Psychiatric outcomes associated with citalopram dose reduction in veterans after food and drug administration warning

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INTRODUCTION

On August 24, 2011, the Food and Drug Administration (FDA) released a Drug Safety Communication which warned that higher citalopram doses, particularly 60 milligrams, were affiliated with QTc-interval prolongation.[1] This abnormality can lead to a potentially fatal arrhythmia, Torsades de Pointes (TdP). Although there is considerable intra-individual and inter-individual variability, normal QTc length can be roughly defined as 400 milliseconds. The upper limit of normal is 450 milliseconds for men and 460 milliseconds for women. Intervals longer than 500 milliseconds are considered to be a major risk factor for the development of TdP.[2] Additionally, a commonly cited threshold for clinically significant QTc-intervals is ≥500 milliseconds or an increase of ≥60 milliseconds.[3]

The cardiac concern for citalopram originated from isolated patient cases of cardiotoxicity after overdose. Toxicology studies elucidate that didesmethylcitalopram (DDCT), the product of citalopram's minor cytochrome (CYP) 2D6 metabolism, mediates the overdose cardiotoxicity.[4] DDCT binds to cardiac potassium channels and prevents efflux from cardiomyocytes thus prolonging repolarization (i.e., the QTc-interval).[5] When given at therapeutic doses (≤ 60 milligrams daily), DDCT composes less than 10% of citalopram's metabolites.[3-4,6] Citalopram and demethylcitalopram (DCT), the product of citalopram's major CYP3A4 and CYP2C19 metabolism, exhibit only a weak inhibitory effect on potassium channels.[4-5] However, surrogate markers such as inhibition of cardiac ion channels are not reliable predictors of clinical manifestations. Therefore, clinical studies are needed to clarify our understanding.[7]

The first case in the United States of citalopram-induced TdP not associated with overdose was described in 2008.[8] Numerous additional post-market surveillance reports and overviews of cases have since followed detailing the impact on QTc observed with acute intoxication or maintenance therapy with citalopram.[4-5,9] In response, the FDA performed an analysis of citalopram 20 milligram and 60 milligram daily doses which demonstrated 90% confidence intervals of 6.2 to 10.8 and 16 to 21 millisecond increases in the QTc-interval respectively. Interpolation of 20 and 60 milligram data estimates that 40 milligram daily doses would increase the QTc-interval by 10.9 to 14.3 milliseconds.[1,10-11]

Furthermore, the FDA concluded that citalopram fails to show any additional antidepressant benefit of daily doses greater than 40 milligrams.[1,11]Articles used in supporting this conclusion were powered to detect differences between citalopram daily doses and placebo, not to make distinctions between efficacies of daily doses.[12-13] However, the aforementioned evidence is representative of the best available data.

Caution of the cardiac consequences of citalopram has yielded published and unpublished inquiry. Some experts even challenge the statistical and clinical significance of the body of knowledge surrounding the issue.[3,6] Nevertheless, based on the FDA guidance, Veterans Affairs providers were directed by a National Pharmacy Benefits Manager Bulletin to reduce patients to daily doses ≤40 milligrams unless higher doses were deemed clinically necessary.[14-15]

Therefore, the purpose of this study was to measure the impact of citalopram dose reduction recommendations on James H. Quillen Veterans Affairs Medical Center

(JHQVAMC) patients and the facility. As a result, we evaluated psychiatric outcomes by assessing the use of mental health resources in patients taking citalopram before and after the FDA warning.

METHODS

This retrospective follow-up study was approved by the Institutional Review Board and the Research and Development Committee at the JHQVAMC. Data were obtained from the Veterans Integrated Service Network (VISN) 9 data warehouse and individual patient chart review of the computerized patient record system. Data were assimilated into an electronic database for analysis.

Patients taking citalopram 40 or 60 milligrams were included if they had an International Classification of Diseases-9 (ICD-9) code containing a depression component. Additionally, patients must have been adherent to citalopram, which was defined as having citalopram at least 150 days out of each six month study period. This was verified through reviewing refill histories to calculate the number of days covered. Patients were excluded if they had ICD-9 codes containing any anxiety component or a documented allergy, intolerance, or adverse event to citalopram. Figure 1 depicts the delineation of the patient population to the sample population.

Two distinct citalopram groups were identified: an intervention group (IG) composed of patients who were converted from 60 milligrams to 40 milligrams daily after the FDA warning and a control group (CG) of those who were on 40 milligrams daily before and after the warning. Baseline patient demographic data were extracted including race, gender, and age. Outcomes data were derived from six months prior to the FDA warning (February 1, 2011 to July 31, 2011) and six months after the FDA warning (October 1, 2011 to March 31, 2012) for both groups.

The primary outcome was the change in composite mental health resource utilization before the FDA warning to after the FDA warning. Mental health resources were specified as psychiatric emergency room visits, psychiatric hospitalizations, mental health clinic visits, and concomitant psychiatric medications used for depression. Each resource was also evaluated individually as secondary outcomes. Other secondary outcomes included the number of patients that reverted to 60 milligrams daily, change in QTc-interval from before the FDA warning to after FDA warning, and documented death by suicide. Outcomes data are presented as the average change per patient. Demographic and outcomes data were compared using the student t-test and chi-squared methods. A post-hoc power analysis was performed based on the results of the study.

RESULTS

Of the total study population (n=246), 76 patients and 170 patients comprised the intervention group (IG) and control group (CG), respectively. Table 1 details specific baseline demographics for both groups. The majority of patients were Caucasian males with an average age of

Figure 1. Patient population to sample population delineation after inclusion and exclusion criteria.

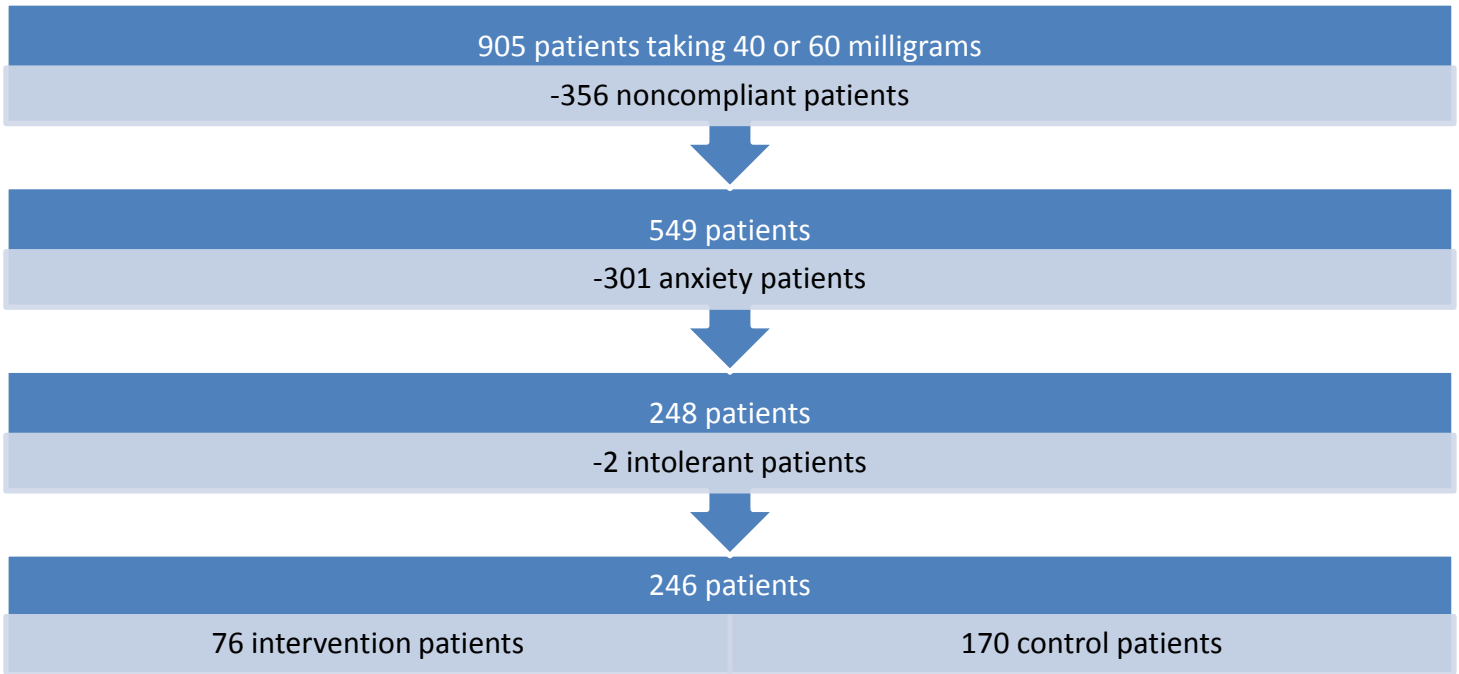

Table 1. Baseline demographics

Demographic	Intervention (n=76)	Control (n=170)	*p-value
RACE, n (%)			0.3
White/Caucasian	63 (82.9%)	145 (85.3%)	
Black/African American	2 (2.6%)	10 (5.8%)	
Pacific Islander/Hawaiian	1 (1.3%)	3 (1.8%)	
Missing/Unknown	10 (13.2%)	12 (7.1%)	
SEX, n (%)			0.56
Male	74 (97.4%)	163 (95.9%)	
AGE, average years [range]	63.53 [29-85]	61.34 [38-90]	0.14

*T-test used for age; otherwise chi-squared used for analysis.

approximately 62. Appreciable differences between groups for examined characteristics were unremarkable.

Individual patients rarely utilized resources notably more than their peers on average. The average change in resource utilization per patient was compared between groups (Table 2). Overall, the change in mental health resources utilization differed only slightly before and after the FDA warning and results were not statistically significant. In the IG, the average change in mental health resources per patient was +0.07 as compared to no change in the CG (p=0.407).

Psychiatric ER visits decreased in both groups after FDA warning by 0.12 visits on average per patient in the IG and by 0.1 visits in the CG (p=0.433). Likewise, psychiatric hospitalizations decreased by 0.03 admissions on average per patient in the IG whereas a minute increase of 0.01 admissions was noted in the CG (p=0.258).

The greatest distinction between groups could be appreciated in mental health clinic visits and concomitant psychiatric medications used for depression. For both outcomes, an IG patient required on average an additional 0.20 uses of these resources as compared to 0.05 in the CG (p=0.056). Stated differently, 1 in 5 versus 1 in 20 patients required these additional resources.

Incidentally, 3 patients reverted to 60 milligram daily doses in the IG and 1 patient committed suicide in the CG. Eight patients in the intervention group and 17 patients in the CG had EKGs available for comparison. Before and after inter- and intra-individual QTc-intervals varied greatly. No trends could be identified in patients or between groups.

When considering statistical significance, no computed value was statistically significant. However, values attained for mental health clinic visits and concomitant psychiatric medications used for depression may have trended toward significance. Of note, the post-hoc power analysis confirmed that the study achieved 80.5% power.

Table 2. Primary composite outcome with secondary outcome subcomponents.

Outcome	Intervention (n=76) Average Δ/Patient	Control (n = 170) Average Δ/Patient	p-value
RESOURCE UTILIZATION	+ 0.07	0	0.407
Psychiatric ER visits	- 0.12	- 0.10	0.433
Psychiatric admissions	- 0.03	+ 0.01	0.258
Mental health clinic visits	+ 0.20	+ 0.05	0.056
Concomitant psych medications	+ 0.20	+ 0.05	0.056

DISCUSSION

Resource utilization is commonly used in mental health studies based on its established value in accurately and comprehensively measuring disease state management needs.[16-21] Our hypothesis presumed that patients who previously required citalopram 60 milligrams daily but were reduced to 40 milligrams would be negatively impacted compared to those who were stable on 40 milligrams before and after the FDA warning. Specifically, we anticipated patients who received this dose reduction would require an increased use of mental health resources.

Before the present study, citalopram 40 milligrams and 60 milligrams have not been directly compared against each other but rather always independently against placebo. In patients suffering from anxiety, citalopram 60 milligrams has shown some additional benefit over 40 milligrams. However, this has not been observed in depressed patients.[12-13] In fact, this was a clear point of communication within the FDA warning which concluded that citalopram fails to show any additional antidepressant benefit of daily doses greater than 40 milligrams.[1,11] Therefore ,the authors designed this study to only evaluate depressed patients without any anxiety disorder to avoid interjecting a confounding variable.

Similarly, adherence criteria are also often instituted or evaluated in mental health studies to limit confounding, especially considering the potential for impact on medication use and resource utilization.[18-19,21] Using a proportion of days covered equation, adherence was set as an inclusion criterion in this study and was defined as

citalopram being available to patients at least 150 days during each six month study period.

After inclusion and exclusion criteria were applied, 246 patients were analyzed, 76 in the intervention group (IG) and 170 in the control group (CG). Baseline characteristics examined were comparable between the two groups (Table 1). Likewise, change in mental health resource utilization as a composite primary outcome was similar between groups. The greatest distinction between groups could be appreciated in mental health clinic visits and concomitant psychiatric medications used for depression. For both outcomes, 1 out of 5 patients in the IG required an additional mental health clinic visit, an additional psychiatric medication used for depression, or both. In contrast, 1 out of 20 CG patients additionally required one or both of these resources. The authors believe that this may be a clinically significant finding although the results did not reach statistical significance.

Overall, the lack of expected effects could be attributed to a smaller sample size or another point of speculation. The restriction of 60 milligram dosing not only affected those in the IG but also those in the CG. Patients in the CG who might have previously increased to 60 milligrams would be much less likely after FDA warning to be placed on 60 milligrams. Therefore, these patients might have sought out other mental health resources.

The VA provided more extensive guidance on September 29, 2011 for managing Veterans taking citalopram. Mainly, providers were directed to document strict monitoring of electrolytes, EKGs, risk factors for QTc prolongation, and any adverse events reported.[14] On March 27, 2012, the FDA released revised recommendations, which clarified appropriate citalopram dosing, warning, and monitoring package insert details. Perhaps the most significant change was the de-escalation of congenital long QT syndrome from being "contraindicated" to "not recommended."[10-11] In response, on April 17, 2012, the VA relayed the updated recommendations and amended the previously mentioned VA-specific guidance.[15]

There are some potential weaknesses of the study to consider. First, this retrospective follow-up study only appraised VA resource utilization. Any use of non-VA resources would not have been captured in the data collection. Also, our Veteran patients were mostly Caucasian male and were from one geographic location, which could constrain external validity. There was also a significant portion of our population who were over 60 years of age for which the maximum recommended daily dose is 20 milligrams.[1,10-11,14-15] Appropriateness of dosing was determined to be beyond the scope of the study but this could also be a possible limitation of external validity. Likewise, concomitant medications reported were limited to those used in depression, which eliminated investigation of potential drug interactions, a particularly interesting consideration for citalopram patients who may be CYP2C19 poor metabolizers. Lastly, only 10 percent of patients in both groups had electrocardiograms performed during both study time periods, which prohibited an extensive analysis of citalopram's effect on the QTc-interval. A recent cross-sectional study analyzed citalopram QTc-interval data which exhibited dose-dependent increases but also showcased variability, including patients on 20 milligrams having similar mean QTc-intervals to those on 60 milligrams.[22]

CONCLUSION

This study of citalopram dose reduction after FDA warning in depressed Veterans without anxiety failed to demonstrate a significant impact on psychiatric outcomes evaluated. Mental health clinic visits and concomitant psychiatric medications used for depression represented the most distinct parameters affected and may be clinically significant, despite not being statistically significant ($p<0.06$). Investigation of our study's outcomes and others in a larger, more diverse population is warranted and may reveal effects this study was unable to detect. Examination of patients suffering from anxiety would also prove enlightening to currently limited evidence.

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