CYP2C19 genotype, physician prescribing pattern, and risk for long QT on serotonin selective reuptake inhibitors

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Aim: To examine the impact of *CYP2C19* genotype on selective serotonin reuptake inhibitor (SSRI) prescribing patterns. **Patients & methods:** Observational cohort containing 507 unique individuals receiving an SSRI prescription with *CYP2C19* genotype already in their electronic medical record. Genotype was distributed as follows: $n = 360$ (71%) had no loss of function alleles, 136 (26.8%) had one loss of function allele and 11 (2.2%) had two loss of function alleles. **Results & conclusion:** For poor metabolizers exposed to sertraline, citalopram or escitalopram, providers changed prescribing patterns in response to alerts in the electronic medical record by either changing the drug, changing the dose or monitoring serial EKGs longitudinally. For intermediate metabolizers exposed to sertraline, citalopram or escitalopram, no alert was needed (mean QTc = 440.338 ms [SD = 31.1273] for *CYP2C19**1/*1, mean QTc = 440.371 ms [SD = 29.2706] for *CYP2C19**1/*2; $p = 0.995$).

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CYP2C19 genotype is becoming routinely available in electronic medical records (EMRs). Healthcare providers are increasingly ordering this test in patients undergoing percutaneous coronary intervention (PCI), to guide choice of antiplatelet therapy [1]. Because a key principle in gene-based drug dosing has been that variation in a single pharmacogene can impact clinical outcome for many classes of drugs, decision support for *CYP2C19* genotype must be deployed within a flexible framework capable of providing guidance for additional medications beyond antiplatelet agents [2]. For example, *CYP2C19* metabolizes antifungals (e.g., voriconazole), proton pump inhibitors (e.g., omeprazole) and many other commonly prescribed drugs, including several types of antidepressants [3–5].

Antidepressants are among the most commonly prescribed drugs in the USA. As many as 10% of adults have a depressive disorder [6], and the prevalence of depression is even higher in patients with cardiovascular disease [7]. Uncontrolled depression is a poor prognostic indicator for patients with coronary artery disease (CAD) [8], and prescribing strategies are needed to optimize efficacy and decrease toxicity for antidepressants specifically in this population [9].

Serotonin selective reuptake inhibitors (SSRIs) are often prescribed to treat depression [10]. Three frequently prescribed SSRIs, sertraline, citalopram and escitalopram, are metabolized by *CYP2C19*, and *CYP2C19* genotype can affect the efficacy of these drugs. The STAR*D trial quantified impact of *CYP2C19* genotype on SSRI efficacy in a setting designed to approximate real-world conditions [11]. Within this treatment-based cohort, *CYP2C19* genotype was associated with remission ($p = 0.03$) in patients adherent to therapy for the full duration of the study [12].

In addition to influencing efficacy, *CYP2C19* genotype influences risk for toxicity in patients taking sertraline, citalopram and escitalopram [4]. Adverse drug reactions (ADRs) accompanying the use of SSRIs can include gastrointestinal upset (constipation, diarrhea, nausea and vomiting), sleep disorders (insomnia or somnolence), sexual dysfunction (abnormal ejaculation and reduced libido) and cardiac rhythm disturbances (QT prolongation and *torsades de pointes*) [13]. Gender-specific thresholds have been published for QTc (QT interval adjusted by RR interval, to correct for heart rate). While these thresholds can help clinicians identify QT prolongation (QTc >440 ms in men and QTc >460 ms in women), the strength of the correlation between QT interval and potentially lethal ventricular arrhythmias like *torsades de pointes* increases when QTc exceeds 500 ms [14].

Because *CYP2C19* enzyme activity influences risk for QT prolongation with sertraline, citalopram and escitalopram, many EMRs now have the capability to deploy automated best practice advisories (BPAs) to guide physicians with SSRI dosing based on *CYP2C19* genotype [2]. *CYP2C19* poor metabolizers (patients with two loss of function alleles) have higher plasma concentrations of sertraline, citalopram and escitalopram, and gene-based dosing guidelines have been published for these drugs by the Clinical Pharmacogenetics Implementation Consortium (CPIC) [4]. The US FDA has also recommended changes to the product label for some SSRIs based on *CYP2C19* genotype. While the prescription package insert for citalopram now states that 20 mg/day is the maximum recommended dose for this medication in patients with two loss of function *CYP2C19* alleles, guidance is less clear for patients with one loss of function allele [15].

We therefore sought to describe the impact of *CYP2C19* genotype on SSRI prescribing patterns in a large observational cohort where BPAs based on CPIC guidelines are available in the context of routine clinical care. We report examples of changes in physician behavior for patients with two loss of function alleles, and we quantify the relationship between genotype and QTc in patients with one loss of function allele.

Methods

The current study protocol was approved by the Sanford Research Center Institutional Review Board. Design was retrospective assessment of prescribing pattern in a large observational cohort. The setting was a multi-specialty group practice located in the upper Midwest. Sanford Health and Sanford Medical Center represent a fully integrated healthcare system with a longstanding comprehensive EMR. The majority of patient records within this system have been electronic for over a decade. Our EMR includes comprehensive lists of patient problems, a summary of each clinic encounter (including diagnoses and procedures), a variety of medication alerts and online access to over a decade of laboratory results. Since the majority of patients in the current study (92.3%) receive primary care through Sanford Health, chart fragmentation is minimal and this record is considered both longitudinal and comprehensive.

Study subjects

Patients 18 years or older who had been genotyped for *CYP2C19* during the course of routine clinical care were eligible for study inclusion. This included patients genotyped pre-emptively in the context of primary care, and patients who had been genotyped reactively, to guide antiplatelet therapy within the context of PCI for CAD. On 1 January 2018, our EMR contained longitudinal data from ~2000 patients genotyped for *CYP2C19*. A total of 507 of these patients have also had an SSRI prescribed at some point. Because gene-based dosing guidelines for *CYP2C19* published by CPIC are limited to *CYP2C19* *1, *2, *3, *17 [4], our analyses included only those variants.

Patient summary: demographics & covariates

Our EMR contains data from 1.8 million unique individuals. Our study cohort consisted of 507 unique individuals who had received an SSRI prescription with extant *CYP2C19* genotype already available in their chart. Mean age of these study subjects was 64 years (64.03; 15.14 SD). Gender was evenly distributed, 48.5% males and 51.5% females. Based upon self-reported race, 96.3% of study subjects were White/Caucasian, 2.6% were American Indian or Alaskan Native and less than 1% were African-American or Hispanic/Latin-American (0.4 and 0.2% respectively). A very small percentage of the cohort (0.6%) declined to provide race or ethnic information. Most study subjects were married or partnered (57.8%) or widowed (13.2%). Average years of education was 14 years (SD = 2.1 years). Alcohol use was reported in 40.8% of study participants (with at least one 12-ounce beer, one 5-ounce glass of wine or 1.5 ounces of a distilled alcohol containing beverage per week set as criteria for alcohol use). History of smoking was reported in 42% of the cohort (n = 213), and 40.8% of subjects reported being active smokers (N = 207). Hypertension was common in study subjects, at 82.2% with at least one historical diagnosis

in the EMR. Nearly half of study participants (44%; N = 223) met criteria for diabetes (at least one episode of a diabetes diagnosis listed within their EMR as indicated by diagnostic codes).

Event summary: electronic extraction of longitudinal data

Longitudinal data were electronically extracted from the EMR for cardiovascular events (CAD and PCI) and for diagnostic codes linked to behavioral health (depression and anxiety). Approximately 25% of the cohort had been genotyped pre-emptively in the context of routine primary care, and the remainder were genotyped reactively (at the point of prescribing) in the coronary angiography suite. The study included more than 3 years of encounter data between 1 October 2014 and 1 January 2018. We used commonly captured EMR data, including ICD-9 codes, ICD-10 codes, CPT codes and laboratory test results for discrete variable abstraction (encounter diagnosis, hospital account diagnosis, hospital admission diagnosis; claims diagnosis/codes; as well as medical history, abstracted from the problem list). Coronary artery disease was identified using ICD-9 and ICD-10 diagnostic and procedural codes in the EMR. Greater than three quarters of the study population met criteria for a diagnosis of CAD (76.1%; N = 386), and greater than 60% of study participants (62.5%; N = 317) had undergone a PCI. Furthermore, 70.2% of study participants had at least one diagnostic code for depression (311.**, 296.2, 296.3), and 67.9% has at least one diagnostic code for anxiety (300.00, 300.01 and 300.02).

Validation & manual chart review

Documents for all 507 study subjects with *CYP2C19* genotype and exposure to an SSRI were reviewed by a licensed practicing physician, and 50 of these records (10%) were reviewed in duplicate by two licensed practicing physicians for quality control. Clinical text documents and EKGs were manually reviewed for subject identifiers, and charts were reviewed longitudinally for SSRI prescribing history. QT interval was abstracted as QTc from time windows where subjects were observed to have been on one of three target SSRIs: sertraline, citalopram and escitalopram. Medication use was also confirmed at the time of most recent clinic visit. The reviewer also confirmed the presence or absence of electronically extracted covariates by reviewing clinical text documents dating back to 1997 (two decades). Types of documents encompassed a variety of clinical encounters (e.g., primary care office notes, routine physical exams and cardiology consultations). In order to manually reconstruct complete SSRI exposure histories, each physician reviewer recorded drug name (generic and/or trade name), drug dose and the time period over which the drug had been prescribed. In all cases, there was sufficient information embedded in the clinical text documents to identify specific dates when each SSRI had been started and stopped.

Statistical analysis

Association between *CYP2C19* genotype and prescribing pattern for each SSRI was assessed using χ^2 test or Fisher's exact test as appropriate. The mean QTc in carriers of *CYP2C19* loss of function alleles was compared with the mean of patients with no loss of function allele for each of three target drugs (sertraline, citalopram, escitalopram) using a two sample t-test. Next, the effects of genotype and gender on QTc were examined through two-way ANOVA with post-hoc pairwise comparison using the TukeyHSD method. A p-value of less than 0.05 was considered significant for each of these analyses.

Results

On 1 January 2018, our EMR contained longitudinal data from approximately 2000 unique individual patients genotyped for *CYP2C19*; of these, 507 of patients had been prescribed an SSRI at some point. Table 1 contains a description of the cohort. As anticipated, most study subjects in this treatment-based cohort – defined by prior exposure to an SSRI – had either a diagnostic code for depression or anxiety.

Provider response to BPAs in poor metabolizers

According to guidelines published by CPIC [4], our EMR activates an automated BPA for any patient with two loss of function *CYP2C19* alleles, when a provider attempts to prescribe sertraline, citalopram or escitalopram [2]. Within our study cohort of 507 individuals, the EMR was reviewed manually for every subject where a BPA had fired in the context of two loss of function *CYP2C19* alleles (*CYP2C19* poor metabolizer status). BPA events were extracted (with date stamps) electronically, then confirmed manually. Drug prescription dates were also extracted and confirmed longitudinally using the same approach. These two longitudinal datasets (BPA events, and SSRI prescribing events) were then merged to construct schematic timelines illustrating provider prescribing behavior in

Table 1. Patient summary.					
Patient information and history	Reported as	Total† (n = 507)	UM/RM/EM (n = 360)	IM (n = 136)	PM (n = 11)
Age	Mean (SD)	64.03 (15.14)	64.540 (14.775)	62.440 (15.536)	67.270 (21.119)
BMI	Mean (SD)	52.79 (12.72)	52.569 (12.785)	53.458 (12.374)	51.631 (16.336)
Gender	Males n (%)	246 (48.5%)	172 (69.9)	71 (28.9)	3 (1.2)
	Females n (%)	261 (51.5%)	188 (72.0)	65 (24.9)	8 (3.1)
Diabetes	n (%)	223 (44.0%)	158 (70.9)	59 (26.5)	6 (2.7)
Hypertension	n (%)	417 (82.2%)	302 (72.4)	105 (25.2)	10 (2.4)
CAD	n (%)	386 (76.1%)	276 (71.5)	101 (26.2)	9 (2.3)
PCI	n (%)	317 (62.5%)	225 (71.0)	85 (26.8)	7 (2.2)
Angiogram	n (%)	337 (66.5%)	238 (70.6)	90 (26.7)	9 (2.7)
Alcohol use	n (%)	207 (40.8%)	147 (71.0)	57 (27.5)	3 (1.4)
Smoking history	n (%)	213 (42.0%)	161 (75.6)	47 (22.1)	5(2.3)
Depression	n (%)	356 (70.2%)	256 (71.9)	92 (25.8)	8 (2.2)
Anxiety	n (%)	344 (67.9%)	251 (73.0)	85 (24.7)	8 (2.3)
† All percentages are within phenotype, except under column 'Total'. CAD: Coronary artery disease; PCI: Percutaneous coronary intervention; SD: Standard deviation.					

response to the BPAs. As shown in [Figure 1](#), provider response to BPAs in these *CYP2C19* poor metabolizers was found to fit into three distinct patterns: change drug, change dose or no change. In situations where no change in prescribing was implemented, patients were followed longitudinally to monitor risk/benefit ratio ([Figure 1A](#)).

Net impact on prescribing pattern

Sertraline is the most commonly prescribed SSRI in our EMR. Among the 2000 unique individuals with *CYP2C19* genotype available in our EMR, 159 have at some point received a sertraline prescription. Based upon temporal data, over half of these individuals showed a sertraline ‘start date’ that preceded their medication order date, indicating they had already been on the drug prior to the first prescription in our system (i.e., as a historical medication). Out of 159 study subjects in our cohort that ever received a prescription for sertraline, the prescription was initiated after the *CYP2C19* genotype for 75 individuals. Within these 75, electronically extracted data indicate that sertraline was discontinued (for any reason) in 23 individuals, while the dose was later decreased in ten individuals and increased in five individuals.

The specific relationship between *CYP2C19* genotype and current prescribing pattern for sertraline is illustrated in [Figure 2](#). The relationship between genotype and prescription numbers are shown for all six available SSRIs (three *CYP2C19* substrates, and three non-*CYP2C19* substrates) as of January 2018.

Thus, in our study cohort of 507 individuals, only four *CYP2C19* poor metabolizers are still on an SSRI known to be metabolized by *CYP2C19* (only four on sertraline, 0 on citalopram and 0 on escitalopram). While the descriptive data illustrated in [Figure 1](#) (representative timelines) clearly indicate that providers change their prescribing pattern in response to BPAs in *CYP2C19* poor metabolizers (homozygous loss of function), the very small number of individuals with two loss of function alleles limits our statistical power to demonstrate a difference in prescribing patterns quantitatively in poor metabolizers. With respect to heterozygotes, we observed no difference in drug choice by genotype in patients with only one loss of function allele ($p = 0.7335$, Fisher’s exact test). This is anticipated, because according to published guidelines [4], our EMR does not fire a BPA in heterozygotes for this class of drugs. However, given that STAR*D showed a difference in efficacy in heterozygotes [16], we opted to quantify the impact of *CYP2C19* heterozygosity on toxicity as well (Part III, below).

QT interval in intermediate metabolizers

Last, to quantify the impact of *CYP2C19* genotype on QT interval in heterozygotes, we manually abstracted all QT interval data (QTc) for study subjects with EKG data available specifically within the context of *CYP2C19**1/*1 genotype and *CYP2C19**1/*2 genotype. We limited our analysis to these two genotypes to maximize sample size while simultaneously avoiding misclassification bias introduced by other rare loss of function alleles (*CYP2C19**3) as well as any gain of function alleles (*CYP2C19**17). *CYP2C19**2 is the most common loss of function allele for this gene in our study population, and other loss of function alleles beyond *2 may influence *CYP2C19*

Figure 1. Provider response to Best Practice Advisories during sertraline prescription in *CYP2C19* poor metabolizers. Longitudinal data are shown for three representative examples, demonstrating three patterns of response. **(A)** No change: although QTc went up on sertraline, the provider did not change the prescription (but psychiatry was consulted to follow the patient and monitor the patient's risk/benefit ratio). **(B)** Change dose (decrease dose): The provider decreased sertraline dose, and since QTc stayed within normal range, the patient continues on a lower dose of sertraline (after documented discussion with provider). **(C)** Change drug (switch to a serotonin selective reuptake inhibitors not metabolized by *CYP2C19*): QTc goes up, BPA fires, provider stops offending agent (in this case, sertraline) the provider then starts a different serotonin selective reuptake inhibitors not metabolized by *CYP2C19* (paroxetine per BPA). BPA: Best practice advisories.

enzyme activity to a different degree. Because misclassification can drive the odds ratio toward 1.0, a direct focused assessment of *CYP2C19**1/*1 versus *1/*2 genotype retained phenotypic homogeneity among the heterozygotes, and it optimized sample size by utilizing the single most common detrimental allele. Results are summarized in Table 2.

Figure 2. Current distribution of serotonin selective reuptake inhibitor prescription in 507 individuals based upon CYP2C19 genotype. Histograms illustrate prescription frequency for three CYP2C19 substrates, and three non-CYP2C19 substrates.

Table 2. There is no difference in mean QTc in intermediate metabolizers versus normal metabolizers.					
SSRI	CYP2C19 genotype	Mean	N	Standard deviation	p-values using t-test
Citalopram	*1/*1	440.558	52	33.4416	0.961 (two-tailed)
	*1/*2	441.028	18	35.5844	0.519 (one-tailed)
	Total	440.679	70	33.7434	
Escitalopram	*1/*1	441.875	28	28.1772	0.834 (two-tailed)
	*1/*2	439.969	16	29.1379	0.417 (one-tailed)
	Total	441.182	44	28.2057	
Sertraline	*1/*1	439.366	56	30.8100	0.906 (two-tailed)
	*1/*2	440.146	24	25.1627	0.547 (one-tailed)
	Total	439.600	80	29.0748	
Total	*1/*1	440.338	136	31.1273	0.995 (two-tailed)
	*1/*2	440.371	58	29.2706	0.503 (one-tailed)
	Total	440.348	194	30.5085	

Current guidelines recommend action (i.e., change drug or change dose) if an SSRI known to be metabolized by CYP2C19 is prescribed in patients who are homozygous for CYP2C19 loss of function alleles (poor metabolizers) [4]. They do not recommend action in patients who are heterozygous for loss of function (intermediate metabolizers). However, if heterozygotes were found to have a clinically significant increase in QT interval on these SSRIs, these patients may be at higher risk for a serious ADR (ventricular arrhythmia). We therefore tested the hypothesis that mean QTc on sertraline, citalopram and escitalopram may be increased in heterozygotes (CYP2C19*1/*2) when

compared with patients with no loss of function alleles (*CYP2C19**1/*1). As shown in Table 2, there is no difference in mean QTc between these two groups, indicating that BPAs are not needed in intermediate metabolizers.

Discussion

CYP2C19 genotype is becoming routinely available within EMRs. We now report the impact of extant *CYP2C19* genotype (genotype already in the chart for another reason) on provider prescribing behavior for one of the most commonly prescribed class of drugs in the US, the SSRIs. This observational cohort study is unique because it describes the impact of automated decision support (BPAs based on *CYP2C19* genotype) in the context of routine clinical care. Based on our findings, providers clearly change the drug (or reduce the dose and monitor) in response to BPAs fired in *CYP2C19* poor metabolizers exposed to sertraline, citalopram and escitalopram. This is consistent with recommendations published by CPIC [4], as well as recent product label changes recommended by the FDA. For example, the citalopram product label now specifically warns against prescribing more than 20 mg daily in *CYP2C19* poor metabolizers [15].

While the actionability of this drug–gene relationship is unequivocal in poor metabolizers, neither CPIC nor FDA currently recommend any intervention in intermediate metabolizers. We therefore compared mean QTc in patients with one loss of function *CYP2C19* allele to mean QTc in patients with no loss of function alleles, for SSRIs known to be metabolized by *CYP2C19* (sertraline, citalopram, escitalopram). It is reassuring to observe no difference between *CYP2C19**1/*1 and *CYP2C19**1/*2. Thus, the current approach to deploy BPAs in only poor metabolizers seems prudent for this drug–gene relationship.

One limitation of this study that must be noted is an inadequate sample size for quantifying the rate of adverse clinical events related to QT prolongation in poor metabolizers (*torsades de pointes*, other ventricular arrhythmias and death). Due to the relatively low frequency of the poor metabolizer genotype, and the rarity of clinical ADR events like *torsades de pointes*, larger observational studies aggregating data across multiple institutions will be needed to quantify the impact of this approach on event reduction for ventricular arrhythmias. Efforts are underway to address this limitation [17].

There is also great need to define the impact of this drug–gene relationship on the efficacy of SSRIs, particularly in patients with cardiovascular disease. Patients with CAD have a higher frequency of depression, and medication nonadherence in the context of failed antidepressant therapy can lead to poor outcome for CAD as well. In a recent systematic review of antidepressant efficacy in patients with CAD, current prescribing strategies are only ‘moderately efficacious’ [18]. Yet uncontrolled depression is an independent risk factor for CAD [19,20]. After controlling for covariates such as smoking, each additional mental health diagnosis further increases the odds of CAD by 44%, and patients with depression alone have a 60% higher odds of developing CAD [21]. In the future, the impact of *CYP2C19* genotype on efficacy for SSRIs needs rigorous assessment specifically within patients that have CAD.

Summary points

- Variation in a single pharmacogene can impact clinical outcome for many classes of drugs.
- *CYP2C19* genotype influences risk of toxicity for sertraline, citalopram and escitalopram.
- Providers changed prescribing patterns in response to poor metabolizer alerts in the electronic medical record by either changing the drug, changing the dose or monitoring serial EKGs.
- Mean QTc was not different for intermediate metabolizers compared with normal metabolizers.
- This observational cohort study is unique because it describes the impact of automated decision support (*CYP2C19* genotype-based prescribing for serotonin selective reuptake inhibitors) in the context of routine clinical care.

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Ethical disclosure

In first section of methods, the authors state that they have obtained appropriate institutional review board approval for all human experimental investigations. No informed consent used as study was retrospective chart review.

Author's contributions

N Petry substantially contributed to the conception or design of the work, interpretation of data, drafting and revising the work, final approval and agreement to be accountable for work. R Lupu substantially contributed to the conception or design of the work, acquisition and analysis/interpretation of data, drafting and revising the work, final approval and agreement to be accountable for work. A Gohar substantially contributed to the acquisition and analysis of data for the work, drafting and revising the work, final approval and agreement to be accountable for work. EA Larson substantially contributed to the conception or design of the work, interpretation of data, drafting and revising the work, final approval and agreement to be accountable for work. C Peterson substantially contributed to the conception and acquisition of data for the work, drafting and revising the work, final approval and agreement to be accountable for work. V Williams substantially contributed to the conception and acquisition of data for the work, drafting and revising the work, final approval and agreement to be accountable for work. J Zhao substantially contributed to the conception or design of the work, acquisition and analysis/interpretation of data, drafting and revising the work, final approval and agreement to be accountable for work. RA Wilke substantially contributed to the conception or design of the work, interpretation of data, drafting and revising the work, final approval and agreement to be accountable for work. LJ Hines substantially contributed to the conception or design of the work, interpretation of data, drafting and revising the work, final approval and agreement to be accountable for work.

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