Psychotropic Pharmacotherapy associated with QT Prolongation among Veterans with Posttraumatic Stress Disorder

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INTRODUCTION

The QT interval refers to the length of time required for the heart to repolarize following ventricular depolarization, characterized by ions (potassium, sodium, calcium) rapidly moving across the cellular membrane. It is measured from the start of the QRS complex (or Q wave) to the end of the T wave (Figure 1). If an excess sodium influx or decreased potassium efflux occurs, an abundance of positively charged ions results, prolonging the interval.

Figure 1. QT interval on an electrocardiogram (EKG).

QT prolongation among patients with severe mental illness (SMI) was triple that among non-SMI patients (40 vs. 14 per 100,000) and elevated for specific SMI (Figure 2): schizophrenia, bipolar disorder, posttraumatic stress disorder (PTSD), and major depressive disorder (MDD).

Figure 2. Prevalence of QT Prolongation among Veterans in the VA (FY2006-2009): SMI vs. non-SMI, by Gender, reporting 95% confidence interval.

Prevalence of QT Prolongation

In recent years, the Food and Drug Administration has issued Drug Safety Communications on several drugs associated with QT prolongation; this includes citalopram, an antidepressant in the class of selective serotonin reuptake inhibitors (SSRIs) commonly prescribed off-label for PTSD.1,2 This study sought to identify medications, specifically psychotropic drugs, associated with QT prolongation among Veterans diagnosed with PTSD.

METHODS

Administrative extracts from the Veterans Health Administration’s (VA) medical record system were aggregated for the study, “Surgical Treatment Outcomes for Patients with Psychiatric Disorders” (STOPP).3 Data included diagnosis codes and outpatient prescriptions. Among 7.1 million surgery and non-surgery patients treated in VA during October 2005-September 2009, 176 with PTSD (ICD-9: 309.81) were diagnosed with QT prolongation (426.82).

A case-control study design matched patients 1:4 on:
1. Age (± 1 year)
2. Gender
3. Visit setting (inpatient outpatient) and date (within 15 days)
4. Physical comorbidity (per Selim Physical Index)
5. Prior-year diagnosis of PTSD
6. For a combined sample of 880 patients, prior-year medication use was correlated with QT prolongation utilizing Spearman’s rank correlation coefficient, r.
7. A classification tree further assessed risk for QT prolongation among patients with more complex pharmacotherapies.

RESULTS

• Receipt of any drug with known risk of prolonging the QT interval varied by matched group (23% QT vs. 15% control, p < 0.01).

• Medications putting patients significantly (p < 0.05) at risk included:
  1. Anti-arrhythmics (propafenone, r = 0.07; sotalol, r = 0.10)
  2. Antibiotics (clarithromycin, r = 0.07)
  3. Typical antipsychotics (APs) (chlorpromazine, r = 0.07)
  4. Atypical APs (perphenazine, r = 0.07; ziprasidone, r = 0.09)
  5. Antiarrhythmics (buspirone, r = 0.10)

• SSRI trending toward an increased risk included citalopram (14% QT vs. 10% control, p = 0.07) and fluoxetine (8% vs. 5%, p = 0.08)

• Prior-year use of multiple drugs suspected of altering cardiac repolarization leading to QT prolongation varied (9% QT vs. 4% control, p < 0.01); e.g., use of moxifloxacin and amiodarone (67% vs. 20%, p = 0.04)

• Use of the anoxic/lytic alprazolam and tricyclic antidepressant (TCA) amitriptyline was associated with greater risk among patients with heart complications (e.g., heart failure, arrhythmias; Figure 3).

• For patients with non-cardiac conditions, the atypical AP aripiprazole with either typical AP haloperidol or SSRI escitalopram also carried greater risk.

DISCUSSION

• This study’s findings may be useful in clinical decision-making concerning treatment for PTSD, where first-line pharmacotherapy currently comprises monotherapy with a SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI).

• For patients posing a particular risk for QT prolongation, the SNRIs or alternative second-line medications to the TCA amitriptyline should be considered with adjunctive medications closely monitored.

• Limitations: 1) difficulty discerning between inherited and drug-induced QT prolongation; 2) an unknown rate for monitoring QT prolongation, reducing the ability to detect cases; and 3) data preceding the 2011-2012 FDA Drug Safety Communications; citalopram use may have change in the wake of the warnings.

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References: