2014

The Risk of Hepatotoxicity with Fluoroquinolones: A National Case-Control Safety Study

T M. Alshammari

E. Paul Larrat
University of Rhode Island, larrat@uri.edu

See next page for additional authors

Citation/Publisher Attribution
Alshammari, T. M., Larrat, E. P., Morrill, H. J., Caffrey, A. R., Quilliam, B. J., LaPlante, K. L. (2014). Risk of hepatotoxicity associated with fluoroquinolones: a national case-control safety study. *Am J Health Syst Pharm*, *71*(1), 37-43. doi: 10.2146/ajhp130165
Available at: http://dx.doi.org/10.2146/ajhp130165

The Risk of Hepatotoxicity with Fluoroquinolones: A National Case-Control Safety Study

Abstract

Purpose. Fluoroquinolones are generally considered safe and well-tolerated. However, suspected fluoroquinolone induced hepatotoxicity has been increasingly reported, but data are lacking. Thus, the objective of this study was to assess the risk of hepatotoxicity in patients using fluoroquinolones compared to non-users.

Methods. National Veterans Affairs (VA) hospital admissions were assessed between January 1, 2002 and December 31, 2008. Our case-control study matched patients with a primary diagnosis of hepatotoxicity (cases) to those with myocardial infarction (controls) on admission date (matched up to 1:6). Conditional logistic regression was used to compute adjusted odds ratios (OR) and 95% confidence intervals (CI) of hepatotoxicity associated with fluoroquinolone exposure.

Results. Our study included 7,862 cases and 45,512 matched controls. The majority of study patients were white (63.4%), males (97.7%), with a mean age of 61 years. After adjusting for confounders, fluoroquinolone use was significantly associated with a 20% increased risk of hepatotoxicity development (OR 1.20, 95% CI 1.04-1.38) compared to non-users. A statistically significant increased risk of hepatotoxicity was associated with ciprofloxacin use individually (OR 1.29, 95% CI 1.05-1.58), but not with levofloxacin or moxifloxacin use.

Conclusion. The use of fluoroquinolones was associated with an increased risk of hepatotoxicity relative to non-users in our national VA study population.

Purpose

Fluoroquinolones have had a major impact on the treatment of moderate-to-severe infections ever since their introduction over 20 years ago.[1] They are used extensively worldwide, in both community and nosocomial settings, because of their broad-spectrum bactericidal activity, clinical utility, excellent oral bioavailability, and ease of dosing.[2] Further adding to their appeal is their favorable side effect profile. Fluoroquinolones are generally well tolerated, with the most common adverse effects being mild and reversible gastrointestinal and central nervous system reactions.[3]

Despite their popularity, fluoroquinolone antibiotics are not exempt from serious safety concerns, including a potential risk of hepatotoxicity.[4] Mild, transient elevations in aminotransferase are considered a class effect, however severe liver toxicity potentially associated with fluoroquinolone use is relatively rare.[4] With the exception of trovafloxacin, which was removed from the marked due to a strong association between the drug and fatal acute liver failure, the literature supporting fluoroquinolone induced hepatotoxicity is scant, mostly limited to case reports and reviews.[5-14] However, there have been selected reports of death from suspected fluoroquinolone induced hepatic failure, thus this toxicity remains an important concern.[15-17]

The association between fluoroquinolones and hepatotoxicity remains unclear and epidemiologic studies are needed to further assess this risk. Recently, a case-control study of elderly Canadian outpatients demonstrated an increased risk of acute

liver injury associated with moxifloxacin and levofloxacin use.[18] Further real-world safety studies are necessary to confirm these results. As such, we conducted a case-control study to assess the risk of hepatotoxicity associated with fluoroquinolone use (ciprofloxacin, levofloxacin, and moxifloxacin) among adult patients admitted to Veterans Affairs (VA) facilities nationally.

Methods

Study design and data source.

We used a retrospective, matched case-control design using data extracted from national Veterans Affairs (VA) databases capturing clinical care from electronic medical records. The Veterans Health Administration is the largest integrated healthcare system in the United States and includes 152 acute care hospitals and over 800 outpatient clinics, which are located throughout the country.[19] Each year over 5.5 million Veterans are treated at VA facilities.

The VA has used and electronic medical record since 1999, and at each facility inpatient and outpatient care is captured and compiled into national databases. These databases include data on diagnoses, as documented with *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) diagnostic and procedure codes, demographics, provider characteristics, vital status, inpatient and outpatient prescriptions, laboratory tests performed, select laboratory results, and vital

measurements.[20, 21] The design and methods were defined a priori in the study protocol, which was approved by the medical center's and university's Institutional Review Boards.

Case and control identification.

We identified cases from VA hospital admissions between January 1, 2002 and June 30, 2008 with a primary diagnosis for hepatotoxicity, defined as hepatic necrosis (ICD-9-CM 570) and toxic hepatitis (ICD-9-CM 573.3).[22, 23] Patients with a known cause of hepatotoxicity or a history of liver disease were excluded including individuals with ICD-9-CM codes (**Table 1**) for liver cirrhosis, liver cancer, viral hepatitis (including types A, B, C, D, or E), alcoholic hepatotoxicity, acetaminophen induced-hepatotoxicity, human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), liver abscess, and Wilson's disease. Additionally, to avoid possible confounding effects from recent illness, patients who were hospitalized during the 180 days prior to the admission date were excluded. If patients had multiple admissions for hepatotoxicity during the study period, only the first episode was assessed. For all analyses, the date of admission served as the index date.

Controls were defined as hospitalized patients with a primary diagnosis of myocardial infarction (ICD-9-CM 410.00-410.92). As with acute liver injury, myocardial infarctions are acute events with potentially serious outcomes. Patients with these

conditions usually have the similar care and treatment, which differ from treating more chronic conditions. Due to the similarities between the conditions, a control group of patients experiencing myocardial infarction was identified. Further, patients with myocardial infarction were selected as controls in an attempt to have the exposure independent from the outcome. Controls were randomly selected using case-base sampling from the source population. Up to six controls were matched to each case on hospital admission month and year.

Data analyses.

The purpose of our primary analysis was to quantify the association between exposure to fluoroquinolone antibiotics on the development of hepatotoxicity. Exposure to fluoroquinolones was defined as outpatient prescriptions for ciprofloxacin, levofloxacin, or moxifloxacin in the six months prior to the admission date.

Demographic and clinical characteristics of cases and controls were analyzed using chi-square or Fisher's exact tests for categorical data and the Student's *t*-test or Mann-Whitney *U*-test for continuous data. We used conditional logistic regression models to compute odds ratios (ORs) and 95% confidence intervals (CIs) for the association between fluoroquinolone exposure and hepatotoxicity.[24] Potential confounding factors assessed included age, gender, race and ethnicity, history of alcohol-related or alcohol dependency treatment, smoking status, illicit drug use, comorbidities (history of diabetes, renal diseases, hypotension, heart failure, gall

bladder disease), or use of other hepatotoxic drugs (tetracyclines, macrolides, amoxicillin, amoxicillin/clavulanic acid, isoniazid , rifampicin, pyrazinamide, ethambutol, antifungal medications, thiazolidinediones, metformin, proton pump inhibitors [PPIs], and phenytoin) in the 180 days prior to admission. Significant factors from bivariate analyses were entered into a multivariable regression model using a non-computer generated, forward entry method.[24] Subgroup analyses were conducted to study the association between each drug (ciprofloxacin, levofloxacin, and moxifloxacin) and their individual risk of hepatotoxicity. All statistical analyses were conducted with a two-tailed α-value of 0.05 using SAS version 9.1.3 (SAS Institute, Inc, Cary, NC).

Results

We identified 21,404 patients with hepatotoxicity during the study period. Of these patients, 45% (n=9,543) had liver cirrhosis and hepatotoxicity secondary to alcohol, 6% (n=1,302) had viral hepatitis, 5% (n=1,033) had liver cancer, 2% (n=349) had HIV/AIDS or Wilson's disease, 1% (n=231) had a liver abscess or acetaminophen induced hepatotoxicity, and 5% (1,084) had a hospital admission in the preceding 180 days. The remaining 7,862 patients were included in the final analysis as cases and were matched on admission date to 45,512 controls.

The majority of study patients were white (63.4%), males (97.7%), with a mean age of 61 years. Several significant ($p<0.01$) variations in demographics and clinical

characteristics existed between cases and controls, including age, sex, race and ethnicity, comorbidities, substance use, and previous medication exposures (**Table 2**). Diabetes (22.7% vs. 33.0%) was more common in the control group, while renal disease was more frequently reported among cases (13.0% vs. 6.0%). Cases were more likely to abuse alcohol (6.3% vs. 0.6%) and illicit drugs (1.8% vs. 0.4%), and controls were more likely to smoke tobacco (10.2% vs. 12.9%). More controls were recently exposed to thiazolidinediones (1.5% vs. 3.0%), metformin (4.5% vs. 10.0%), statins (9.2% vs. 23.0%), and proton pump inhibitors (10.9% vs. 14.3%). Other comorbidities and clinical characteristics were similar between cases and controls.

The findings from the unadjusted and multivariable analyses are presented in **Table 3**. Fluoroquinolone use was associated with a 20% increased risk of hepatotoxicity development as compared to controls after adjusting for all potential confounders (OR 1.20, 95% CI 1.04-1.38). Our subgroup analyses estimated the risk of hepatotoxicity associated with each individual drug of interest (ciprofloxacin, levofloxacin, and moxifloxacin) (**Table 4**). Patients taking ciprofloxacin were 1.29 times more likely to develop hepatotoxicity than controls (95% CI 1.05-1.59). Levofloxacin and moxifloxacin use were not associated with a significantly increased risk of hepatotoxicity relative to controls. There was no collinearity between the variables in our model.

Presented in **Table 3** are the odds ratios of study variables associated with hepatotoxicity. Women were more likely to develop hepatotoxicity than men (OR 1.51, 95% CI 1.30-1.75). Black, Hispanic, Asian, and Native American patients were all more likely to develop hepatotoxicity than Caucasian patients. Alcohol abusers had nearly an 8 fold increased likelihood of hepatotoxicity development as compared to non-abusers (OR 7.77, 95% CI 6.63- 9.11). Renal disease and gall bladder disease were predictive of the development of hepatotoxicity, while diabetes was protective against hepatotoxicity. Interestingly, previous antifungal use was the only other medication exposure, besides fluoroquinolone use, that was predictive of hepatotoxicity in our study (OR 1.67, 95% CI 1.03-2.69).

Discussion

The literature supporting fluoroquinolone induced hepatotoxicity is limited primarily to case reports and reviews.[6-17] To our knowledge, this is the first pharmacoepidemiologic study to investigate the risk of liver injury associated with fluoroquinolone antibiotic utilization in adult VA patients. Overall, we found that patients exposed to fluoroquinolones (including ciprofloxacin, levofloxacin, and moxifloxacin) had a 20% increased likelihood of developing hepatotoxicity than persons not exposed to these agents. While gatifloxacin was used during our study period, it was not included in our analysis, because it was removed from the market in 2006 due to an increased risk of dysglycemia.[1]

The pathophysiology of fluoroquinolone hepatotoxicity is not well understood. There is a higher incidence of liver damage in molecules (temafloxacin and trovafloxacin) that generate reactive intermediates, and this mechanism may be applicable to other fluoroquinolones.[25-27] It may also be a hypersensitivity reaction, as frequent immunologic features and increased injury on re-exposure have been described.[10] However, it is likely that fluoroquinolone liver toxicity is predominantly idiosyncratic.[10, 28]

A "class-effect" of fluoroquinolone induced liver injury has been supported in a review by the national Drug-Induced Liver Injury Network.[9] In their study, fluoroquinolones were listed as a potential cause of hepatotoxicity in 30 cases. In our subgroup analyses, only ciprofloxacin was associated with a statistically significant increased risk of liver injury as compared to controls. These differences between individual agents may be a result of utilization, rather than hepatotoxicity potential.[10] In the United States, from 1996 to 2001, prescriptions written for ciprofloxacin exceeded that of levofloxacin and moxifloxacin by over 40 million and 60 million, respectively.[29] The reporting rates of acute liver failure to the Food and Drug Administration per 10 million prescriptions are similar for several fluoroquinolones, specifically reporting rates for levofloxacin and moxifloxacin were 2.1 and 6.6 per 10 million prescriptions, respectively.[30] However, these are reporting rates and not incidence rates, and as such these figures do not represent the risk of hepatotoxicity associated with the drugs as

other factors such as patient co-morbidities may impact rates. The overall incidence rate of acute liver injury associated with fluoroquinolones ranges from less than 1 to 6 cases per 100,000 exposures.[18, 31]

In contrast to our findings, a population-based Canadian case-control study[18] found that moxifloxacin (OR 2.20, 95% CI 1.21-3.98) and levofloxacin (OR 1.85, 95% CI 1.01-3.39) use were significantly associated with an increased risk of hospital admission for acute liver injury compared to clarithromycin in patients aged 66 years and older. However, ciprofloxacin use was not significantly associated with this risk. These conflicting results may be related to age and gender differences between the two study populations. The Canadian study limited their analysis to older adults, and thus the patients in our study were younger (mean age of cases 77.4 ± 7.9 years compared to 58 ± 12.7 years). Further, our study was conducted in a largely male population, where 96.3% of our cases were male, compared to 52.8% in the other case-control study. Additionally, differences in control selection between the two studies may account for differences. In case-control studies, selection of an appropriate control can be challenging. Population controls, as compared to hospital controls, may not reflect the underlying health status of cases which affects confounding, potentially biasing the results away from the null.[18] Alternatively, use of patients with myocardial infarctions as the control group may be limited. Ischemic injury to the liver may result from cardiogenic shock, which is a common complication of severe myocardial infarctions.[32]

If this were to affect our study results, we'd expect it to pull the measure of association towards the null, indicating a lesser association with fluoroquinolones.

In our study, younger, female, non-Caucasian subjects were at an increased risk of hepatotoxicity. Age was protective against the development of hepatotoxicity. While advanced age is widely considered a risk factor for drug induced liver toxicity for a number of compounds, younger age is a risk factor for certain agents including aspirin and valproic acid.[4, 33-35] Moreover, younger patients may have a higher risk of purely idiosyncratic drug-induced liver injury.[33] While only 5% of patients in our analysis were female, we were able to demonstrate that females were more likely to develop hepatotoxicity than males, which is similar to previous findings.[4, 33, 36] Race and ethnicity was associated with an increased likelihood of hepatotoxicity development. Genetic variability has been described as the most important risk factor for hepatotoxicity.[37, 38] Genetic polymorphisms influence drug metabolism and may affect a patient's risk of liver toxicity.[39]

Our analysis demonstrated that alcohol abuse was associated with an increased risk of hepatotoxicity, while smoking was protective. Previous literature supports the increased likelihood of hepatotoxity we observed in alcohol abusers.[4, 40, 41] Some research suggests cigarette smoke could contain hepatotoxic compounds and that smoking may be a risk factor for hepatotoxicity.[40, 42] This relationship, however, is not well described and requires further investigation. There is the potential that we may

have underestimated the prevalence of these behaviors due to underreporting or lack of documentation with ICD-9-CM codes.

Antifungal use was the only other medication exposure, besides fluoroquinolone use, which was associated with an increased risk of hepatotoxicity development in our study. This increased risk of hepatotoxicity with antifungals, especially the azole antifungals, is well described in the literature.[43] We observed a protective effect against hepatotoxicity development with statin, metformin, and PPI exposures. Statin use has been associated with mild elevations in hepatic aminotransferases and as such statin package inserts contain hepatotoxicity warnings.[44] Postmarketing experience however, suggests that liver failure due to statin use is quite low, with a reported incidence of just one case per million person-years of use.[45] Metformin and PPI induced hepatotoxicity are not well recognized with suggestive evidence limited to selected case reports.[46, 47] However, all PPI use may not have been captured as patients may purchase these drugs over-the-counter.

Our study had several limitations. Firstly, enzyme levels were not available. Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and bilirubin elevations are the most commonly reported enzyme abnormalities associated with fluoroquinolones use.[28, 48] Previously reported cases of potential fluoroquinolone induced hepatotoxicity were marked by elevations in these enzymes.[9] Additionally, we were not able to assess the time between drug initiation and the development of

hepatotoxic symptoms. In general, this period is highly variable for antibiotic induced hepatotoxicity, ranging from rapidly after administration to months after cessation of therapy.[4] The median time between initiation of the drug and symptom development has been reported as eight days, with a range from 1 to 39 days.[9] However, there has been a case report of delayed cholestatic liver disease occurring after 6 months of treatment with ciprofloxacin.[49] To avoid missing cases of late onset disease, we included patients admitted within 6 months of fluoroquinolone prescription receipt. By using such a broad time period it is possible that cases of hepatotoxicity may be unrelated to the fluoroquinolone exposure, but we attempted to control for this through exclusion of other causes of liver disease and adjusting for potential confounders.

By using administrative data we were unable to validate fluoroquinolone adherence. Moreover, exposures were not adjusted for dose or duration. There is evidence however that the mechanism of toxicity is predominantly idiosyncratic and not dose-dependent.[10, 28] Confounding by indication can also not be excluded, as infection itself can predispose patients to hepatotoxicity. Patients with serious infections or with underlying comorbidities may have been more likely to receive fluoroquinolone antibiotics than other narrow spectrum agents and thus been more likely to develop the outcome of interest. Additionally, while which antimicrobial agents to carry on formulary is not a national decision throughout the VA and is rather a local/regional decision based on local susceptibility data, it is possible that more

expensive brand name fluoroquinolones (moxifloxacin and levofloxacin) were reserved for sicker patients. However, we would have thus expected a larger association with moxifloxacin and levofloxacin than ciprofloxacin. Furthermore, we excluded patients with recent hospital admissions to avoid including patients that may have already been ill.

The accuracy of our findings may be affected by varying coding practices among institutions. There is the potential that demographic and clinical characteristics may have been miscoded, however the disease coding in the VA database has been validated for a number of conditions and is determined to be of high quality.[28, 50-52] While the sensitivity and specificity of hepatotoxicity diagnosis codes are not well-defined, the positive predictive value for acetaminophen-induced hepatotoxicity is high (95%).[53] Still, diagnosis codes may not be the most accurate method to identify rare drug induced liver injury since diagnosing such conditions can be challenging.[54]

Although there were several significant baseline differences between cases and controls, we used multivariable models to adjust for these confounders. As with other observational studies, residual confounding by unobserved covariates cannot be excluded. Finally, the generalizability of our analysis is limited to our VA patient population.

In conclusion, fluoroquinolone use was significantly associated with an increased risk of developing hepatotoxicity compared to non-use in our large, national

pharmacoepidemiologic safety study. At present, while fluoroquinolones are generally believed to be safe and well tolerated, clinicians must be conscious of the potential risks of use including potential fluoroquinolone-induced hepatotoxicity. Further comprehensive pharmacoepidemiologic analyses and multicenter surveillances are warranted to confirm these findings and better understand the pathogenesis of this rare adverse event.

References

1. LaPlante KL, Mersfelder TL, Ward KE et al. Prevalence of and risk factors for dysglycemia in patients receiving gatifloxacin and levofloxacin in an outpatient setting. *Pharmacotherapy*. 2008;28(1):82-9.

2. LaPlante KL, Rybak MJ, Tsuji B et al. Fluoroquinolone resistance in Streptococcus pneumoniae: area under the concentration-time curve/MIC ratio and resistance development with gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin. *Antimicrob Agents Chemother*. 2007;51(4):1315-20.

3. Owens RC, Jr., Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis*. 2005;41 Suppl 2:S144-57.

4. Andrade RJ, Tulkens PM. Hepatic safety of antibiotics used in primary care. *J Antimicrob Chemother*. 2011;66(7):1431-46.

5. Food and Drug Administration. Trovan Information. www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm052276.htm. (accessed 2012 September 9).

6. Coban S, Ceydilek B, Ekiz F et al. Levofloxacin-induced acute fulminant hepatic failure in a patient with chronic hepatitis B infection. *Ann Pharmacother*. 2005;39(10):1737-40.

7. Zimpfer A, Propst A, Mikuz G et al. Ciprofloxacin-induced acute liver injury: case report and review of literature. *Virchows Arch*. 2004;444(1):87-9.

8. Verma R, Dhamija R, Batts DH et al. Moxifloxacin induced fatal hepatotoxicity in a 72-year-old man: a case report. *Cases J*. 2009;2:8063.

9. Orman ES, Conjeevaram HS, Vuppalanchi R et al. Clinical and histopathologic features of fluoroquinolone-induced liver injury. *Clin Gastroenterol Hepatol*. 2011;9(6):517-23 e3.

10. Licata A, Randazzo C, Morreale I et al. Fluoroquinolone-induced liver injury: three new cases and a review of the literature. *Eur J Clin Pharmacol*. 2012;68(5):525-32.

11. Hautekeete ML, Kockx MM, Naegels S et al. Cholestatic hepatitis related to quinolones: a report of two cases. *J Hepatol*. 1995;23(6):759-60.

12. Schwalm JD, Lee CH. Acute hepatitis associated with oral levofloxacin therapy in a hemodialysis patient. *CMAJ*. 2003;168(7):847-8.

13. Contreras MA, Luna R, Mulero J et al. Severe ciprofloxacin-induced acute hepatitis. *Eur J Clin Microbiol Infect Dis*. 2001;20(6):434-5.

14. Soto S, Lopez-Roses L, Avila S et al. Moxifloxacin-induced acute liver injury. *Am J Gastroenterol*. 2002;97(7):1853-4.

15. Grassmick BK, Lehr VT, Sundareson AS. Fulminant hepatic failure possibly related to ciprofloxacin. *Ann Pharmacother*. 1992;26(5):636-9.

16. Fuchs S, Simon Z, Brezis M. Fatal hepatic failure associated with ciprofloxacin. *Lancet*. 1994;343(8899):738-9.

17. Spahr L, Rubbia-Brandt L, Marinescu O et al. Acute fatal hepatitis related to levofloxacin. *J Hepatol*. 2001;35(2):308-9.

18. Paterson JM, Mamdani MM, Manno M et al. Fluoroquinolone therapy and idiosyncratic acute liver injury: a population-based study. *CMAJ*. 2012;184(14):1565-70.

19. United States Department of Veterans Affairs. National Center for Veterans Analysis and Statistics. Quick Facts. www.va.gov/vetdata/ (accessed 2013 Jun 2).

20. Caffrey AR, LaPlante KL. Changing epidemiology of methicillin-resistant Staphylococcus aureus in the Veterans Affairs Healthcare System, 2002-2009. *Infection*. 2012;40(3):291-7.

21. Caffrey AR, Quilliam BJ, LaPlante KL. Comparative effectiveness of linezolid and vancomycin among a national cohort of patients infected with methicillin-resistant Staphylococcus aureus. *Antimicrob Agents Chemother*. 2010;54(10):4394-400.

22. Heaton PC, Fenwick SR, Brewer DE. Association between tetracycline or doxycycline and hepatotoxicity: a population based case-control study. *J Clin Pharm Ther*. 2007;32(5):483-7.

23. Traversa G, Bianchi C, Da Cas R et al. Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. *BMJ*. 2003;327(7405):18-22.

24. Hosmer DW, Lemeshow S. Applied Logistic Regression. 2nd ed. New York, NY: John Wiley & Sons, Inc; 2000.

25. Blum MD, Graham DJ, McCloskey CA. Temafloxacin syndrome: review of 95 cases. *Clin Infect Dis*. 1994;18(6):946-50.

26. Sun Q, Zhu R, Foss FW, Jr. et al. In vitro metabolism of a model cyclopropylamine to reactive intermediate: insights into trovafloxacin-induced hepatotoxicity. *Chem Res Toxicol*. 2008;21(3):711-9.

27. Chen HJ, Bloch KJ, Maclean JA. Acute eosinophilic hepatitis from trovafloxacin. *N Engl J Med*. 2000;342(5):359-60.

28. Kramer JR, Davila JA, Miller ED et al. The validity of viral hepatitis and chronic liver disease diagnoses in Veterans Affairs administrative databases. *Aliment Pharmacol Ther*. 2008;27(3):274-82.

29. Iannini PB. The safety profile of moxifloxacin and other fluoroquinolones in special patient populations. *Curr Med Res Opin*. 2007;23(6):1403-13.

30. Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. *Drug Saf*. 2009;32(5):359-78.

31. De Valle MB, Av Klinteberg V, Alem N et al. Drug-induced liver injury in a Swedish University hospital out-patient hepatology clinic. *Aliment Pharmacol Ther*. 2006;24(8):1187-95.

32. Bernal W, Auzinger G, Dhawan A et al. Acute liver failure. *Lancet*. 2010;376(9736):190-201.

33. Chalasani N, Bjornsson E. Risk factors for idiosyncratic drug-induced liver injury. *Gastroenterology*. 2010;138(7):2246-59.

34. Dreifuss FE, Santilli N, Langer DH et al. Valproic acid hepatic fatalities: a retrospective review. *Neurology*. 1987;37(3):379-85.

35. Heubi JE, Partin JC, Partin JS et al. Reye's syndrome: current concepts. *Hepatology*. 1987;7(1):155-64.

36. Bell LN, Chalasani N. Epidemiology of idiosyncratic drug-induced liver injury. *Semin Liver Dis*. 2009;29(4):337-47.

37. Navarro VJ, Senior JR. Drug-related hepatotoxicity. *N Engl J Med*. 2006;354(7):731-9.

38. Larrey D, Pageaux GP. Genetic predisposition to drug-induced hepatotoxicity. *J Hepatol*. 1997;26 Suppl 2:12-21.

39. Evans WE, McLeod HL. Pharmacogenomics--drug disposition, drug targets, and side effects. *N Engl J Med*. 2003;348(6):538-49.

40. Lozano-Lanagran M, Robles M, Lucena MI et al. Hepatotoxicity in 2011--advancing resolutely. *Rev Esp Enferm Dig*. 2011;103(9):472-9.

41. Andrade RJ, Camargo R, Lucena MI et al. Causality assessment in drug-induced hepatotoxicity. *Expert Opin Drug Saf*. 2004;3(4):329-44.

42. Pessione F, Ramond MJ, Njapoum C et al. Cigarette smoking and hepatic lesions in patients with chronic hepatitis C. *Hepatology*. 2001;34(1):121-5.

43. Brown SJ, Desmond PV. Hepatotoxicity of antimicrobial agents. *Semin Liver Dis*. 2002;22(2):157-67.

44. Tolman KG. The liver and lovastatin. *Am J Cardiol*. 2002;89(12):1374-80.

45. Cohen DE, Anania FA, Chalasani N. An assessment of statin safety by hepatologists. *Am J Cardiol*. 2006;97(8A):77C-81C.

46. Cone CJ, Bachyrycz AM, Murata GH. Hepatotoxicity associated with metformin therapy in treatment of type 2 diabetes mellitus with nonalcoholic fatty liver disease. *Ann Pharmacother*. 2010;44(10):1655-9.

47. Romero-Gomez M, Otero MA, Suarez-Garcia E et al. Acute hepatitis related to omeprazole. *Am J Gastroenterol*. 1999;94(4):1119-20.

48. Fish DN. Fluoroquinolone adverse effects and drug interactions. *Pharmacotherapy*. 2001;21(10 Pt 2):253S-72S.

49. Bataille L, Rahier J, Geubel A. Delayed and prolonged cholestatic hepatitis with ductopenia after long-term ciprofloxacin therapy for Crohn's disease. *J Hepatol*. 2002;37(5):696-9.

50. Petersen LA, Wright S, Normand SL et al. Positive predictive value of the diagnosis of acute myocardial infarction in an administrative database. *J Gen Intern Med*. 1999;14(9):555-8.

51. Schneeweiss S, Robicsek A, Scranton R et al. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. *J Clin Epidemiol*. 2007;60(4):397-409.

52. Abraham NS, Cohen DC, Rivers B et al. Validation of administrative data used for the diagnosis of upper gastrointestinal events following nonsteroidal anti-inflammatory drug prescription. *Aliment Pharmacol Ther*. 2006;24(2):299-306.

53. Myers RP, Leung Y, Shaheen AA et al. Validation of ICD-9-CM/ICD-10 coding algorithms for the identification of patients with acetaminophen overdose and hepatotoxicity using administrative data. *BMC Health Serv Res*. 2007;7:159.

54. Jinjuvadia K, Kwan W, Fontana RJ. Searching for a needle in a haystack: use of ICD-9-CM codes in drug-induced liver injury. *Am J Gastroenterol*. 2007;102(11):2437-43.