Electrocardiogram Monitoring After the Food and Drug Administration Warnings for Citalopram: Unheeded Alerts?

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OBJECTIVES: To evaluate national trends in electrocardiogram (EKG) monitoring in Veterans Affairs (VA) beneficiaries prescribed high-dose citalopram before and after the 2011–12 Food and Drug Administration (FDA) safety warnings.

DESIGN: Interrupted time-series analyses.

SETTING: National VA healthcare system data linked to Medicare data for veterans dually eligible for VA and Medicare services.

PARTICIPANTS: Adult VA outpatients prescribed citalopram or sertraline from February 2010 to September 2013 (N=1,068,816).

MEASUREMENTS: EKG monitoring for VA outpatients prescribed high-dose citalopram (>40 mg/d aged ≤60, >20 mg/d aged >60) or sertraline.

RESULTS: For individuals prescribed high-dose citalopram, EKG monitoring increased from 9.0% before the start of the first FDA warning to a peak of 12.6% for individuals aged 18 to 60 and from 14.0% to 19.4% for individuals aged 61 to 100. However, following the second FDA warning in 2012, EKG monitoring declined, returning to prewarning levels in both age groups. EKG monitoring did not increase in individuals with a history of previous cardiac risk factors prescribed high-dose citalopram in either age group.

CONCLUSIONS: EKG frequency did not significantly change in individuals with cardiac risk factors at greatest potential risk for QT prolongation. Lack of responsiveness to the FDA warnings may be due to many factors, including lack of clarity about which individuals should undergo EKG monitoring, provider substitution of alternative antidepressants for citalopram, conflicting evidence regarding risk for adverse cardiac events with high-dose citalopram use, and lack of provider knowledge regarding the warnings. **J Am Geriatr Soc 66:1562–1566, 2018.**

Key words: citalopram; FDA warning; EKG

In 2011, the U.S. Food and Drug Administration (FDA) issued a drug safety warning for citalopram, cautioning providers against using doses greater than 40 mg/d, given concerns about potential QT prolongation.[1] The FDA issued a revised warning in 2012 recommending against using doses greater than 20 mg/d in individuals older than 60 years of age.[2] The FDA based these recommendations on postmarketing reports of QT interval prolongation and concerns about development of torsades de pointes (TdP) associated with high-dose citalopram use.[3,4] The FDA concluded that there was no evidence of additional effectiveness of citalopram doses greater than 40 mg/d to justify the potential cardiac risk.[2,5] For individuals for whom citalopram use was not recommended but was considered essential, the FDA recommended more frequent electrolyte and electrocardiogram (EKG) monitoring.[2]

After the 2011 and 2012 FDA warnings, prescribers needed to determine how to monitor and weigh the potential cardiac risk associated with high-dose citalopram use against the risk of psychiatric destabilization in individuals previously taking therapeutic doses of citalopram.[6] In addition, the 2011 and 2012 recommendations left room for interpretation regarding which individuals should undergo EKG monitoring, therefore, prescribers needed to decide whether to order EKGs for: 1) individuals who might be at greater risk of adverse cardiac outcomes, 2) those newly prescribed citalopram, 3) individuals taking any dose of citalopram, or 4) patients prescribed higher-than-recommended doses. Although a randomized clinical trial evaluating use of citalopram for treatment of agitation in individuals with dementia (Citalopram for

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Agitation in Alzheimer Disease Study) found that high-dose citalopram prolonged the QT interval,[7] several studies have questioned whether the actual risk of adverse cardiac events related to citalopram justifies the FDA warning.[4,8] Previous research has found no greater cardiac mortality or ventricular arrhythmia in individuals taking high doses of citalopram,[8] with some studies finding that QT prolongation with citalopram and other antidepressants has been modest.[9,10] In our previous work, we found low rates of EKG monitoring (8.5%) in a university-based outpatient primary care clinic in individuals (N=199) maintained on higher-than-recommended doses of citalopram after the FDA warnings.[11] This low rate of EKG monitoring occurred despite a pharmacist intervention to alert prescribing providers to the warning.[11] To our knowledge, no other studies have evaluated EKG monitoring since the citalopram drug safety warnings.

In the current study, we compared national trends in EKG monitoring in individuals prescribed high-dose citalopram after the 2011 and 2012 FDA drug safety warnings in the Veteran's Affairs (VA) healthcare system and those taking an alternative antidepressant, sertraline, that was not subject to the drug safety warnings. We sought to determine whether trends in EKG monitoring observed in our previous work in a single healthcare system[11] reflected national prescribing practices, given that the VA engaged in several systematic efforts to ensure broad communication of the citalopram drug safety warnings and to monitor subsequent prescribing.[12,13] We anticipated that the drug safety warnings would be associated with an increase in EKG monitoring in individuals taking high-dose citalopram and in those with a history of cardiovascular risk factors that would place them at greater potential risk of negative cardiac outcomes associated with citalopram use.

METHODS

Study Cohort

We assembled a rolling cohort of VA beneficiaries aged 18 to 100 from February 2010 to September 2013. The cohort included individuals with citalopram prescriptions from at least 12 months before the first FDA warning (8/2011) and 12 months after the last warning (3/2012). The VA Ann Arbor Healthcare System Institutional Review Board approved this study.

Measures of Citalopram and Sertraline Use

We compiled quarterly citalopram and sertraline prescribing rates for VA users. To be included in the denominator for each 3-month period, we required individuals to have at least one VA outpatient appointment during the observation period. We linked Pharmacy Benefits Management (PBM) data to demographic data from the Corporate Data Warehouse to construct the study cohort. We defined the index dispense date as the date of the first citalopram prescription fill. Citalopram use data included new (no prescription claims in the 180 days before the index dispense date) and continuing citalopram prescriptions during each 3-month period. We calculated daily dose of citalopram by calculating the quantity of tablets dispensed divided by the number of days supplied multiplied by the dose per tablet. For each quarter, we calculated the proportion of individuals with high-dose and any-dose citalopram prescription fills. Because the definition of high-dose citalopram varied by age (high dose $\geq$40 mg/d aged 18–60, $>$20 mg/d age $>$60), we created a younger (18–60) and an older (61–100) cohort.

Rates of EKG Monitoring

To determine the rate of EKG monitoring, we evaluated the number of EKGs performed (Current Procedural Terminology codes 93000, 93005, 93010, 93040, 93041, 93042) during the quarter observed divided by the number of individuals with fills for citalopram or sertraline during that quarter. We determined quarterly proportion of EKG monitoring in individuals newly prescribed citalopram, maintained on any dose of citalopram, and prescribed above recommended doses of citalopram compared to an alternative antidepressant not subject to the FDA warning (sertraline). For veterans dually eligible for VA and Medicare services, we linked VA administrative data to Centers for Medicare and Medicaid Services (CMS) data to account for veterans who received medical care and EKG monitoring outside of the VA healthcare system.

In individuals with previous cardiac risk factors, we assessed whether an EKG had been performed within the past 3 months in individuals maintained on high-dose citalopram, as compared to any dose of citalopram and sertraline. Prior cardiac risk factors included a diagnosis of myocardial infarction, congestive heart failure, arrhythmia, or angina within the past 12 months of the antidepressant medication fill. (See Supplemental Table S1 for *International Classification of Diseases, Ninth Revision*, codes.)

Statistical Analysis

To understand changes in EKG monitoring in individuals maintained on citalopram and sertraline after the FDA warnings, we calculated the proportion of individuals prescribed citalopram who had an EKG performed within the past 3 months and compared findings across three study periods: 1) February 2010 to August 2011 (before the first warning: prewarning period), 2) September 2011 to March 2012 (between the first and second warnings: warning 1 period), and 3) April 2012 to September 2013 (after the second warning: warning 2 period). To examine the effect of the FDA warnings on the proportion of individuals who underwent EKG monitoring, we fit separate interrupted time series regression models[14,15] with first-order autoregressive errors for high-dose citalopram users based on age ($>$40 mg/d and $>$20 mg/d in adults aged $\geq$60 after the second warning), citalopram users of any dose, and users of any dose of sertraline (a comparison antidepressant not subject to the FDA warning). We used a 3-phase interrupted time series regression model to describe the changes in level (intercept) and trend over time (slope) of change in EKG monitoring during the study period across age groups (18–60, 61–100). Based on

the model, we tested for the statistical significance of the difference in the levels in the quarter before warning 1 to the end of the study period in September 2013, controlling for prewarning level and trend. Lastly, we conducted analyses to assess EKG monitoring in those individuals diagnosed with previous cardiac risk factors (myocardial infarction, congestive heart failure, arrhythmia, angina) within the past year. We conducted all statistical analyses using SAS version 9.4 (SAS Institute, Inc., Cary NC).

RESULTS

Sample Characteristics

The study sample included 1,068,816 VA outpatient service users aged 18 to 100 prescribed an antidepressant of interest (citalopram or sertraline), of whom 602,388 were dually eligible for Medicare. Of VA service users, 58.3% (N=623,498) were prescribed citalopram. The majority of individuals prescribed citalopram were male (N=561,485, 90.1%), white (N=452,844, 72.6%), and non-Hispanic (N=554,522, 88.9%); 48.8% (N=304,332) were aged 61 to 100. At the start of the study, 21.8% of younger (18–60) and 17.3% of older (61–100) citalopram users were prescribed higher than recommended doses.

EKG Monitoring In Individuals Taking High-Dose Citalopram

At the start of the study period in February 2010, 8.4% of younger and 9.7% of older high-dose citalopram users underwent EKG monitoring. In younger individuals prescribed high-dose citalopram, EKG monitoring increased from 9.2% just before the first FDA warning in August 2011 to a peak of 12.6%. In users aged 61 to 100, EKG monitoring increased from 10.6% just before the first FDA warning to a peak of 14.9%. By the time of the second FDA warning in March 2012, the rates of EKG monitoring began to decline in both age groups. At the end of the study period in September 2013, 10.6% of the younger cohort and 9.8% of the older cohort underwent EKG monitoring, which was unchanged from prewarning monitoring levels (p=.18 and p=.89). Overall rates of EKG monitoring did not change significantly after the drug safety warnings in individuals prescribed any dose of citalopram or sertraline.

For veterans dually eligible for Medicare services, we linked VA and CMS data to account for additional EKG monitoring that may have occurred outside of the VA healthcare system. When accounting for CMS data, trends and patterns in EKG use remained unchanged from rates in the VA healthcare system alone. Figure 1 demonstrates the quarterly proportion of citalopram users who underwent EKG monitoring throughout the study period. Supplemental Table S2 depicts changes in level and trend of EKG monitoring during the 3 study periods for individuals prescribed high-dose citalopram, any dose of citalopram, or sertraline. The inclusion of CMS data resulted in an additional observed increase in EKG monitoring in individuals prescribed high-dose citalopram of 1.4 percentage points (total increase from 12.6% in VA healthcare system alone to 14.0% in combined VA and CMS data) in individuals aged 18 to 60 and 4.5 percentage points (increase from 14.9% to 19.4%) in individuals aged 61 to 100. Similarly, trends in EKG monitoring for any dose of citalopram and sertraline remained unchanged when accounting for CMS data.

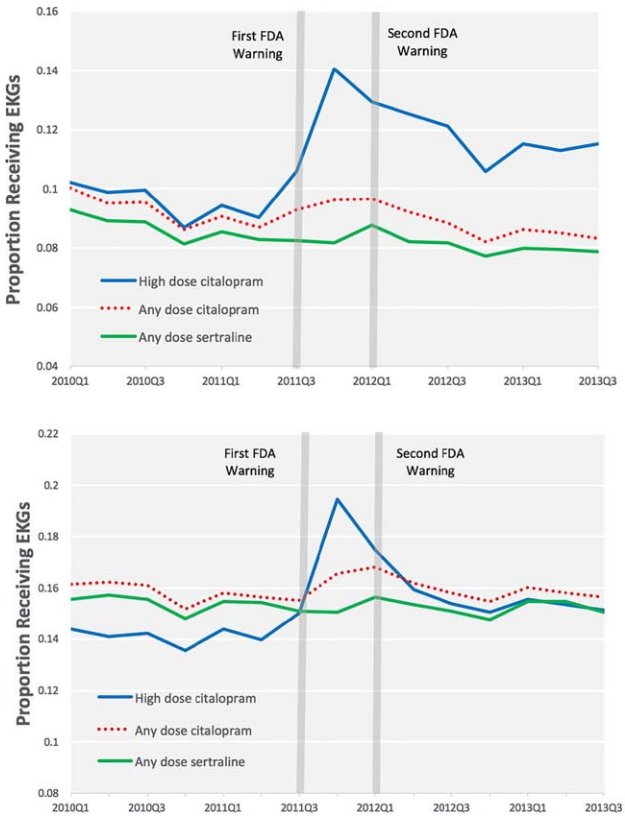

Figure 1. Quarterly proportion of citalopram or sertraline users aged (A) 18 to 60 and (b) 61 to 100 undergoing cardiac monitoring in Veterans Affairs or Centers for Medicare and Medicaid Services.

EKG Monitoring In Individuals Newly Prescribed Citalopram

In individuals newly prescribed high-dose citalopram (no previous prescription within the past 180 days), EKG monitoring increased after the first FDA warning in the younger (increase in EKG monitoring from 7.8% in August 2011 to a peak of 14.0%) and older (12.4% to 15.5%) cohorts (Supplemental Figure S1). For the younger cohort, after an initial decline after the second FDA warning, rates of EKG monitoring for individuals newly prescribed high-dose citalopram increased to 14.5% at the end of the study period, significantly greater than prewarning monitoring levels (p<.001). For older adults, after the initial increase, rates in EKG monitoring decreased and returned to near baseline levels (12.3% at end of study period) and were unchanged from prewarning monitoring levels (p=.09). Rates of EKG monitoring did not change significantly in younger or older individuals newly prescribed any dose of citalopram or sertraline.

EKG Monitoring In Individuals with Previous Cardiac Risk Factors

We examined EKG monitoring of individuals prescribed citalopram and sertraline who had a history of cardiac risk factors within the past year. Supplemental Figure S2 demonstrates the quarterly proportion of citalopram users with previous cardiac risk factors who underwent EKG monitoring within the previous 3 months. EKG monitoring rates did not change for individuals with previous cardiac risk factors prescribed high-dose citalopram, any dose of citalopram, or sertraline.

DISCUSSION

After the first FDA warning, there was an initial increase in rates of EKG monitoring for younger and older veterans prescribed higher than recommended doses of citalopram receiving services through the VA and Medicare. However, after this initial period of responsiveness, rates of EKG monitoring had largely declined back to baseline levels by the end of the study period in 2013. We found no change in rates of EKG monitoring of younger or older individuals with previous cardiac risk factors taking high-dose citalopram, for whom the FDA recommended more frequent monitoring. Older adults with prior cardiac comorbidities that can predispose to poor cardiac outcomes would be at highest risk of QT prolongation highlighted by the FDA warnings. In these highest risk individuals—who could potentially benefit most from cardiac monitoring—EKG monitoring did not change. However, these results are similar to previous results found outside the VA healthcare system demonstrating low overall rates of EKG monitoring (8.5%) after the FDA warnings and no increase in monitoring of individuals with previous cardiac risk factors at greatest risk of negative cardiac outcomes.[11]

Studies evaluating the implementation of and responsiveness to FDA drug safety warnings have found that the warnings often have variable, and at times limited, effects in influencing changes in prescribing practices,[16,17] with one study that reviewed 200 black box warnings finding that more than 40% of individuals still received a potentially inappropriate medication after the black box warning.[18] Many factors may influence the decision of an individual provider to order an EKG after the citalopram safety warnings, including lack of clarity about who should undergo EKG monitoring, lack of health system incentives to adhere to the FDA warnings, provider knowledge regarding the drug safety warnings, and how concerned a provider is regarding a particular FDA warning. Since the FDA warnings were issued, several large-scale observational studies have had conflicting results regarding the effect of citalopram on QT prolongation and risk of subsequent ventricular arrhythmia, calling into question whether the risk of adverse cardiac events associated with citalopram use justifies the FDA warning.[8,9,19] Perhaps another explanation for the low rate of EKG monitoring we observed in this study may have occurred if a majority of individuals were switched to a new antidepressant or reduced their citalopram dose. We previously found that rates of high-dose, any dose, and new citalopram prescribing declined significantly and remained low after the 2011 and 2012 drug safety warnings throughout the VA healthcare system—with citalopram falling from being the most widely prescribed antidepressant in the VA before the FDA warnings to third, below sertraline and bupropion, 1 year after the second warning.[11,20] We also observed concomitant increases in other antidepressant use during the same time periods, suggesting that providers substituted alternative antidepressants for citalopram.[20] Given the uncertainty about whether, when, and how often individuals should undergo EKG monitoring, providers may have found it less burdensome to make medication adjustments than perform periodic cardiac monitoring and the associated medical documentation as recommended in the FDA warning.

There are several limitations to our current study. The VA is the largest integrated healthcare system in the United States,[21] so our sample included a high proportion of men, and our results may not be fully generalizable to other clinical populations and healthcare systems. However, this study is the first analysis of EKG monitoring since the citalopram warnings in a national sample. For individuals with previous cardiac risk factors, we assessed EKG monitoring only within the previous 3 months. It is possible that providers may have elected not to repeat such monitoring if an individual had had an EKG within a longer time frame than we evaluated in this study (e.g., within the past 6 or 12 months). Lastly, although we were able to determine whether an individual had had an EKG performed, we were not able to see the results to understand the proportion of individuals with a prolonged QT interval taking high-dose citalopram or determine why an EKG was ordered (e.g., directly related to the drug safety warning or for monitoring of another condition).

This study demonstrated that, for individuals prescribed high-dose citalopram, after an initial increase in EKG monitoring after the first FDA warning, cardiac monitoring returned largely to prewarning levels. This limited responsiveness to the FDA warnings occurred despite several VA PBM activities[22] designed to reduce inappropriate prescribing, including 3 national PBM bulletins related to citalopram use[13]—suggesting that rates of EKG monitoring may be even lower in health systems without such interventions. Lack of responsiveness to the citalopram drug safety warnings may in part be due lack of clarity about which individuals should undergo EKG monitoring, provider substitution of other antidepressants for citalopram, and lack of provider knowledge regarding the warnings. Although there are frequent FDA drug safety warnings, and concerns about QT prolongation are among the most common reasons for drug safety warnings,[23] there have been limited rigorous studies evaluating the effect of these warnings[16,17]—with previous studies having methodologic limitations such as lack of a control group. Given the paucity of previous studies evaluating health system responses to drug safety warnings, as well as the large number of individuals maintained on citalopram in the VA and elsewhere at the time of the drug safety warning, this study adds to the limited studies evaluating drug safety warnings, demonstrating a small, temporary response to the warnings.[18] Lastly, in light of this low responsiveness to drug safety warnings, it is crucial for

health systems to evaluate and understand what the barriers and facilitators to adhering to the drug safety warnings are to help health systems best determine how to communicate and monitor drug safety warnings. In another part of the current study, we will be identifying and interviewing VA facilities with low and high responsiveness to the citalopram drug safety warnings to evaluate the ways in which the drug safety warnings were directly communicated across VA facilities and determine whether specific strategies were more effective in improving adherence to the citalopram warnings. This work highlights the need for future studies aimed at understanding how health systems can best help providers and individuals make decisions regarding medication use, considering both the risk of the medication as well as the potential risks and benefits of adhering to the drug safety warnings.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site

Table S1. List of International Classification of Diseases (ICD9), Ninth Revision codes for cardiac risk factors.

Table S2. Rates and trends of quarterly EKG monitoring among citalopram or sertraline users ages 18–60 and 61–100 among Veterans receiving healthcare services through the VA and Medicare.

Figure S1. Quarterly proportion of individuals receiving EKG monitoring newly prescribed citalopram among A. individuals aged 18–60 and B. individuals 61–100 as compared to sertraline.

Figure S2. Quarterly proportion of individuals receiving EKG monitoring among individuals with previous cardiac risk factors among A. individuals aged 18–60 and B. individuals 61–100 as compared to sertraline.

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