NIH Public Access
Author Manuscript
Am J Geriatr Pharmacother. Author manuscript; available in PMC 2013 August 01.

Published in final edited form as:
Am J Geriatr Pharmacother. 2012 August ; 10(4): 264–271. doi:10.1016/j.amjopharm.2012.05.002.

FDA Drug Safety Communications: A Narrative Review and Clinical Considerations for Older Adults

Zachary A. Marcum, PharmD, MS[1], **Joseph P. Vande Griend, PharmD**[2], and **Sunny A. Linnebur, PharmD**[2]

[1]Department of Medicine, Division of Geriatric Medicine, University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania

[2]Department of Clinical Pharmacy, University of Colorado, Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, Colorado

Abstract

Background—The United States Food and Drug Administration (FDA) has new regulatory authorities intended to enhance drug safety monitoring in the post-marketing period. This has resulted in an increase in communication from the FDA in recent years about the safety of certain drugs. It is important to stay abreast of the current literature on drug risks in order to effectively communicate these risks to patients, other health care providers, and the general public.

Objective—To summarize four new FDA drug safety communications by describing the evidence supporting the risks and the clinical implications for older adults.

Methods—The FDA website was reviewed for new drug safety communications from May 2011 to April 2012 that would be relevant to older adults. Approved labeling for each drug or class was obtained from the manufacturer, and PubMed was searched for primary literature supporting the drug safety concern.

Results—FDA drug safety communications for four drugs were chosen based on the potential clinical importance in older adults. A warning for citalopram was made due to potential problems with QT prolongation in patients taking >40 mg/day. The evidence suggests minor changes in QT interval. Given the flat dose-response curve in treating depression with citalopram, the new 20 mg/day maximum dose in older adults is sensible. Another warning was made for proton pump inhibitors (PPIs) and an increased risk of *Clostridium difficile* infection. A dose-response relationship has been shown for this drug risk. With *C. difficile* infections on the rise in older adults, along with other safety risks of PPI therapy, PPIs should only be used in older adults indicated for therapy for the shortest duration possible. In addition, a warning about dabigatran was made. There is strong evidence from a large clinical trial, as well as case reports, of increased

© 2012 Excerpta Medica, Inc. All rights reserved

Corresponding Author: Zachary A. Marcum, PharmD, MS 3471 Fifth Avenue Suite 500 Pittsburgh, PA 15213; Phone: 412-864-2894; Fax: 412-692-2370; zam12@pitt.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

CONFLICT OF INTEREST STATEMENT None of the authors has any relevant conflicts of interest. The sponsor of this manuscript had no role or influence in matters related to the research design, methods, data collection, interpretation of data, or in the writing of the manuscript.

This work was presented in part at the Pharmacotherapy Update Symposium at the annual American Geriatric Society Meeting, Seattle, WA on May 5, 2012.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

bleeding risk in older adults taking dabigatran, especially in those with decreased renal function. This medication should be used with caution in older adults. Finally, several warnings were made regarding statins. Routine periodic monitoring of liver enzymes does not appear to be effective in detecting or preventing serious liver injury from statin use, and thus liver enzymes are no longer recommended to be routinely monitored. Statin-induced cognitive changes are rare and insufficient evidence is currently available to establish causality. Statins appear to moderately increase the risk of developing diabetes (versus placebo), and regular screening for diabetes should be considered, especially for those taking high-dose statins and those with multiple risk factors for diabetes.

Conclusion—FDA drug safety communications incorporate complex methodologies which investigate the risks (and relative benefits) of medication therapy. Clinicians caring for older adults need to be aware of the most current evidence behind these drug risks in order to effectively communicate with and care for their patients.

Keywords

drug safety; elderly; FDA; safety communication

INTRODUCTION

The United States (US) Food and Drug Administration (FDA) is responsible for ensuring the safe use of prescription medications. Part of this responsibility includes regular evaluation of approved medications for new evidence about drug safety. On September 27, 2007, the Food and Drug Administration Amendments Act (FDAAA) was signed into law.[1] This new legislation gave the FDA greater authority, including several provisions intended to enhance drug safety in the post-marketing period.[2] Some examples of these key provisions include Risk Evaluation and Mitigation Strategies (REMS)[3], the Sentinel Initiative[4], and new regulatory authorities to require post-market studies and safety labeling changes.[1] As a consequence, the FDA's drug safety communication has increased in frequency as well as complexity over the past few years.[2] Thus, it is important to stay abreast of the current literature on drug risks in order to effectively communicate these risks to patients, other health care providers, and the general public. The importance of drug safety communication was recently highlighted in an Institute of Medicine report.[5] This review summarizes four new FDA drug safety communications by describing the evidence supporting the risk and the clinical implications for older adults.

METHODS

The FDA website was reviewed for new drug safety communications from May 2011 to April 2012 of relevance to the care of older adults. Drug risks were included in this review according to the following criteria: 1) the drug implicated was currently being prescribed in the general population of older adults; and 2) the risk implicated was expected to have a significant impact on the care of older adults. Approved product labeling for each drug or drug class was obtained from the manufacturer, and PubMed was searched (from the initial FDA drug approval date to April 2012) for primary literature supporting the drug risk.

RESULTS

The four FDA drug safety communications selected for this review were: 1) citalopram use and risk of QT prolongation; 2) proton pump inhibitor (PPI) use and risk of *Clostridium difficile*-associated diarrhea; 3) dabigatran use and risk of serious bleeding; and 4) HMG-CoA reductase (statin) use and labeling changes, including new recommendations for

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

monitoring of liver enzymes as well as adverse event information on cognitive impairment and increased blood sugar/diabetes mellitus.

Citalopram

In August 2011, the FDA warned that citalopram "should no longer be used at doses greater than 40 mg per day (or greater than 20 mg per day for patients 60 and older) because it can cause abnormal changes in the electrical activity of the heart."[6] In addition, the FDA stated that "studies did not show a benefit in the treatment of depression at doses higher than 40 mg per day."[6] The previous maximum daily dose had been 60 mg per day. The age-related maximum dose of 20mg per day is due to the risk of increased serum concentrations in patients ≥60 years and the risk of QT prolongation.[6] The concern is that QT prolongation increases the risk for torsade de pointes, a type of cardiac ventricular tachyarrhythmia associated with sudden death.[6] More recently in March 2012, the FDA provided further clarification regarding citalopram and QT prolongation.[7] For patients at risk for QT prolongation, they softened their initial communication by stating that citalopram in these patients is "not recommended" rather than "contraindicated."[7] They acknowledge that some high-risk patients may benefit from low-dose citalopram.

Citalopram is metabolized primarily by CYP3A4 and CYP2C19 with a small amount by CYP2D6[8], and the clearance of citalopram is prolonged in older adults with resultant increases in area-under-the-curve and half-life.[9,10] As such, the age-related maximum dose of 20mg per day is due to the potential risk of increased serum concentrations in patients ≥60 years and the risk of QT prolongation.[6] The major metabolite is demethylcitalopram (DCT) while the minor metabolite is didemethylcitalopram (DDCT), both of which are not active metabolites.[8] However, DDCT has been implicated with changes in the QT interval in the original animal studies of citalopram.[8] However, this is believed to be a cardiotoxic effect unique to beagle dogs since concentrations of DDCT relative to citalopram are higher in dogs compared to human beings.[11,12]

Yet, recent evidence has indicated that QT interval changes may occur in humans taking citalopram. The FDA based their decision to issue a risk communication on two main sources of data: 1) results of a "thorough QT study" of citalopram that became available; and 2) post-marketing reports of QT prolongation and torsade de pointes in some patients taking the drug. The "thorough QT study" was an unpublished, randomized, multi-center, double-blind, placebo-controlled (using moxifloxacin), crossover study of 199 healthy non-depressed participants.[6] This study assessed the effect of citalopram 20mg and 60mg on QT interval prolongation, extrapolating to determine the effect of citalopram 40mg (Table 1). In their most recent communication, the FDA also included results from a similar study using escitalopram (Table 1).[7] For the citalopram study, there was a statistically significant difference in QT interval prolongation between the 60 mg dose and moxifloxacin control; no significant difference was noted in the escitalopram study.

In looking at the literature more in-depth, the total number of reports sent to the FDA is unknown describing citalopram-induced QT prolongation and/or torsade de pointes.[11,12] One report found that approximately one-third of 600 citalopram overdose cases had QT prolongation or other ECG changes.[11,12] Much less data are available supporting the risk of QT prolongation in patients receiving approved doses of citalopram.[13] In contrast to the unpublished data from the FDA, a systematic review including both prospective and retrospective findings from 40 clinical studies of citalopram (doses ranging from 5–60 mg per day) reported that citalopram caused a small reduction of heart rate (≤ 8 bpm), but no significant effects on QT intervals.[14]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

In summary, based on the current evidence available, the clinical significance of citalopram-induced QT prolongation is not clear despite the presence of statistical significance at the 60 mg dose in one study. What is not known is how many of the participants from the "thorough QT study" met the criteria for a clinically significant increase in QT interval – ie, QT ≥ 500 msec or increase in QT ≥ 60 msec from baseline. Unless patients had a QT interval of ~450–480 msec at baseline, an absolute increase of 18 msec is likely not clinically significant. Future guidance from the FDA will be necessary to better place this warning in clinical context. Moreover, the recommendation for a new maximum dose of 20 mg per day for older adults was based on the potential for increased concentration of citalopram and, in turn, increased risk for QT prolongation in older adults. Unfortunately, there is no clear guidance for clinicians caring for older adults taking > 20 mg per day and receiving therapeutic benefit who have no evidence of QT prolongation. Of note, citalopram (along with other SSRIs) has been shown to have a flat dose response curve across the 20–60 mg range, suggesting 20 mg to be the minimum effective dose for depression in adults.[15] Until further guidance becomes available, monitoring key electrolytes (eg, potassium, magnesium) and conducting more frequent monitoring (eg, EKG) for those patients at increased risk of prolonged QT interval would be prudent. Establishing a baseline QT interval should be considered prior to initiating citalopram therapy. For those patients already receiving citalopram, increased monitoring should be considered if the patient's risk for QT prolongation changes over time. Citalopram should be discontinued in patients who consistently have QT measurements > 500 msec. However, this new warning must be weighed against the possibility of a therapeutic failure if patients receive too low of a dose, or are discontinued from therapy, and the underlying condition (eg, depression, anxiety) becomes symptomatic.

Proton Pump Inhibitors

In February 2012, the FDA warned that "use of PPIs may be associated with an increased risk of *C. difficile*-associated diarrhea (CDAD)."[16] They stated that "a diagnosis of CDAD should be considered for patients taking PPIs who develop diarrhea that does not improve."[16] It is important to note that the FDA is also reviewing this same risk in users of H_2 receptor blockers.[16]

PPIs reduce gastric acidity, which serves as a defense mechanism against ingested pathogens. Loss of this defense mechanism is associated with colonization of the normally sterile upper gastrointestinal tract. Moreover, PPIs have been shown to affect leukocyte function, which could lead to increased risk of enteric infections such as *C. difficile*.[17] PPIs are some of the most commonly used medications by older adults. The use of PPIs has drastically increased in recent years partly due to their availability over-the-counter.

The FDA based their decision to issue a safety communication on two main sources of data: 1) results of 28 observational studies; and 2) post-marketing reports of *C. difficile* infection in some patients taking these drugs.[16] According to the FDA, 23 of the 28 studies showed an increased risk of *C. difficile* infection or disease with PPI use versus no use, with the risk ranging from 1.4 to 2.75 times higher among patients with PPI exposure versus without exposure.[16] While a detailed summary of all available data on this drug risk is beyond the scope of this review, two well-designed observational studies will be described.

First, Dial et al conducted a population-based case-control study using data from the United Kingdom's General Practice Research Database.[17] Cases were defined as those with community-acquired (ie, not hospitalized in the previous year) *C. difficile*, and 75% of the sample was > 65 years.[17] The primary outcome was the incidence of *C. difficile* (defined as either a positive toxin and/or a based on clinical diagnosis), and the primary independent variable was gastric acid suppressive agent (PPI or H_2 receptor blocker) use in the previous

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

90 days. The adjusted rate ratio of CDAD with current use of PPIs was 2.9 (95% CI, 2.4–3.4), and with H_2 receptor blockers the rate ratio was 2.0 (95% CI, 1.6–2.7).[17] In another study, Howell et al conducted a retrospective cohort study at a large, urban, tertiary care hospital to assess for a dose-response relationship.[18] Adults (mean age ~57 years) with a hospital stay of at least 3 days were included. The primary outcome was a nosocomial *C. difficile* infection (defined as a newly + *C. difficile* toxin assay ≥ 3 days after admission), and there were four levels of exposure during the hospitalization: 1) no acid suppression; 2) H_2 receptor blocker daily use; 3) PPI once daily use; and 4) PPI more than once daily use. In the main adjusted analysis, they found that as the level of potential acid suppression increased, the adjusted odds of developing *C. difficile* infection also increased, from an odds ratio of 1 (reference) to 1.53 for H_2 receptor blocker only, 1.74 for daily PPI, and 2.36 for PPI more frequently than daily.[18] It is important to realize that the current data available supporting this risk are observational and, thus, have inherent limitations.

In summary, *C. difficile* is a major cause of health care-associated infections, and the incidence of *C. difficile* infection is increasing.[19] Older adults, in particular, are at an increased risk for this infection due to chronic co-morbidities, use of broad-spectrum antibiotics, and presence in long-term care settings, among others.[19] Current evidence indicates an increased risk of *C. difficile* infection among those using PPIs, along with a potential dose-response relationship. Further, there appears to be a similar (albeit slightly less) risk with H_2 receptor blocker use compared to PPI use. Although older adults may require long-term acid suppression, the potential increased risk of *C. difficile* infection is a serious concern. Providers may need to be more vigilant at re-evaluating the need for long-term PPI therapy in older adults, especially those with other risk factors for *C. difficile* infection.

Dabigatran

Dabigatran was approved in 2010 to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation and is the only oral direct thrombin inhibitor available in the US.[20] In December 2011, the FDA warned that they were “evaluating post-marketing reports of serious bleeding events in patients taking dabigatran.”[20] They stated that they “continue to believe that dabigatran provides an important health benefit when used as directed and recommend that healthcare professionals who prescribe dabigatran follow the recommendations on the drug label.”[20] Of note, the new American College of Chest Physicians (ACCP) guidelines recommend “for patients with atrial fibrillation, including those with paroxysmal atrial fibrillation, for recommendations in favor of oral anticoagulation, we suggest dabigatran 150 mg twice daily rather than adjusted-dose vitamin K antagonist therapy” as a Grade 2B recommendation (defined as a weak recommendation based on moderate-quality evidence).[21]

This new warning was based on two main sources of data: 1) a pre-planned analysis of the phase III clinical trial that led to dabigatran approval (RE-LY); and 2) post-marketing case reports of serious bleeding in patients taking dabigatran. First, the RE-LY trial was a 2-year non-inferiority randomized controlled trial that enrolled over 18,000 patients with atrial fibrillation. Subjects were randomized to dabigatran 110 mg or 150 mg twice daily or dose-adjusted warfarin (resulting in INRs in therapeutic range 64% of the time).[22] The primary safety outcome was `major bleeding' defined as a reduction in hemoglobin level of ≥ 2.0 g/dL, transfusion of ≥ 2 units of blood, or symptomatic bleeding into a critical area of an organ (intracranial or extracranial).

In a sub-study of the RE-LY trial, Eikelboom et al reported the safety results of both doses of dabigatran compared with warfarin for different types of major bleeding and in key subgroups, including older adults.[23] Table 2 presents select data from RE-LY on the relative

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

risks of major, intracranial, extracranial, gastrointestinal, and nongastrointestinal extracranial bleeding in patients aged 75 and 75 years. Overall, dabigatran 150mg twice daily (versus warfarin) was associated with a lower risk of major bleeding in those aged <75 years and a trend toward higher risk of major bleeding in those aged ≥75 years. Dabigatran 150 mg twice daily significantly reduced the risk of intracranial bleeding compared to warfarin across all ages. However, the risk of extracranial bleeding was significantly increased in older adults taking the 150 mg twice daily dose, including a significantly increased risk for gastrointestinal bleeding (Table 2).[23]

Moreover, case reports of fatal bleeding in older, frail adults have recently been reported in the literature, highlighting the potential risk of using dabigatran in older, frail adults (who had worse renal function and weighed less than those included in the RE-LY trial).[24,25] Furthermore, the most recent Institute for Safe Medication Practices (ISMP) quarterly newsletter (which monitors all serious, disabling, and data adverse drug events reported to the FDA) reported that during the first quarter of 2011 dabigatran was linked to 932 serious adverse events, including 120 deaths, 25 cases of permanent disability, and 543 cases requiring hospitalization.[26] Of the 932 events, 505 cases involved hemorrhage; among the hemorrhage cases, the median age was 80 with a quarter of these patients being ≥84 years.[26]

In summary, there is strong evidence from a large clinical trial as well as case reports of increased bleeding risk in older adults taking dabigatran. Because the most recent ACCP guidelines suggest dabigatran rather than warfarin for patients with a CHADS2 score ≥1[21], older adults may be prescribed dabigatran with increased frequency. This is concerning for older adults, especially those who may have reduced kidney function and/or be frail as highlighted by recent case reports and ISMP safety data. A dose reduction to 75 mg twice daily is recommended for patients with a CrCl 15–30 mL/min.[27] This dosage recommendation is different from that appearing in the new American Geriatrics Society Beers Criteria, which recommend using caution with a CrCl <30 mL/min due to a lack of evidence for efficacy and safety in these patients.[28] This reduced dose was not studied in clinical trials and is based on a pharmacokinetic analysis. It is unknown if some of the increased bleeding events in older adults come from changes in the renal clearance of dabigatran or from other age-related changes. Until further evidence is available, the patient's individualized risk for bleeding and embolic events must be considered. In addition, incorporating patient preferences and values is essential when determining which type of anticoagulation is most appropriate. For patients well-controlled on warfarin, continuation of warfarin is appropriate and still recommended by the ACCP guidelines. For those patients desiring treatment with dabigatran, unfortunately there is no proven antidote that has been established. Thus, it remains crucial to closely monitor for the signs and symptoms of bleeding as well as to ensure appropriate renal dosing in older adults receiving dabigatran.

Statins

In March 2012, the FDA provided new recommendations the use of statin medications, including monitoring of hepatic enzymes, adverse event information on cognitive impairment and increased blood glucose, as well as drug interaction label changes to lovastatin (see new package insert for updated drug interaction changes).[29]

Liver Function Testing—In 2006, the National Lipid Association Statin Safety Task Force published as assessment of statin safety as well as conclusions and recommendations.[30,31] These recommendations were based on a review and independent research of New Drug Application information, FDA Adverse Event Reporting System data, cohort and clinical trial results, and analysis of administrative claims database information, as well as the assessment of expert panels.[30,31] The task force reported that significant liver

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

damage appears to be extremely uncommon with statins, especially when considering the magnitude of their use worldwide. Specifically, an estimated rate of 1 case per 1 million statin prescriptions was reported, and only 1 of the 51,741 patients who underwent liver transplantation between 1990 and 2002 was taking a marketed statin. Based on this information, the FDA changed the statin labels to now recommend that hepatic function testing be performed before starting statin therapy and as clinically indicated thereafter rather than routine monitoring as previously recommended.[29]

Cognitive Impairment—Statins have been previously studied as a potential treatment option to prevent cognitive impairment and/or dementia; yet, there is some limited evidence that statin use can lead to cognitive impairment. A report of 60 cases from November 1997–February 2002 was published suggesting that statins (ie, simvastatin, atorvastatin, and pravastatin included) may be associated with cognitive impairment.[32] Approximately 50% of cases noted cognitive impairment within 2 months of therapy, and memory loss recurred in four patients rechallenged. Importantly, the majority of cases resolved upon discontinuation of the statin. The main symptom appeared to be short-term memory loss.[32]According to a recent narrative review of the literature on this topic, the majority of the evidence suggests that statins do not have a clinically meaningful effect on cognition.[33] The authors of the review recommend that if a statin must be discontinued, one suggestion is to consider the degree of lipophilicity of the statin. For example, atorvastatin, simvastatin, lovastatin, fluvastatin, and pitavastatin are relatively lipophilic and are able to cross the blood brain barrier, whereas pravastatin and rosuvastatin are less lipophilic and are less likely to penetrate into the brain.[33] Based on the current data available, the FDA stated that their analysis “did not reveal an association between the adverse event and the specific statin, the age of the individual, the statin dose, or concomitant medication use.”[29] Further, the FDA concluded that their review “did not suggest that cognitive changes associated with statin use are common or lead to clinically significant decline.”[29] On the whole, statins clearly offer substantial cardiovascular benefits, and a small number of case reports of memory loss should not discourage appropriate statin administration.

Diabetes Mellitus—Statin-induced diabetes has only recently begun to be assessed in clinical trials. Initially, a post-hoc analysis in 2001 of data from WOSCOPS suggested pravastatin therapy may reduce the chance of developing diabetes mellitus (DM).[34] Subsequent statin studies rarely included new-onset DM as an outcome, but among those that did, a nonsignificant increased risk of DM was noted.[34] In 2008, the JUPITER trial (rosuvastatin versus placebo for primary prevention of cardiovascular events) included new-onset DM as secondary outcome, and rosuvastatin was found to have a 25% increased risk in physician-diagnosed new-onset DM versus placebo.[35] This led to a meta-analysis being conducted on 13 statin trials with 91,140 patients, which showed that statins were associated with a 9% increased risk for incident DM.[36] In addition, meta-regression showed that the risk of developing DM with statins was highest in trials with older subjects. The authors pointed out that treating 255 people with statins for 4 years would result in one additional case of DM.[36] A second meta-analysis confirmed these findings.[37] Finally, a follow-up meta-analysis assessed the potential for a dose-dependent effect and reported that intensive-dose statin therapy is associated with 12% higher risk for new-onset DM versus moderate dosing.[38] Importantly, the authors of this study were also able to compare the risk to benefit of preventing incident cardiovascular disease and confirmed the benefit of intensive-dose therapy in high cardiovascular risk populations studies.[38] Based on this information, the FDA now warns of this potential risk but does not give specific recommendations for monitoring or adjusting statin therapy. Thus, clinicians should consider regular DM screening, especially for those taking high-dose statins and those with multiple risk factors for diabetes.[39]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

In summary, routine periodic monitoring of liver enzymes does not appear to be effective in detecting or preventing serious liver injury from statin use, and thus is not necessary. Statin-induced cognitive changes are rare and insufficient evidence is currently available to establish causality; thus, this risk should not change current practice. If statin-induced cognitive impairment is suspected, discontinuation of the statin and monitoring for resolution is appropriate. Replacement with a hydrophilic statin is also an option. Finally, statins appear to moderately increase the risk of developing DM (versus placebo), and regular DM screening should be considered, especially for those taking high-dose statins. However, in many patients, the cardiovascular benefits of statins may outweigh the potential risk of diabetes.

CONCLUSION

FDA drug safety communications are a complex effort to continuously provide updates on the risks (and relative benefits) of prescription drugs. Clinicians caring for older adults need to be aware of the most current evidence behind these drug risks in order to effectively communicate with and care for their patients.

Acknowledgments

This work was supported in part by a National Institute on Aging grant (P30AG024827). Dr. Marcum conducted the literature search and drafted the initial manuscript. Drs. Vande Griend and Linnebur added substantial contributions to the literature search and provided key contributions to the development of this manuscript.

REFERENCES

1). [Accessed January 26, 2012] Food and Drug Administration Amendments Act (FDAAA) of 2007. Available at: http://www.fda.gov/RegulatoryInformation/Legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/foodanddrugadministrationamendmentsactof2007/default.htm

2). Dusetzina SB, Higashi AS, Dorsey ER, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. Med Care. 2012 e-pub ahead of print.

3). Qato DM, Alexander GC. Improve the Food and Drug Administration's mandate to ensure postmarketing drug safety. JAMA. 306:1595–96. [PubMed: 21990303]

4). Robb MA, Racoosin JA, Sherman RE, et al. The US Food and Drug Administration's sentinel initiative: expanding the horizons of medical product safety. Pharmacoepidem Drug Saf. 2012; 21:9–11.

5). IOM (Institute of Medicine). Ethical and Scientific Issues in Studying the Safety of Approved Drugs. The National Academies Press; Washington, DC: 2012.

6). FDA Drug Safety Communication. [Accessed January 11, 2012] Aug 24. 2011 Available at: http://www.fda.gov/Drugs/DrugSafety/ucm269086.htm.

7). FDA Drug Safety Communication. [Accessed March 28, 2012] Mar 28. 2012 Available at: http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm.

8). Celexa® [package insert]. Forest Pharmaceuticals, Inc.; St. Louis, MO: 2011.

9). Gutierrez M, Abramowitz W. Steady-state pharmacokinetics of citalopram in young and elderly subjects. Pharmacother. 2000; 20:1441–1447.

10). de Mendonça Lima CA, Baumann P, Brawand-Amey M, et al. Effect of age and gender on citalopram and desmethylcitalopram steady-state concentrations in adults and elderly depressed patients. Prog Neuropsychopharmacol Biol Psychiatry. 2005; 29:952–956. [PubMed: 16006029]

11). Howland RH. A critical evaluation of the cardiac toxicity of citalopram: part 1. J Psychosoc Nurs. 2011; 49(11):13–16.

12). Howland RH. A critical evaluation of the cardiac toxicity of citalopram: part 2. J Psychosoc Nurs. 2011; 49(12):13–16.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

13). de Gregorio C, Morabito G, Cerrito M, Dattilo G, Oreto G. Citalopram-induced long QT syndrome and torsade de pointes: role for concomitant therapy and disease. Int J Cardiol. 2011; 148:226–228. [PubMed: 19540606]

14). Rasmussen SL, Overo KF, Tanghoj P. Cardiac safety of citalopram: prospective trials and retrospective analyses. J Clin Psychopharmacol. 1999; 19:407–415. [PubMed: 10505582]

15). Montgomery SA. Selecting the optimum therapeutic dose of serotonin reuptake inhibitors: studies with citalopram. Int Clin Psychopharmacol. 1995; 10(Suppl 1):23–27. [PubMed: 7622808]

16). FDA Drug Safety Communication. [Accessed February 9, 2012] Feb 8. 20112 Available at: http://www.fda.gov/Drugs/DrugSafety/ucm290510.htm.

17). Dial S, Delaney JAC, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. JAMA. 2005; 294:2989–2995. [PubMed: 16414946]

18). Howell MD, Novack V, Grgurich P, et al. Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection. Arch Intern Med. 2010; 170:784–790. [PubMed: 20458086]

19). Kee VR. *Clostridium difficile* infection in older adults: a review and update on its management. Am J Geriatr Pharmacother. 2012; 10:2–12. [PubMed: 22330099]

20). FDA Drug Safety Communication. [Accessed January 11, 2012] Dec 7. 2011 Available at: http://www.fda.gov/Drugs/DrugSafety/ucm282724.htm.

21). You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST. 2012; 141:e531S–e575S. [PubMed: 22315271]

22). Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361:1139–51. [PubMed: 19717844]

23). Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial. Circulation. 2011; 123:2363–2372. [PubMed: 21576658]

24). Legrand M, Matteo J, Aribaud A, et al. The use of dabigatran in elderly patients. Arch Intern Med. 2011; 171:1285–1288. [PubMed: 21788545]

25). Cano EL, Miyares MA. Clinical challenges in a patient with dabigatran-induced hemorrhage. Am J Geriatr Pharmacother. 2012; 10:160–163. [PubMed: 22386824]

26). ISMP Medication Safety Alert! Institute for Safe Medication Practices. 2012; 17:1–4.

27). Pradaxa® [package insert]. Boehringer Ingelheim Pharmaceuticals, Inc.; Ridgefield, CT: 2011.

28). The American Geriatrics Society 2012 Beers Criteria Update Expert Panel. AGS Updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012; 60:616–631. [PubMed: 22376048]

29). FDA Drug Safety Communication. [Accessed April 9, 2012] Feb 28. 2012 Available at: http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm.

30). Cohen DE, Anania FA, Chalasani N. An assessment of statin safety by hepatologists. Am J Cardiol. 2006; 97:77C–81C. [PubMed: 16377288]

31). McKenney JM, Davidson MH, Jacobson TA, Guyton JR. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol. 2006; 97:89C–94C.

32). Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy. 2003; 23:871–880. [PubMed: 12885101]

33). Rojas-Fernandez CH, Cameron JCF. Is statin-associated cognitive impairment clinically relevant? A narrative review and clinical recommendations. Ann Pharmacother. 2012; 46 online.

34). Preiss D, Sattar N. Statins and the risk of new-onset diabetes: a review of recent evidence. Curr Opin Lipidol. 2011; 22:460–466. [PubMed: 21897230]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

35). Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008; 359:2195–2207. [PubMed: 18997196]

36). Sattar N, Preiss D, Murray HM, et al. Statins and risk of incidence diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010; 375:735–742. [PubMed: 20167359]

37). Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diab Care. 2009; 32:1924–1929.

38). Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011; 305:2556–2564. [PubMed: 21693744]

39). Goldfine AB. Statins: is it really time to reassess benefits and risks? JAMA. 2012; 366:1752–1755.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

Increase in the Corrected QT Interval for Citalopram and Escitalopram*

Citalopram Dose	↑ in QTc Interval, msec (90% CI)	Escitalopram Dose	↑ in QTc Interval, msec (90% CI)
20 mg/day	8.5 (6.2, 10.8)	10 mg/day	4.5 (2.5, 6.4)
40 mg/day†	12.6 (10.9, 14.3)	20 mg/day†	6.6 (5.3, 7.9)
60 mg/day	18.5‡ (16.0, 21.0)	30 mg/day	10.7 (8.7, 12.7)
Moxifloxacin 400 mg	13.4 (10.9, 15.9)	Moxifloxacin 400 mg	9.0 (7.3, 10.8)

Abbreviations: CI, confidence interval; FDA, Food & Drug Administration

*Adapted from references 6 and 7

†Data extrapolated

‡P<0.05 compared to control

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 2

Risk of Major, Intracranial and Extracranial Bleeding With Dabigatran 150mg BID and Warfarin in Patients Aged <75 and ≥75 Years*

Safety Outcome	Dabigatran 150mg BID vs. Warfarin (n= 12,098); RR (95% CI)
Major Bleeding	
Age <75 years	0.70 (0.57–0.86)
Age ≥75 years	1.18 (0.98–1.42)
Intracranial Bleeding	
Age <75 years	0.43 (0.25–0.74)
Age ≥75 years	0.42 (0.25–0.70)
Extracranial Bleeding	
Age <75 years	0.78 (0.63–0.98)
Age ≥75 years	1.39 (1.13–1.70)
Gastrointestinal Bleeding	
Age <75 years	1.19 (0.87–1.63)
Age ≥75 years	1.79 (1.35–2.37)

Abbreviations: BID, twice daily; CI, confidence interval; RR, relative risk

*Adapted from reference 23