Impact of the 2008 US FDA warnings for fluoroquinolone use in veterans ≥ 60 years of age with lung cancer

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Abstract

Objectives: To evaluate the impact of the United States Food and Drug Administration's 2008 warnings on the use of fluoroquinolones in patients with lung cancer.

Methods: The impact of the 2008 FDA warnings on fluoroquinolone use in patients with lung cancer ≥ 60 years old in the VA system (2002-2022) was evaluated. Patients ≥ 60 years of age with lung cancer from January 1, 2002 to December 31, 2022, were included. The number of patients with a fluoroquinolone prescription or inpatient order for each calendar year was standardized as a percentage of newly diagnosed patients. Patients receiving a fluoroquinolone were also evaluated for the concomitant use of corticosteroids and QTc-prolonging medications, which were also standardized as a percentage of newly diagnosed patients. Interrupted time series analyses were used to evaluate the impact of the FDA warnings issued in 2008. The pre-period was 2002-2007, and the post-period was 2009-2022.

Results: Statistically significant reductions were observed in fluoroquinolone use for patients with lung cancer aged ≥ 60 years as well as the use of concomitant QTc-prolonging agents. Numerical reductions in the concomitant use of fluoroquinolones and corticosteroids were not statistically significant.

Conclusions: The use of fluoroquinolones and concomitant medications associated with safety risks has decreased over time. Healthcare providers caring for veterans with lung cancers have been responsive to the 2008 FDA warnings.

Keywords: fluoroquinolones, lung neoplasms, veteran, United States Food and Drug Administration, Interrupted Time Series Analysis

Background

Fluoroquinolones are a valuable antimicrobial option for patients with lung cancer and suspected or confirmed infections, as they are the only orally available compounds marketed in the United States (U.S.) that are active against *Pseudomonas aeruginosa*.[1] However, their routine use has been called into question with the addition of black box warnings issued in 2008 for the increased risk of tendinitis and tendon rupture in patients over 60 years of age.[2] In addition, older patients have higher rates of corticosteroid use for concomitant conditions and QTc prolongation, which are associated with increased risks of tendon rupture and torsades de pointes, respectively.[3-5] Fluoroquinolone use has decreased.[6, 7] However, these studies did not specifically describe characteristics of the patients studied.

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Since patients with lung cancer have a different risk-benefit profile in terms of fluoroquinolone use compared to healthier populations, we sought to determine if fluoroquinolone use has changed in patients with lung cancer in response to the U.S. Food and Drug Administration (FDA) warnings. Therefore, we conducted a cohort study evaluating the use of fluoroquinolones in veterans with lung cancer who were ≥ 60 years old. The primary objective was to provide initial data regarding the scope of fluoroquinolone prescribing in this at-risk population, including whether FDA black box warnings had changed prescriber behavior for these patients.

Methods

This cohort study evaluated the prevalence of fluoroquinolone use in adults with lung cancer and was approved by both the Veteran's Administration (VA) North Texas (#1589998-4) and Texas Tech University Health Science Center (#A19-4060) Institutional Review Boards. Patients ≥ 60 years of age with lung cancer from January 1, 2002 to December 31, 2022 were included. The number of patients with a fluoroquinolone (ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin) prescription or inpatient order for each calendar year was standardized as a percentage of newly diagnosed patients. Patients receiving a fluoroquinolone were also evaluated for the concomitant use of corticosteroids (oral: budesonide, cortisone, fludrocortisone, prednisone, prednisolone; injectable: betamethasone, triamcinolone; either oral or

injectable: dexamethasone, hydrocortisone, methylprednisolone) and QTc-prolonging medications, which were also standardized as a percentage of newly diagnosed patients. CredibleMeds was used to determine which medications had a known or possible risk of QTc prolongation.[8-10] Baseline characteristics were compared using a t-test or chi-square test, as appropriate. We utilized an interrupted time series analysis to evaluate the impact of the FDA warnings issued in 2008. The pre-period was 2002-2007, and the post-period was 2009-2022. SAS 9.4 (SAS Institute Inc., Cary, NC, United States) was utilized to conduct the analysis.

Results

Fluoroquinolone use in patients ≥ 60 years of age

The baseline characteristics of the 345,629 patients in the cohort (pre = 127,262; post = 218,367) are included in Table 1. Overall, the population had a mean age of 73 years, with most patients being white (98%) and male (71%). Over half of the cohort had an unknown stage of lung cancer (53%). Each geographic region comprised 15-25% of the cohort.

The frequency of fluoroquinolone is depicted in Figure 1-A. Fluroquinolone use was highest in 2002 at 22% and had dropped to 9% by 2006. Fluroquinolone use continued to decrease in the post-intervention period to about 2% in 2022. The interaction of time and the intervention was statistically significant (p = 0.003), indicating a potential effect of the guideline recommendations.

Fluoroquinolone use in patients ≥ 60 years of age + QTC prolonging medication

The frequency of concomitant QTc prolonging medication in lung cancer patients receiving a fluoroquinolone is depicted in Figure 1-B. Concomitant use was highest in 2002 at 25% and had dropped to 14% by 2006. Fluroquinolone use continued to decrease in the post-intervention period to about 3% in 2022. The interaction of time and the intervention was statistically significant (p = 0.02), indicating a potential effect of the guideline recommendations.

Fluoroquinolone use in patients ≥ 60 years of age + corticosteroid

The frequency of concomitant corticosteroid use in lung cancer patients receiving a fluoroquinolone is depicted in Figure 1-C. Concomitant use was highest in 2002 at 9% and had dropped to 5% by 2006. Fluroquinolone use briefly rose to 6.5% in 2012 and 2013 before decreasing over time to about 1.5% in 2022. The interaction of time and the intervention was not statistically significant (p = 0.19).

Discussion

Our study found that rates of fluoroquinolone use in patients ≥ 60 years of age with lung cancer have decreased over time in association with the issuance of the FDA warnings in 2008. The concomitant use of fluoroquinolones and QTc-prolonging medications also decreased in this sample. The concomitant use of fluoroquinolones and corticosteroids has numerically decreased, but was not statistically associated with the issuance of the 2008 FDA warnings.

Healthcare providers included in our study appear to have been more responsive to the 2008 FDA warnings than some data suggest. A study that evaluated U.S. outpatient prescribing using IQVIA Xponent databases revealed that fluoroquinolone prescribing in U.S. outpatient clinics was relatively flat from 2011 to 2015 before declining in response to the 2016 FDA warning, which strengthen the 2008 warning by recommending doctors avoid these drugs for uncomplicated acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections (UTIs) when alternatives are available.[11] The same study found that patients 65 years and older were 2.37 times more likely to receive a fluoroquinolone than 20 – 64 year-olds. On the other hand, a study evaluating UTIs treated in the hospital or emergency room using the Premier Healthcare database found a significant decrease in fluoroquinolone use regardless of age group.[7] The hospital-specific focus of their study may have made it more likely for a significant difference to be observed given that antimicrobial stewardship programs are more common in the hospital setting. However, overall inpatient fluoroquinolone use in the VA from 2007 to 2015 had a non-statistically significant decrease from 18% to 13% (p = 0.95) of overall antibiotic use.[12] A stewardship program within the VA that began in 2010 produced a 12% overall decrease in antibiotic consumption compared to baseline data, but as mentioned fluroquinolone use did not decrease greater than other antimicrobials.

The sustained decrease in the use of fluoroquinolones in lung cancer patients ≥ 60 years of age shows that healthcare providers caring for veterans with lung cancer have adapted to the guidance of the 2008 FDA warnings. Other providers caring for patients without cancer can take further confidence from this study showing that avoidance of fluoroquinolones has been sustainable over time in a population who is also receiving immunocompromising medications. This type of risk profile would make patients with lung cancer among the most likely to benefit from fluoroquinolone therapy and not having a long-time horizon to worry about the burden from adverse effects that happen infrequently.

The current study has limitations, including its retrospective design. These results may not be applicable to non-VA settings. Additionally, since our cohort consists only of patients with lung cancer, the findings may not be generalizable to patients with other types of cancer. We also did not assess the indication-specific warnings issued in 2016 by the FDA to restrict fluoroquinolone use for acute bacterial sinusitis, acute exacerbations of chronic bronchitis, and uncomplicated UTIs. Furthermore, we did not evaluate how

changes in fluoroquinolone use affected trends in other antibiotic use or fluoroquinolone resistance.

The use of fluoroquinolones and concomitant medications associated with safety risks has decreased over time. Healthcare providers caring for veterans with lung cancers have been responsive to the 2008 FDA warnings.

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Table 1. Characteristics of patients ≥ 60 years old with lung cancer

Characteristic	Total N=345,629 n (%)	Pre (2002-2008) N=127,262 n (%)	Post (2009-2022) N=218,367 n (%)	*P* value
Age, Mean (SD)	73.3 +/- 7.8	73.6 +/- 7.4	73.2 +/- 8.0	<.0001
Sex				
Male	339259 (98.2)	125507 (98.6)	213752 (97.9)	<.0001
Female	6370 (1.8)	1755 (1.4)	4615 (2.1)	
Race				
White	243515 (70.5)	73896 (58.1)	169619 (77.7)	<.0001
Black	36777 (10.6)	10335 (8.1)	26442 (12.1)	
Other	4910 (1.4)	1305 (1.0)	3605 (1.7)	
Unknown	60427 (17.5)	41726 (32.8)	18701 (8.6)	
Stage				
Unknown	182602 (52.8)	70719 (55.6)	111883 (51.2)	<.0001
0	2153 (0.6)	681 (0.5)	1472 (0.7)	
I	38152 (11.0)	12248 (9.6)	25904 (11.9)	
II	23441 (6.8)	7288 (5.7)	16153 (7.4)	
III	36793 (10.7)	14258 (11.2)	22535 (10.3)	
IV	62488 (18.1)	22068 (17.3)	40420 (18.5)	
Region				
Continental	54637 (15.8)	20910 (16.4)	33727 (15.5)	0.934
Midwest	85788 (24.8)	29913 (23.5)	55875 (25.6)	
North Atlantic	85474 (24.7)	32729 (25.7)	52745 (24.2)	
Pacific	49971 (14.5)	17707 (13.9)	32264 (14.8)	
Southeast	69759 (20.2)	26003 (20.4)	43756 (20.0)	

Fluoroquinolone use in VA patients with lung cancer from 2002-2022

The percent of fluoroquinolone use each year is depicted for 1-A all patients with lung cancer ≥ 60 years of age, 1-B patients receiving a fluoroquinolone with concomitant use of a QTc-prolonging agent, and 1-C patients receiving a fluoroquinolone with concomitant use of a steroid. The x-axis depicts the year of the cohort. The y-axis depicts the percentage of patients with lung cancer using a fluoroquinolone (1-A) or the percentage of patients who received a fluoroquinolone who also received concomitant QTc-prolonging agent (1-B) or steroid (1-C).

Figure 1-A. Patient rate ≥ 60 years of age receiving a fluoroquinolone

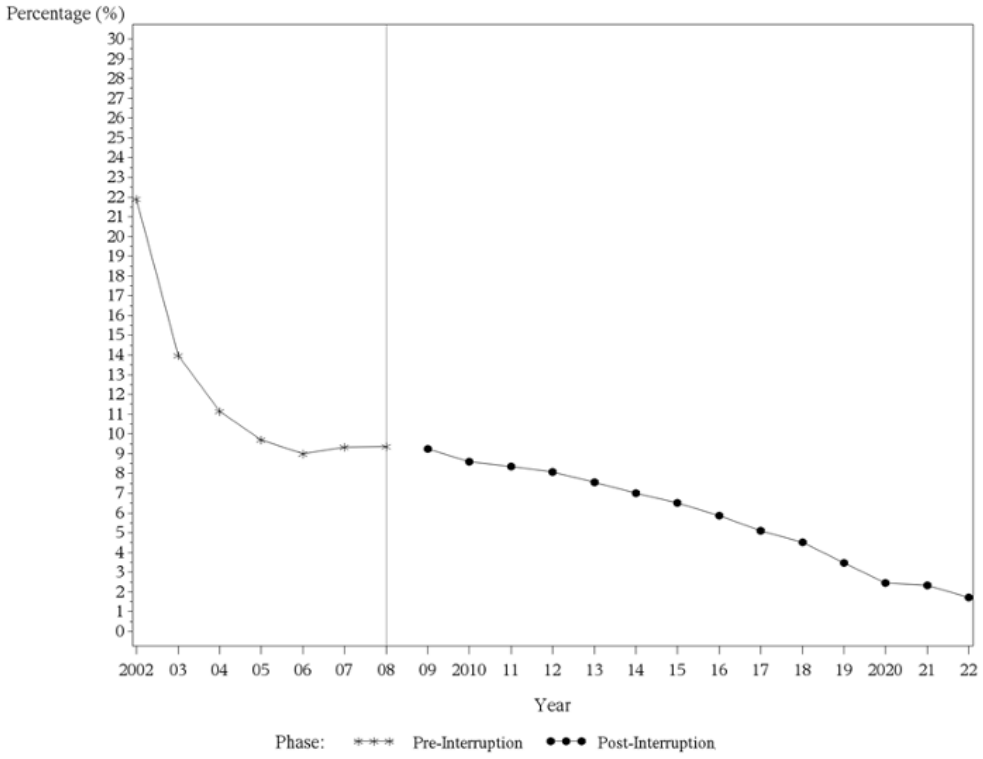

Figure 1-B. Patient rate ≥ 60 years of age receiving a fluoroquinolone + QTc prolonging

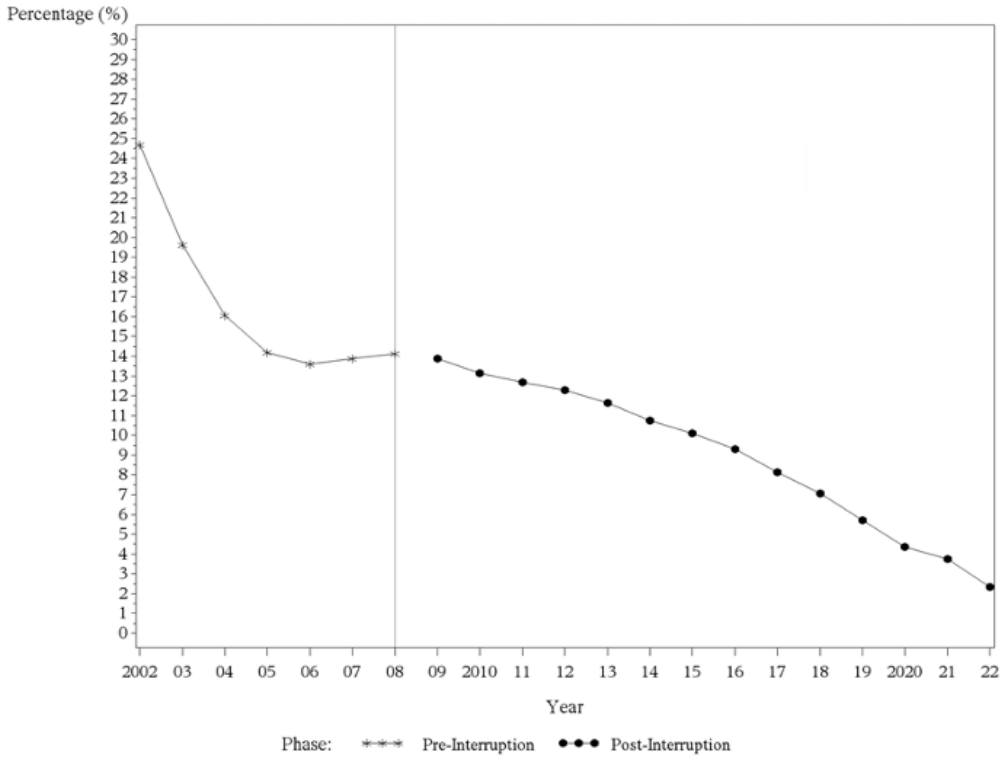

Figure 1-C. Patient rate ≥ 60 years of age receiving a fluoroquinolone + corticosteroid