Assessing Responsiveness of Health Systems to Drug Safety Warnings

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Objective: *In 2011–2012 the U.S. Food and Drug Administration (FDA) issued safety announcements cautioning providers against prescribing high doses of citalopram given concerns for QT prolongation. The authors evaluated Veterans Affairs (VA) national trends in citalopram use and dose compared with alternative antidepressants after the FDA warnings.* **Methods:** *Time series analyses estimated the effect of the FDA warnings on citalopram and other antidepressant across three periods: before the first FDA warning in August 2011, after the 2011 FDA warning until the second warning in March 2012, and after the 2012 FDA warning. In a National VA health system, adult VA outpatients prescribed citalopram or alternative antidepressants from February 2010 to September 2013 were studied. Outpatient use of high-dose citalopram (>40 or >20 mg daily in adults aged > 60 years) including the proportion of patients prescribed citalopram and difference between study periods.* **Results:** *Between the first and second FDA warnings, among patients aged 18–60, high-dose citalopram use decreased by 2.0% per month ($p < 0.001$) and by 1.9% per month ($p < 0.001$) for older adults. After the second FDA warning in 2012, 30.7% of older patients remained on doses higher than the newly recommended dose of 20 mg. Reductions in overall use of citalopram were accompanied by significant increases in prescriptions of alternative antidepressants, with sertraline most widely prescribed.* **Conclusion:** *Although trends in high-dose citalopram use declined after the 2011–2012 FDA warnings, roughly one-third of older adults still remained on higher than recommended doses. Concomitant increases in sertraline and other antidepressant prescriptions suggest potential substitution of these medications for citalopram.* (Am J Geriatr Psychiatry 2017; ■■:■■–■■)

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INTRODUCTION

In August 2011 the U.S. Food and Drug Administration (FDA) issued a safety announcement cautioning providers against prescribing citalopram at doses above 40 mg/day, given concerns for potential QT prolongation.[1] The warning recommended that citalopram not be used in patients with a higher risk of developing torsades de pointes, including individuals with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, and those predisposed to hypokalemia or hypomagnesemia. For these patients the FDA recommended more frequent electrocardiographic and laboratory monitoring.[2] A subsequent warning in March 2012 recommended against the use of doses above 20 mg/day in patients over age 60.[1–3]

The citalopram warnings were of particular concern to mental health and primary care providers given the large number of patients affected. Before the 2011 FDA warning, citalopram was the most widely prescribed antidepressant in the United States, with 37.8 million prescriptions.[4] Many treating clinicians considered citalopram a first-line antidepressant given its few drug–drug interactions and relatively benign side effect profile.[5] The FDA warnings in 2011 and 2012 created an uncertain clinical situation for many prescribers. Providers were faced with the challenge of weighing and monitoring the potential risk of a cardiovascular event against the risk of psychiatric destabilization of patients on a therapeutic dose of citalopram now considered too high.[6]

FDA warnings are common; over 60 drug safety communications were issued within the United States during 2011 alone,[7] the same year as the first citalopram warning. However, despite the frequency of FDA warnings, currently a limited number of rigorous studies evaluate the impact and responsiveness of health systems to FDA warnings.[8] Prior studies demonstrate variable compliance with the warnings and the potential for unintended consequences.[8–11] Additionally, previous studies have suffered from substantial methodologic limitations, such as lacking a comparison group. Evaluation of response to drug safety warnings is critical to understand their impact on patient health outcomes and avoid patient exposure to risk. The 2011–2012 FDA citalopram drug safety warnings provide a natural experiment to assess how health systems respond to safety communications.

This study aimed to evaluate the response of the Veterans Health Administration, the largest integrated health system in the United States,[12] to the 2011 and 2012 FDA warnings for citalopram. This study sought to overcome the methodologic limitations of prior studies by using strong quantitative methods to evaluate the FDA warnings related to citalopram, the most commonly prescribed antidepressant in the United States at the time of the first drug safety warning. We hypothesized that the warnings would contribute to a significant decline in high-dose and overall citalopram use over the study period and that these decreases in system-wide prescribing of citalopram would be associated with subsequent increases in prescriptions of other types of antidepressants, as we found in previous work.[13] We hypothesized that these changes would be more pronounced for older adults (>60) after the second warning, given the greater dose restrictions among this age group.

METHODS

Study Cohort

We assembled a rolling cohort of Veterans Affairs (VA) patients aged 18 years or older. The study period ran from February 2010 to September 2013, which included citalopram prescriptions from at least 12 months before the first FDA warning (August 2011) and 12 months after the last warning (March 2012). The VA Ann Arbor Healthcare System institutional review board approved this study. We have published the study protocol elsewhere.[14]

Measures of Citalopram and Other Antidepressant Medication Use

We compiled monthly citalopram prescribing rates for continuous VA users. To be included in the denominator for a given month during the study period, we required patients to have completed at least one VA outpatient appointment during the month of the observation period. The numerator included every VA patient with a filled citalopram prescription in that month.

We obtained pharmacy data from VA Pharmacy Benefits Management (PBM) and linked it to patient demographic data from the Corporate Data Warehouse.