQ associated disability" was described that included serious and disabling side effects that followed even one or two FQ doses. Given their serious and disabling side effects that can occur even with one to two doses, the Food and Drug Administration (FDA) issued a public health announcement that use of FQs should be reserved for patients who have no other alternate options [2]. In February 2017, the levofloxacin manufacturer expanded the suicide-related events in the warnings section of the product label [3]. Similar revisions were not disseminated for ciprofloxacin and moxifloxacin. In this study, we reviewed FDA reports of suicidal behaviors associated with all FDA-approved FQs and evaluated reporting completeness, as many FDA-reported adverse events lack key clinical information.

FDA's Adverse Event Reporting System (FAERS) database was searched (keywords: "ciprofloxacin, levofloxacin, moxifloxacin, gatifloxacin, and ofloxacin"; suicide; or suicidal attempt) (1994–2015). Included cases had no psychiatric history or stable, controlled, psychiatric illness; had attempted or completed suicide, and were reported to the FDA listing the FQ as the suspected causal drug. FAERS report completeness was analyzed with a 10-point scale evaluating demographics, concomitant drugs, FQ usage, psychiatric history, and suicide details, modified from validated scales developed by us previously (Table 1).

Of the 122 FQ-associated suicide or suicide-attempt events reported to the FDA, 108 met inclusion criteria (Table 1). Half of the events described completed suicides; 61% were male, 18% were < 35 years old, and 40% of the events occurred within two weeks of FQ initiation. Mean completeness scores for attempted versus completed suicides were 5.9 and 6.7 (out of 10-point maximum score), respectively (nominal $p = .03$). Reporting completeness scores were better if the event occurred ≤ two weeks versus later after FQ initiation (mean score of 7.2 versus 5.7, nominal $p = .0003$, Fisher-exact). Psychiatric history was rarely present (8 of 39 events reported as occurring ≤ two weeks after FQ initiation and five of 65 events reported as > two weeks after FQ initiation), particularly for levofloxacin-associated attempted or completed suicides (one of 27 reports). Few reports included information on drugs concomitantly taken with the FQ. Characteristics of reported persons who attempted versus completed suicide were similar for age, gender, and event occurrence ≤ two weeks after FQ initiation.

Forty-three of 108 reported FQ-associated suicide events occurred ≤ 2 weeks of FQ initiation. Since 2013, FQ labeling for neuropsychiatric risks, including suicidal ideation, attempts, or completed suicides has been revised periodically. In 2017, labeling for levofloxacin, but not ciprofloxacin or moxifloxacin, was revised to state that suicide-related events may occur, especially in patients with a medical history of depression, or an underlying risk factor for depression and the descriptor "rare" was no longer included in the labeling information.[3] However, FDA reports rarely included text describing psychiatric histories among FQ-treated persons with reported suicide attempts or completed suicides. Given large numbers of FQ-treated persons, prescribers and patients should be aware of revised use indications and FQ associations with suicides. Our findings suggest that labeling should be revised to be more consistent among levofloxacin, ciprofloxacin, and moxifloxacin with respect to underlying risk factors.

Study limitations exist. Given the strong association of suicide risk with prior psychiatric history in FQ users, our study has a reporting bias inherent to FAERS data. It is possible that persons with FQ-associated suicidal toxicity and underlying psychiatric illness may not have been reported to the FDA as experiencing an FQ-related adverse event, thus leading to underreporting of these events among FQ treated persons with known psychiatric histories [4]. Nonetheless, FAERS have been used in the past to identify rare, important, and serious adverse drug reactions [5].

The study highlights the importance of continued awareness of fluoroquinolone-associated suicide-related events, which can occur even in patients without prior psychiatric illness. FDA should consider

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Table 1
Patient characteristics of reviewed patients who had FQ associated completed or attempted suicides.

Parameter	≤ 2 weeks			> 2 weeks[#]		
Drug used	Levofloxacin n = 11	Ciprofloxacin *n* = 15	Other FQ[**] *n* = 19	Levofloxacin *n* = 16	Ciprofloxacin *n* = 33	Other FQ[**] n = 16
Median age (years) (range)	45 (23–84)	49 (21–84)	50.5 (17–87)	51.5 (22–80)	47 (12–68)	43.5 (19–88)
Male n, (%)	7 (64%)	12 (80%)	15 (79%)	10 (63%)	18 (55%)	6 (38%)
Psychiatric history present n, (%)	0 (0%)	4 (27%)	4 (21%)	1 (6%)	1 (3%)	3 (19%)
Suicide details						
Attempted n, (%)	9 (82%)	3 (20%)	10 (53%)	6 (38%)	18 (55%)	11 (69%)
Completed n, (%)	2 (18%)	12 (80%)	9 (47%)	10 (63%)	15 (45%)	5 (31%)
Reports from USA n, (%)	6 (55%)	4 (27%)	10 (53%)	6 (38%)	12 (36%)	12 (75%)
Quality score[$]						
Demographics (2 points)[a]	9 (82%)	15 (100%)	16 (84%)	12 (75%)	26 (79%)	14 (88%)
Drug related (3 points)[b]	8 (73%)	10 (67%)	7 (37%)	6 (38%)	4 (12%)	2 (13%)
Suicide related details (3 points)[c]	3 (27%)	2 (13%)	3 (16%)	4 (25%)	5 (15%)	2 (13%)
Prior psych history (1 point)[d]	7 (64%)	12 (80%)	13 (68%)	8 (50%)	16 (48%)	11 (69%)
Concomitant medications (1 point)[e]	8 (73%)	12 (80%)	13 (68%)	9 (56%)	18 (55%)	10 (63%)

Quality scoring elements- demographics, drug-related, suicide-related, prior psychiatric history; and concomitant medications: ([$]Maximum score of 10 points for each adverse event report)".

[a] Demographics: Age (1 point) and gender (1 point).
[b] Drug related: Indication for use (1 point), days on FQ before event (1 point), dates of drug use (1 point);
[c] Suicide related: Reported by physician (1 point) or not (0), Suicide modality (1 point), date of event (1 point).
[d] Prior psychiatric history reported (1 point).
[e] Concomitant medications (1 point).
[**] Other fluoroquinolones- Ofloxacin(*n* = 23), Moxifloxacin (*n* = 11), Gatifloxacin (n = 1).
[#] Includes cases for which time of event since drug use is not reported.

instituting active-ascertainment procedures for FQ-associated suicide attempts or completed suicides. Going forward, the post-marketing drug labels of FQs should be paralleled for all FQs as per the recent FDA advisory committee recommendations. When reporting FQ-associated suicide behaviors to the FDA or pharmaceutical industry, it is critical to comprehensively report case information.

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Disclaimers

The views expressed represent the independent work of the authors and should not be considered to represent the views or policy of any entity or agency. No parts of this manuscript are under review at any other publication or are published in any other publication. All authors reviewed and approved the manuscript in its current form.

Conflicts of interest

No author has any potential conflicts of interest to declare. No funding from any pharmaceutical company was obtained for this study.

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