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Quinolone antibiotics and suicidal behavior: analysis of the World Health Organization's adverse drug reactions database and discussion of potential mechanisms

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Abstract

Rationale Several case-reports suggest that the use of quinolones may increase the risk of psychiatric adverse reactions such as suicidal behaviors.

Objectives The aim of this study is to investigate whether there is a safety signal for quinolone-related suicidal behaviors in a global adverse drug reactions database.

Methods All antibiotic-related adverse reactions were extracted from Vigibase, the World Health Organization (WHO) global Individual Case Safety Report (ICSR) database. Disproportionality analyses were performed to investigate the association between reports of suicidal behavior and exposure to quinolones, in comparison with other antibiotics.

Results From December 1970 through January 2015, we identified 992 097 antibiotic-related adverse reactions. Among them, 608 were quinolone-related suicidal behaviors including 97 cases of completed suicides. There was increased reporting of suicidal behavior (adjusted reporting odds ratios [ROR] 2.78, 95 % CI 2.51-3.08) with quinolones as compared to other antibiotics. Candidate mechanisms for quinolone-induced suicidal behaviors include GABA_A antagonism, activation of NMDA receptors, decreased serotonin levels, oxidative stress and altered microRNAs expression.

Conclusions We found a strong safety signal suggesting an increased risk of suicidal behaviors associated with quinolones use. Plausible psychopharmacological mechanisms could underlie this association. Further investigations are urgent to confirm and better understand these findings.

Key words

psychopharmacology, adverse drug reactions, suicidal behaviors, suicide, quinolones

Introduction

Quinolones antibiotics are frequently used for the treatment of a variety of infectious diseases. This drug class is popular because of its relatively broad spectrum of activity, multiple approved indications for use, and high bioavailability, resulting in comparable blood concentrations when given intravenously or orally (Melhorn and Brown, 2007). The mechanism of action of quinolones involves the inhibition of the enzymes topoisomerase type II (also known as DNA gyrase) and topoisomerase type IV. These enzymes are involved in bacterial DNA synthesis, and are essential for bacterial DNA replication. Thus, quinolones are both specific and bactericidal antibiotics. More precisely, DNA gyrase tends to be the primary target of quinolones in Gram-negative organisms, whereas topoisomerase IV is typically the primary target in Gram-positive bacteria but these two mechanisms can be combined (Zhanel and Noreddin, 200; Blondeau, 2004). Well established adverse reactions related to quinolones include allergies, phototoxicity, tendinopathies, cardiac arrhythmias or peripheral neuropathy. In the recent past, several quinolones were withdrawn from the market because of the occurrence of serious adverse drug reactions: temafloxacin for haemolytic anemia, trovafloxacin for hepatotoxicity, grepafloxacin for QTc interval prolongation, clinafloxacin for phototoxicity or gatifloxacin for dysglycemia (Tomé and Filipe, 2011; Lewis and Mohr, 2008; Dukes, 2006; Sprandel and Rodvold, 2003; Smith and Schmid, 2006; Rubinstein, 2001). Other quinolones such as moxifloxacin or norfloxacin are only available in certain countries or are used with restrictions (European Medicines Agency, 2008).

Several case reports have raised concerns that exposure to quinolones antibiotics may increase the risk of suicidal behavior *i.e.* suicidal ideations, suicide attempt or completed suicide. In a review of the literature performed in 2011, Tomé and Filipe identified 111 case reports describing psychiatric adverse drug reactions (ADRs) associated with the use of quinolones, including two depressions, two manic depressions and one report of suicidal ideations. Other published case reports described violent suicidal behaviors like stabbing and cutting with a kitchen knife (Behera *et al*, 2014), defenestration (Tomé and Filipe, 2011), or cutting the both wrists and the neck before electrocution (Barthélemi and Lebrun, 2015) in patients exposed to quinolones. One resulted in the death of the patient (Behera *et al*, 2014). A summary of published case reports is provided in Table S1. Recently, a review of the adverse drug reactions spontaneously reported to the French pharmacovigilance system also suggested a possible association between completed suicide and the use of quinolones. Among the reported cases, three completed suicide by defenestration, two to five days after initiation of quinolones. Patients were men aged from 62 to 82 years and two of them had a history of depression (Barthélemi and Lebrun, 2015). In summary, the case reports suggest violent suicidal behaviors, a predominance of male gender, a relatively short time to onset after exposure to quinolones and suspected drugs which include ofloxacin, levofloxacin and ciprofloxacin (Behera *et al*, 2014; Labay-Kamara *et al*, 2012; Barthélemi and Lebrun, 2015; Ahmed *et al*, 2011; LaSalvia *et al*, 2010). According to the European Medicine Agency, a safety signal is generated from several sources such as spontaneous reports, clinical studies and the scientific literature and informs on an adverse event that is potentially caused by a medicine and that warrants further investigation.

In order to investigate a safety signal for quinolone-related suicidal behaviors in a large adverse event database, we compared the reporting of adverse events of suicidal behaviors among quinolone users with users of other antibiotics by performing a disproportionality analysis within Vigibase, the World Health Organization (WHO) global individual case safety report (ICSR) database (Lindquist, 2008). We also discussed the potential mechanisms involved in quinolone-related suicidal behaviors.

Methods

Data source

The study was based on information extracted from VigiBase, the largest and most comprehensive pharmacovigilance database which collects ICSR from 110 countries over the five continents. The National Pharmacovigilance Centres (NPCs), who are members of the WHO Programme for International Drug Monitoring (Lindquist, 2001), submit the data on their spontaneous reports of ADRs to VigiBase, which is maintained by the Uppsala Monitoring Centre (UMC) in Sweden. The data, which originates from a variety of sources (health care professionals, pharmaceutical companies and patients) is evaluated by the relevant NPCs prior to submission and registration in VigiBase. Over 10 million ICSRs are currently recorded in VigiBase, and about 1 million ICSRs are added each year. The reports usually contain reporter information, patient characteristics (age, gender, and medical history), clinical description of the ADR, its seriousness and its evolution, drug exposures with dates, dosages and indications. In VigiBase, the WHO Adverse Reaction Terminology (WHO-ART) or the Medical Dictionary for Regulatory Activities (MedDRA) (Brown *et al*, 1999) are used to code ADRs (WHO-ART coded reports are assigned a corresponding MedDRA code on the Preferred Term level). Drugs are coded according to the WHO Drug Dictionary Enhanced and classified using the Anatomical Therapeutic Chemical (ATC) classification (WHO, 2013). Details about each suspected adverse reaction received by the UMC may vary from one country to another. Thus, the information in these reports is not homogenous, at least with regard to origin, completeness of documentation, or likelihood that the suspected drug caused the adverse events.

In this study, we extracted from VigiBase all the reports of adverse drug reactions (identified with MedDRA version 18.1) associated with an antibiotic exposure (ATC code J01) recorded from December 9th, 1970 to January 19th, 2015. This selection includes psychiatric and non-psychiatric events as well as serious and non-serious events. In our study, several ICSRs may refer to the same patient.

Study design

We studied the disproportionality of reports for suicidal behaviors associated with quinolones by performing a case-non case study. This design allows the calculation of Reporting Odds Ratios (ROR), which compares the odds of exposure to quinolones between cases and non-cases (Moore *et al*, 2005, van Puijenbroek *et al*, 2005). Cases of suicidal behaviors were reports of an ADR defined by the MedDRA High Level Term (HLT) "Suicidal and self-injurious behaviors". All other reports associated with an antibiotic exposure were considered as non-cases.

Exposure definition

Exposure to quinolones drugs was identified in the ICSR by the use of at least one quinolone (ATC code J01M) preceding the onset of the adverse reaction. The most frequently reported quinolones (ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin) were also identified and analyzed separately. Comedications with antidepressant or antipsychotic drugs were retrieved by the ATC codes "N06A" and "N05A", respectively.

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics retrieved from the case reports of suicidal behaviors and as well as completed suicides. A temporal year-by-year presentation of the reported cases was also provided.

Among all adverse drug reactions reports associated with antibiotic use, our primary analysis consisted in calculating the ROR of suicidal behavior (and corresponding 95% confidence interval) for quinolones compared to other antibiotic drugs using logistic regression models adjusted for age and gender. The ROR for the frequently reported quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin) were also calculated.

Our first secondary analyses studied the variation in reporting rate among different regions and periods: We performed a geographical analysis among the various regions and countries, and the presence of a notoriety

effect (Pariante *et al*, 2007) was studied by a year-by-year analysis of the cumulative crude RORs during the more recent years (from 2000 to 2015). Second, in order to study the influence on ROR estimations of a potential event-competition bias by well-established ADRs associated with quinolones (Salvo *et al*, 2013), we repeated the disproportionality analyses when excluding well-known quinolone-related adverse reactions such as musculoskeletal and dermatological events. Third, we used the same design than the primary analysis to separately study the disproportionality of the reporting of depressive disorders on one hand and completed suicides on the other hand, in association with quinolone use. Cases of depressive disorders were defined as reports of ADRs corresponding to the MedDRA *High Level Group Term (HLGT)* “*Depressed mood disorders and disturbances*” and cases of completed suicide were retrieved by selecting the reports of ADRs including the MedDRA *Preferred Term (PT)* “*Completed suicide*”. Finally, to explore a potential effect modification by age or gender, we performed stratified analyses according to age categories and gender. Analyses were conducted using SAS software version 9.2 (SAS Institute, Cary, NC, USA).

Identification of potential mechanisms

A separate literature survey used the Medline database to search for data on possible underlying mechanisms of psychiatric disorders induced by the use of quinolones.

Results

Descriptive statistics

We identified 992 097 ICSRs associated with antibiotic use reported to VigiBase from 117 countries between December 1970 and January 2015. Reported cases of suicidal behavior were 1627 (0.2%). Among the ADRs with exposure to quinolones, there were 608 cases of suicidal behavior including 97 cases of completed suicide and 171 927 other adverse reactions (Figure 1). The characteristics of reported cases of suicidal behavior and completed suicide that involved quinolones are presented in Table S2. The majority of cases of suicidal behavior exposed to quinolones were reported after 2000 (93.4%) and originated from America and Europe (61.3% and 36.5% respectively). The two countries which reported the most were the United States (57.1%) and Germany (23.5%). Mean age of exposed cases of suicidal behavior was 40.4 and 53% were women. The majority of the cases of completed suicide exposed to quinolones occurred in subjects aged from 45 to 64 (50.5%) and mean age was 44.1. Exposed cases of suicidal behavior were most frequently reported by health care professionals (46.4%). Ciprofloxacin was the most frequently used quinolone in the reports of suicidal behavior (43.2% of the cases), followed by levofloxacin (26.6%), moxifloxacin (14.9%) and ofloxacin (11.4%). In total, 13.7% of the quinolone-related cases of suicidal behavior were also exposed to antidepressants and 5.8% to antipsychotics. Comedications with antidepressants and antipsychotics were more frequent for the quinolone-related cases of completed suicide (37.2% and 26.7% respectively).

Annual counts of reported suicidal behavior and completed suicide exposed to quinolones are presented in Figure 2. The gap in reports for the year 2007 and the following peak in 2008 is an artifact due to the implementation by the UMC in 2007 of a new method to enter ICSRs into VigiBase resulting in delayed import of the ICSRs of 2007 (Uppsala Monitoring Centre, 2008). Nonetheless, the annual number of quinolone-related cases recorded in VigiBase is clearly higher after 2007, for both suicidal behaviors and completed suicides.

Primary analysis

Table 1 presents the disproportionality analysis of reported suicidal behaviors associated with quinolones. Overall, the use of quinolones was associated with a significantly increased reporting of suicidal behavior compared with other antibiotics (adjusted reporting odds ratio [ROR] 2.78, 95% confidence interval [CI] 2.51-3.08). Among the most frequently reported drugs, ciprofloxacin was the most strongly associated with increased reporting of suicidal behaviors (adjusted ROR 4.01, 95% CI 3.50- 4.59). The ROR for the other

quinolones levofloxacin, moxifloxacin and ofloxacin also showed significant increase in reporting, with greater values than the one observed for the whole class (Table 1).

Secondary analyses

The use of quinolones was associated with a statistically significant increase in reporting of suicidal behavior compared with other antibiotics in all the regions and countries where cases were notified, except in Germany where the safety signal was not statistically significant (ROR 0.84, 95% CI 0.69-1.03). Otherwise, among the countries which reported more than 10 cases, ROR ranged from 1.91 (in United Kingdom) to 5.32 (in Canada). The detailed geographic analysis of reported suicidal behaviors associated with quinolones in the main regions and countries is provided in Table S3.

The year-by-year analysis of cumulative ROR of suicidal behaviors associated with quinolones is presented in Figure 3. The cumulative crude ROR in the period from 1970 to 2000 was relatively high but calculated in a small proportion of the total cases exposed to quinolones (40 cases, 6.6%). As of 2000, ROR progressively decreased and, since 2010, stabilized at a value around 3.

When excluding well-known quinolone-related adverse reactions such as dermatological events, musculoskeletal events and both, ROR for quinolone related suicidal behaviors were slightly increased (values ranging between 3.01 and 3.83) but showed a similar significant disproportionality signal than the primary analysis (Table S4).

Disproportionality analyses of reported depressive disorders and completed suicide associated with quinolones are shown in Tables S5 and S6. Compared to other antibiotics, exposure to quinolones was associated with an increased reporting of depressive disorders (adjusted ROR 4.15, 95% CI 3.87-4.45) and completed suicide (adjusted ROR 1.56, 95% CI 1.24-1.97). Among the most frequently reported drugs, ofloxacin was the most strongly associated with increased reporting of depressive disorders (adjusted ROR 5.99, 95% CI 5.20-6.89) (Table S5) and ciprofloxacin was the most strongly associated with increased reporting of completed suicide (adjusted ROR 3.49, 95% CI 2.67-4.55) (Table S6).

Stratified analyses according to age categories and gender are presented in Tables S7 and S8. Slightly increased ROR of suicidal behaviors were observed for the categories <17 years and 65 years – 74 years (adjusted ROR 4.10, 95% CI 2.42-6.91 and 5.85, 95%CI 3.64-9.41, respectively). ROR for completed suicide were clearly increased for the younger category <17 years (adjusted ROR 8.96, 95%CI 3.59-22.33). Stratification according to gender did not provide relevant differences compared to the primary analysis.

Discussion

Our study used a case non-case design to evaluate the association between the use of quinolones and the reporting of suicidal behaviors as well as depressive disorders and completed suicides, recorded in the WHO drug adverse event database from 1970 to 2015. Strong significant disproportionality signals were found, showing an increased reporting of suicidal behaviors, completed suicides and depressive disorders with quinolone drugs and particularly with ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin, the most frequently reported drugs. Although stratified analyses were based on fewer exposed cases, the increased ROR observed for completed suicide in the category <17 years suggests that young patients may be more at risk when using quinolones. Although quinolones are usually not recommended in children, this might be related to a greater vulnerability of younger patients to psychiatric harms of drugs, as it was suggested for suicidality among young patients exposed to antidepressants (Stone *et al*, 2009).

The potential risk of suicidal behaviors and more generally for neuropsychiatric adverse effects associated with quinolones has been suggested by several case reports (Tomé and Filipe, 2011; Behera *et al*, 2013; Labay-Kamara *et al*, 2012; Barthélémi and Lebrun, 2015; Ahmed *et al*, 2011; Lasalvia *et al*, 2010, Montané *et al*, 2009; Mulhall and Bergman, 1995; Feinberg, 1995). Quinolones were associated with various neuropsychiatric adverse drug reactions, including delirium, agitation, confusion, psychosis, seizures/convulsions,

anxiety and major depression (Melhorn and Brown, 2007; Dukes, 2006; Feinberg, 1995; Fish, 2001). Suicidal behavior is a heterogeneous and multifactorial entity involving complex interactions between biological, psychological and socio-environmental factors. Even though suicide is now considered a condition on its own and not just a consequence of other psychiatric disorders, the presence of a psychiatric disorder, particularly depression and psychosis, represents a main risk factor for suicide.

Potential mechanisms

A number of neurobiological actions that could explain the psychiatric adverse effects of quinolones have been reported. Since the neurobiology of suicide may be, at least in part, independent of other psychiatric disorders, the question whether quinolone-induced suicidal behavior is independent or secondary to the psychopathological context remains to be clarified.

Impairment in the GABAergic/glutamatergic balance in the brain has been suggested as a factor contributing to the neurotoxic effects of quinolones. It has been suggested that the Central Nervous System stimulating effects of quinolones could be related to their inhibitory effect on γ -amino-butyric acid (GABA) binding (Tsuji *et al*, 1988), with subsequent decrease of GABA_A-mediated inhibitory neurotransmission. The GABA antagonistic effects of quinolones are possibly related to the GABA-like structures of their substituent at position 7 of the heterocycle, and may explain, at least in part, their epileptogenic activity (Akahane *et al*, 1989). Quinolones were also shown to interact with the benzodiazepine-GABA_A-receptor complex with increased Central Nervous System activity (Unsel *et al*, 1990). Even though the affinity of quinolones for the GABAergic system is weak, a recent study reported that repeated administration of ciprofloxacin in rats could induce anxiety-like behavioral effects in the elevated plus-maze model (Ilgin *et al*, 2015). In that study, the brain GABA content in ciprofloxacin-treated animals was decreased when compared with the control group. These effects are in agreement with the potential induction of anxiety by quinolones, which might represent an additional facilitating factor for suicidal behavior in some individuals at risk.

Quinolones do not bind to glutamate receptors (Dodd *et al*, 1989). However, considering their Mg²⁺ chelating properties (the ketone and carboxylic acid functional groups tend to chelate divalent ions), it has been speculated that the excitatory potency of quinolones might be based on activation of the N-methyl-d-aspartate (NMDA) receptor by abolishing the Mg²⁺ block in the ion channel (Schmuck *et al*, 1998). The direct role of a glutamatergic alteration in suicide is still unclear but its potential implication cannot be excluded, considering the putative anti-suicidal (suppression of suicidal ideations) properties of the NMDA receptor antagonist ketamine (Reinstatler and Youssef, 2015).

On the other hand, the quinolone ciprofloxacin has been shown to significantly decrease serotonin levels in the brain with respect to control values and to induce a depression-like behavioral response in the forced swimming test in rats (Ilgin *et al*, 2015), which is in agreement with many studies linking altered serotonin transmission not only to depression but also to impulsive aggressive behavior (Oquendo and Mann, 2000) and suicide risk (Oquendo *et al*, 2014).

In addition, oxidative stress inducing capacity of quinolones has been discussed as a possible mechanism leading to neuropsychiatric adverse effects. It has been reported that glutathione levels and catalase activities were decreased and malondialdehyde levels increased, after repeated administration of ciprofloxacin in rats, suggesting an enhanced oxidative stress with weakened antioxidant defence system (Ilgin *et al*, 2015). Major depression is accompanied by decreased antioxidant status and induction of oxidative pathways (Maes *et al*, 2011). It was also reported that oxidative stress and lowered antioxidant levels may play a role in the pathophysiology of suicidal behaviour (Vargas *et al*, 2013).

Finally, microRNAs (miRNAs) may have a potential role in some of the central effects of quinolones. MicroRNAs are small non-coding RNAs that regulate gene function, particularly by repressing the translation of target mRNA; these molecules are also involved in cell survival, synaptogenesis and neural plasticity. Alterations of various miRNAs have been implicated in depressive disorders. A global down-regulation of miRNA expression in prefrontal cortex of depressed suicide subjects has been shown (Smalheiser *et al*, 2012). Interestingly, miR-

132 and miR-182 negatively regulate Brain-Derived Neurotrophic Factor (BDNF) expression, and their serum levels were found to be increased in patients suffering from depression (Li *et al*, 2013). Given at doses within the usual anti-bacterial therapeutic range, enoxacin was shown to be quite effective in raising miRNA levels in the cortical area of the brain in a dose-dependent manner (Smalheiser *et al*, 2014); however, in these animals, the drug decreased the proportion of rats exhibiting learned helplessness behavior following inescapable shock, which is a common rat model of depressive behavior. These results are not unequivocal and their relevance to the mechanism of suicidal behavior linked to quinolones still remains to be elucidated.

Overall, the many and diverse neurobiological actions of quinolones discussed above may strengthen the biological plausibility of the link between their use and the onset of suicidal behavior.

Strengths and limits of the study

Our study has several strengths. First, we used the global adverse drug reaction database VigiBase which collects information on adverse drug reactions from nearly all national pharmacovigilance centers in the world, and since nearly the origin of their pharmacovigilance systems. This large pharmacovigilance database allowed us to estimate the RORs with precision and good applicability to the global population. Adjusting for age and gender, ROR for suicidal behaviors were consistently statically significant for the main used quinolones. Second, ROR estimations were getting more precise over the years and showed stability around the value of 3 in the last 4 to 5 years, without evidence for a notoriety effect. Third, the results remained consistent after analyzing events without dermatological and/or musculoskeletal effects suggesting the absence of modifying effect by event-competition bias. Finally, the significant disproportionality signal for suicidal behavior was consistent across countries, except in only one, Germany. Complementary queries to VigiBase showed that, whereas Germany represented 16% of all adverse reactions reported in Europe, it represented 46% of European reports of suicidal behavior (and 63% for suicidal behaviors associated with antibiotics). Moreover, Germany was also the European country with the most numerous reported adverse effects for moxifloxacin and ofloxacin. We could hypothesize that the absence of signal observed in Germany may be either due to a specific effect of competition between quinolones and other drugs associated with suicide (Pariante *et al*, 2010), or due to different practices for reporting of voluntary drug poisoning, or may represent a chance finding.

The limits of this study include the issue of under-reporting of drug adverse reactions, which is a major drawback inherent to studies using reported adverse events databases (Martin *et al*, 1998; Bégaud *et al*, 2002; van der Heijden *et al*, 2002). Under-reporting maybe all the more important than this study concerned non-recent and commonly used drugs. However, suicidal behaviors or depressive disorders are generally considered serious events (which are usually less under-reported) and there is no apparent reason to suggest that these adverse reactions were differentially reported with quinolones in comparison to other antibiotics drugs. Moreover, the absence of safety information by regulatory agencies, the absence of published evidence for this specific risk and our temporal analysis suggest that no notoriety effect could have affected our results. Second, the large amount of ICSRs selected from VigiBase (nearly one million) limited the extraction of all detailed information. For instance, we could not perform our analyses on serious adverse reactions only, it was not possible to analyze the time to onset of the effect after exposure to quinolone, and we could not adjust our analyses for potential confounders of suicidal behaviors or depressive disorders such as personal and family medical history and other drug exposures. We only adjusted our analyses for age and gender, nonetheless, a previous disproportionality analysis of suicidal behaviors performed in VigiBase only in psychiatric events showed that additional adjustment for reporting year, reporting region, reporter type, use of antidepressant and antipsychotic drugs did not substantially change the ROR estimations (data not shown). Third, the high proportion of missing data in spontaneous reports and the substantial risk of data misclassification could have led to information bias. In particular, the analysis of completed suicides may suffer from misclassification as the selection using the MedDRA terms corresponding to completed suicide did not include the cases of suicidal behaviors not coded as completed suicides but resulting in the death of the patient.

Conclusions

Although uncommon, suicidal behaviors may be observed during treatment with quinolones. Even though disproportionality signals could not be automatically associated with increased incidence of the ADR of interest in the population, the results of this study and the potential mechanisms which are discussed clearly support the hypothesis of an increased risk of suicidal behavior as well as depressive disorders with the use of quinolones drugs when compared to other antibiotics. They highlight the need for psychiatrists and physicians to thoroughly consider recent treatment history in their assessment of patients with suicidal behaviors. As quinolones are commonly used and sometimes overused drugs (Werner *et al*, 2011), further investigations, such as large pharmacoepidemiologic studies, are urgent to confirm and better understand this safety signal.

Contributors

All authors participated in the study design. JLF acquired the data. JS did the statistical analyses and wrote the initial draft. All authors critically revised the manuscript.

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The Uppsala Monitoring Centre has provided the data but the study results and conclusions are those of the authors and not necessarily those of the Uppsala Monitoring Centre, National Centres, or WHO.

Research ethics

Since this study did not include individual patients and only studied the data of an existing and anonymously recorded database, ethical approval was not needed.

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Table 1. Disproportionality analysis of suicidal behaviors associated with quinolones compared to other antibiotic drugs.

Drug	Cases of suicidal behaviors	Non-cases	Crude ROR (95% CI)	Adjusted ROR* (95% CI)
All quinolones	608	171 927	2.84 (2.57-3.14)	2.78 (2.51-3.08)
Ciprofloxacin	269	53 792	4.02 (3.51-4.60)	4.01 (3.50-4.59)
Levofloxacin	166	38 678	3.47 (2.95-4.09)	3.44 (2.91-4.07)
Moxifloxacin	93	22 498	3.32 (2.68-4.11)	2.84 (2.28-3.53)
Ofloxacin	71	16 831	3.39 (2.66-4.31)	3.26 (2.56-4.16)
Other quinolones**	24	41 915	0.46 (0.31-0.69)	0.45 (0.30-0.68)
Other antibiotics	1019	818 543	1 [Reference]	1 [Reference]

*Adjusted for age and gender

** This group includes the following drugs: alatrofloxacin/trovafloxacin, enoxacin, fleroxacin, gatifloxacin, lomefloxacin, norfloxacin, pefloxacin, sparfloxacin, temafloxacin, nalidixic acid, and the generic term « fluoroquinolones »

Figures

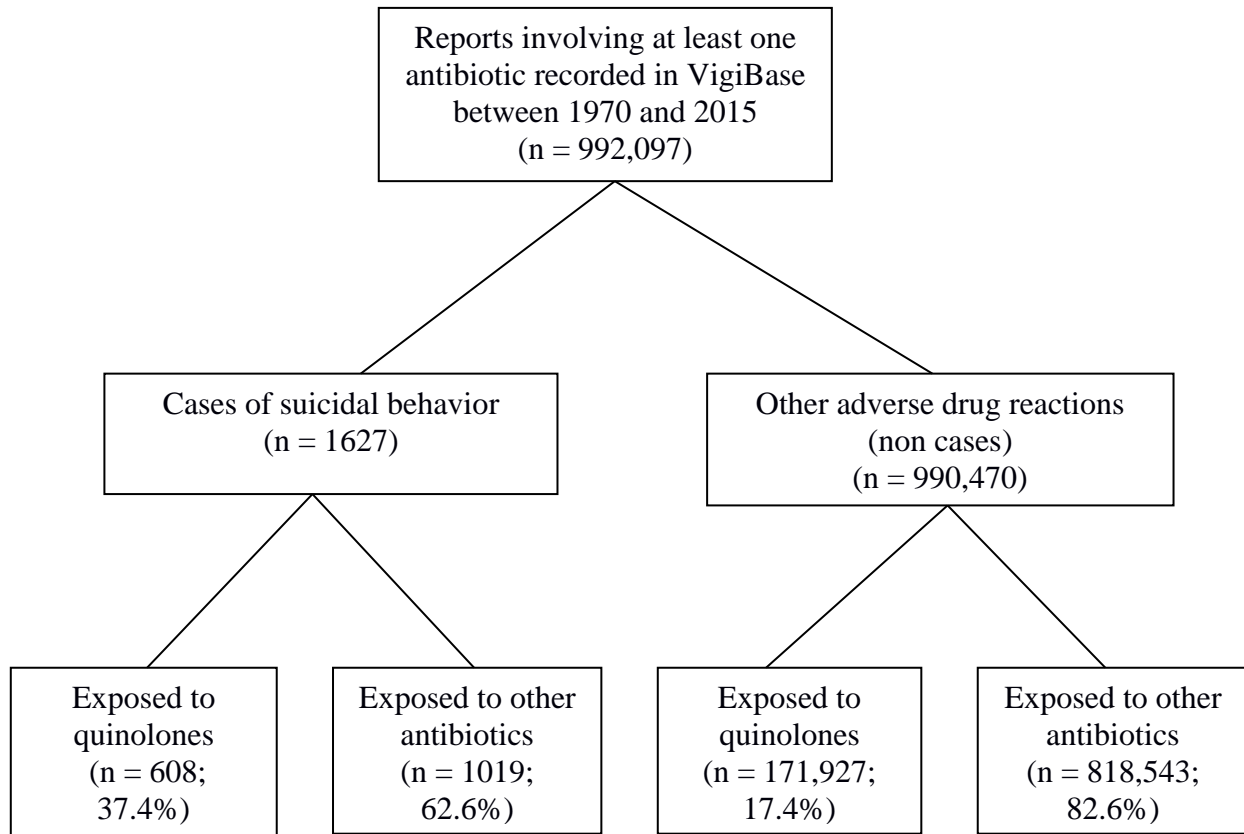


Figure 1. Numbers of reported cases of suicidal behaviors and corresponding non-cases according to exposure to quinolone

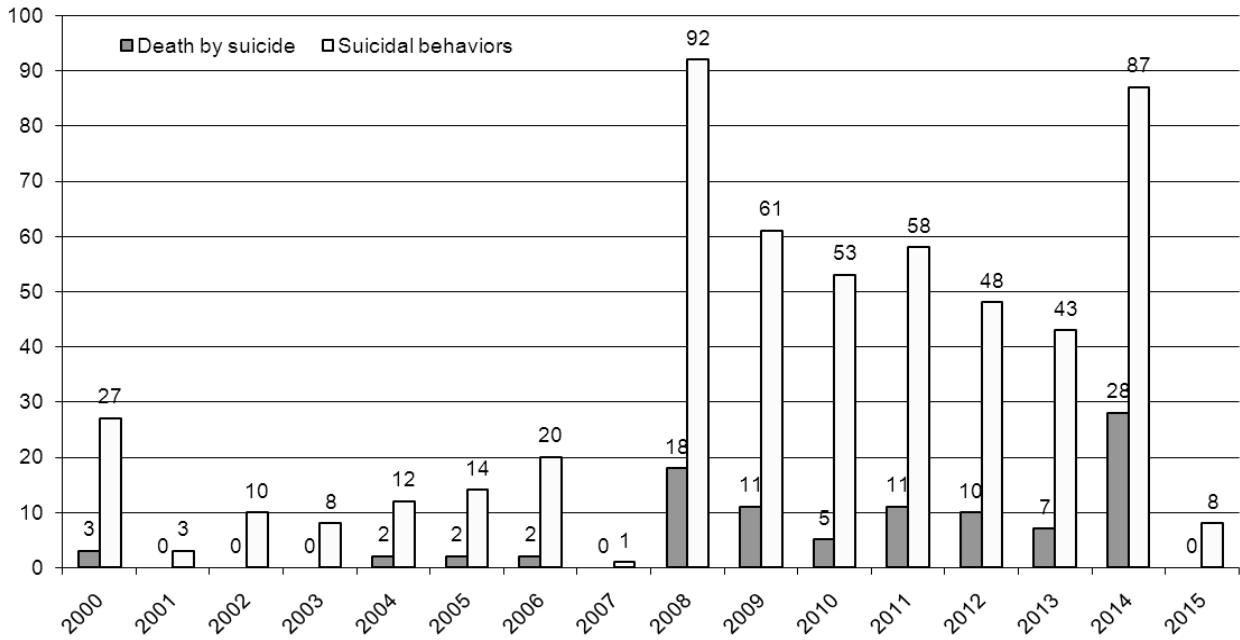


Figure 2. Evolution of reported suicidal behaviors (including completed suicide) and completed suicides associated with quinolones from 2000 to 2015

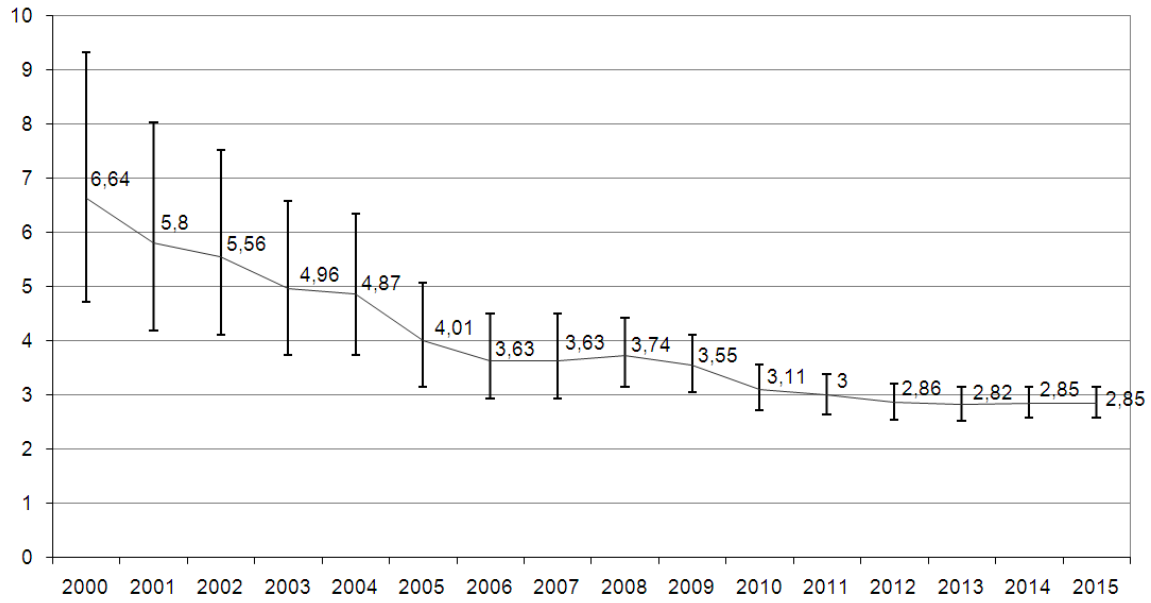


Figure 3. Year by year analysis of cumulative crude Reporting Odds Ratios for suicidal behaviors associated with quinolone use