An Exploratory Study of the Food and Drug Administration Adverse Events Reporting System (FAERS)

by

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Abstract

Adverse drug events (ADEs) are an unfavorable or unintended response to a pharmaceutical product. Adverse drug reactions (ADRs) are a subset of ADEs which imply causality. Approximately 2 million ADRs occur in the United States annually and cost the healthcare system over $130 billion. ADRs can be voluntarily reported to the Food and Drug Administration (FDA) Adverse Event Reporting Systems (FAERS) by healthcare professionals and consumers. A subset of ADRs for certain drugs are recognized as preventable as they have genetic risk factors (variants) which can be identified using pharmacogenomic testing. Pharmacogenomic guidelines are publicly available from the Clinical Pharmacogenetics Implementation Consortium (CPIC); approximately 97% of the population has at least one genetic variant that would benefit from pharmacogenomic testing. Understanding if a patient has a genetic predisposition for an ADR can have direct impact on patient care and healthcare costs by adjusting the drug dose or prescribing an alternate drug for efficacy or safety.

This study analyzed the CPIC pharmacogenomic guidelines and case reports from the FAERS database between January 2018 and December 2019 to better understand which therapeutic areas might be underutilizing pharmacogenomic guidelines and how it may be affecting public health and healthcare costs. Analysis revealed that the most common therapeutic area with available pharmacogenomic guidelines was psychiatry. Most of these psychiatric drugs were identified as selective serotonin reuptake inhibitors (SSRIs) used to treat major depressive

disorder (MDD). Given that citalopram, escitalopram, and sertraline are first line SSRIs for MDD and have well established ADRs, these FAERS case reports were selected for further investigation. Analysis indicated that most case reports were serious ADRs (84.9%) and an average of 26.2% of all cases required hospitalization. The average percent of cases resulting in death was 10.3%, with citalopram having the highest incidence of death (18.4%). Gastrointestinal distress, therapeutic failure, and somnolence or sleep disorder were determined to be the most frequent ADRs, all recognized as preventable using pharmacogenomic testing. The estimated annual cost of these ADRs is estimated to be $23.4 million. Together, these results suggest a need for more informed drug prescribing for MDD to protect public health.

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Preface

I would like to thank Dr. Andrea L. Durst, and Dr. Sarah E. Krier for their thoughtful contributions and support throughout this essay. Thank you to Dr. Dave Dotson, who was critical in my understanding of the role of pharmacogenomics in public health during my practicum, which inspired this essay. A special thanks to Dr. Candace M. Kammerer, who helped me execute my research questions and explore new ideas. I have learned so much from each of you about the practice of public health. Like you did for me, I hope to support and inspire future students in the field. To my family, friends, and classmates, thank you for your love and support throughout my academic career. Finally, thank you to Teddy, my dog, who kept me company as I wrote every page.

1.0 Introduction

Adverse drug events (ADEs) are an unfavorable or unintended response to a pharmaceutical product. This includes medical errors such as misadministration or miscalculation of drugs, however ADEs do not imply causality (Aronson et al., 2005; Lehmann et al., 1956; Waltham, 1972;). Adverse drug reactions (ADRs) are a subset of ADEs which imply causality. An ADR is defined by the American Society of Health-System Pharmacists (ASHP) as an unexpected, unintended, undesired, or excessive response to a drug requiring intervention; intervention may include discontinuation of the drug, an alternative drug, dose modification, hospitalization, or supportive treatment. ADRs are detrimental to public health and the healthcare system. They may complicate patient diagnosis, negatively affect prognosis, or result in harm, disability, or death (Schatz et al., 2015). The Food and Drug Administration (FDA) defines serious ADRs to include outcomes of death, life-threatening incidents, hospitalization, disability or permanent damage, congenital abnormalities, or those requiring surgical or medical intervention. A subset of ADRs are recognized as preventable as they have genetic risk factors which can be identified using pharmacogenomic testing (FDA, 2018).

In the United States, ADRs occur in 2 million individuals per year and account for at least 100,000 deaths. The annual cost of ADRs is estimated to exceed $130 billion (FDA, 2018). Cost and hospitalization increase with the severity of the ADR. Studies suggest that the average cost per patient is over $3,000 and increases their length of hospitalization by approximately three days (Hug et al., 2012). Known risk factors for ADRs include genetics, age, sex, and preexisting disease (Aronson et al., 2005; Evans et al., 2003). When ADRs occur, they can be voluntarily reported to the FDA Adverse Event Reporting Systems (FAERS), which records ADRs. This database is

regularly monitored and acts to support the FDA's post-marketing safety surveillance programs of pharmaceutical products (FDA Post-marketing Surveillance Programs, 2020).

Pharmacogenomics, the practice of using genetic information to guide drug prescribing and predict drug response (Nebert et al., 1999; T. P. et al., 2009), may aid in preventing a subset of ADRs with a known genetic risk factor (Schazts et al., 2015). Understanding if a patient has a genetic predisposition for an ADR can have direct impact on their care. It may result in adjusting the drug dose or prescribing an alternate drug for efficacy or safety. Future implementation of existing pharmacogenomic guidelines in a clinical setting may have the potential to streamline drug prescribing, prevent ADRs, and personalize therapy for various diseases or conditions. This is an exploratory study of the FAERS database case reports between January 2018 and December 2019 to better understand which therapeutic areas might be underutilizing pharmacogenomic guidelines and its potential impacts on public health and healthcare costs.

2.0 Background

2.1 Pharmacogenomics and Adverse Drug Reactions

Individual responses to drugs are highly variable. Some patients may benefit from a drug, while others may experience ADRs including poor response to therapy, no response to therapy, or a serious ADR such as fatal toxicity or anaphylaxis. Drug efficacy and susceptibility to ADRs is meditated largely by genetic variation (Evans et al., 2003; Roden et al., 2011; Wei et al., 2012). Inter-individual differences are related to genes that encode drug-metabolizing enzymes, drug transporters, drug targets, and human-leukocyte antigen (HLA)—referred to as pharmacogenes. Up to 90% of all drugs are metabolized by enzymes produced by cytochrome P450, which encodes 57 pharmacogenes (Lynch et al., 2007). Genetic variation of pharmacogenes is observed across different racial and ethnic groups, though more research is necessary to understand variants unique to minority populations (Wei et al., 2012).

Approximately 97% of the United States population is estimated to carry at least one inherited variation in a pharmacogene and is likely to be prescribed multiple drugs that could benefit from pharmacogenomic testing during their lifetime (Dunnenberger et al. 2015; Volpi et al., 2018; Zierhut et al., 2017). Pharmacogenomic-based personalized medicine has the potential to prevent ADRs using multigene panel tests that predict drug response, the appropriate drug dosage, and the susceptibility of experiencing an ADR by identifying high-risk variants prior to initiating treatment (Sissung et al. 2017). Optimization of drug prescribing may also act to maximize therapeutic effects and expedite patient care by avoiding the laborious process of prescribing multiple, ineffective drugs. Imprecise drug prescription increases outpatient visits,

emergency department visits, and pharmaceutical waste. (Sultana et al., 2013; Vopi et al., 2019). Apart from the economic burden of ADRs, patients also report psychosocial morbidity as a result of ADRs including anxiety and trauma (Sultana et al., 2013).

Pharmacogenomic guidelines are freely available through the Clinical Pharmacogenetics Implementation Consortium (CPIC). These peer-reviewed guidelines provide evidence-based clinical practice guidelines focused on how to use pharmacogenomic tests results in clinical and public health practice. Guidelines are regularly updated and reviewed by an international group of individuals employed by the government, academia, and industry (CPIC, 2019). The usefulness of these guidelines is reflected by the high representation of drugs with a narrow therapeutic index (Sissung et al., 2017). Therapeutic index is a measure of drug safety; it is the ratio of the dose needed to produce an efficacious response without ADRs (Tamargo et al., 2015). Drugs with a narrow therapeutic index require vigilant titration and patient monitoring due to high risk of inefficacy or fatal toxicity (Tamargo et al., 2015; Sissung et al., 2017).

2.1.1 Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines

At the time of this study, there were 23 published guidelines available for 47 drugs in a variety of therapeutic areas. A number of these guidelines include multiple drugs per guideline, indicated in Table 1. The aims of CPIC guidelines are to prevent serious ADRs, optimize drug dose, and select appropriate therapy for a range of acute and chronic diseases and conditions. Professional societies including the American Society of Health-System Pharmacists (ASHP) and the American Society for Clinical Pharmacology and Therapeutics (ASCPT) have endorsed screening for high-risk variants using CPIC guidelines. The development of new CPIC guidelines is prioritized by criteria, including the ability to achieve prescribing actionability, the availability

of genetic testing for the variant, the consequences of not using a genetic test, how often the drug is prescribed, the frequency of high-risk variants, and the inclusion of genetic information, genetic testing, or biomarker information in the FDA drug label (CPIC, 2019).

Table 1 Summary of 2019 CPIC Guidelines

Drug or Drug Class	Gene(s)	Disease, Condition, or Usage	Guideline Rationale/Preventable ADRs
Abacavir	*HLA-B*	Human immunodeficiency virus	Hypersensitivity reaction - multiorgan failure and anaphylaxis; appropriate therapy selection
Allopurinol	*HLA-B*	Hyperuricemia and Gout	Stevens-Johnson syndrome and toxic epidermal necrolysis
Atazanavir	*UGT1A1*	Human immunodeficiency virus	Bilirubin-related discontinuation
Atomoxetine	*CYP2D6*	Attention-deficit/hyperactivity disorder	Drug ineffective; appropriate dosage
Carbamazepine	*HLA-B*	Epilepsy, trigeminal neuralgia, and bipolar disorder	Stevens-Johnson syndrome and toxic epidermal necrolysis
Codeine	*CYP2D6*	Pain management	Toxicity; appropriate dosage (may reduce a patient's risk of opioid addiction or misuse)
Clopidogrel	*CYP2C19*	Acute coronary syndrome or after percutaneous coronary intervention	Hemorrhaging; appropriate dosage

Efavirenz	*CYP2B6*	Human immunodeficiency virus	CNS toxicity; appropriate dosage
Fluoropyrimidines	*DPYD*	Solid tumors	Appropriate dosage; toxicity
Ivacaftor	*CFTR*	Cystic fibrosis	Appropriate therapy selection
Ondansetron	*CYP2D6*	Prevention of chemotherapy/ radiation-induced, and postoperative nausea and vomiting	Appropriate therapy selection; appropriate dosage
Oxcarbazepine	*HLA-B*	Epilepsy, trigeminal neuralgia, and bipolar disorder	Stevens-Johnson syndrome and toxic epidermal necrolysis
Peginterferon-alpha-based regimens	*IFNL3*	Hepatitis C virus	Appropriate therapy selection
Phenytoin	*CYP2C9* *HLA-B*	Epilepsy	Stevens-Johnson syndrome and toxic epidermal necrolysis; appropriate dosage
Rasburicase	*G6PD*	Lymphoma, leukemia, and solid tumors	Hemolysis
Selective Serotonin Reuptake Inhibitors	*CYP2D6* *CYP2C19*	Major depressive disorder	Appropriate dosage
Simvastatin	*SLCO1B1*	High cholesterol	Appropriate dosage
Tacrolimus	*CYP3A5*	Solid organ and hematopoietic transplantation immunosuppressant	Appropriate dosage; reduce risk of graft rejection
Tamoxifen	*CYP2D6*	Breast cancer	Appropriate dosage; risk identification for recurrence
Thiopurines	*NUDT15* *TPMT*	Nonmalignant immunologic disorders, lymphoid	Appropriate dosage; myelosuppression

		malignancies, and myeloid leukemias	
Tricyclic Antidepressants	*CYP2C19* *CYP2D6*	Major depressive disorder, obsessive-compulsive disorder, and neuropathic pain	Appropriate dosage
Tropisetron	*CYP2D6*	Prevention of chemotherapy/ radiation-induced, and postoperative nausea and vomiting	Appropriate therapy selection; appropriate dosage
Volatile anesthetic agents and succinylcholine	*CACNA1S* *RYR1*	Anesthetic and muscle relaxant	Malignant hyperthermia susceptibility
Voriconazole	*CYP2C19*	Fungal infections (Aspergillosis and Candida infections)	Cardiovascular event; appropriate dosage
Warfarin	*CYP2C9* *VKORC*	Prophylaxis and venous thrombosis (blood clots)	Hemorrhaging and thromboembolic events; appropriate dosage

Clinical Pharmacogenetics Implementation Consortium (2019). Guidelines. Retrieved from https://cpicpgx.org/guidelines/

2.1.2 CPIC Guidelines and Metabolizer Status

A notable portion of CPIC guidelines relate to variation in the cytochrome P450 (*CYP*) gene family. Pharmacogenes within this family, such as *CYP2D6* and *CYP2C19*, possess polymorphisms and copy number variations that impact how an individual metabolizes and responds to a drug through the production of drug-metabolizing enzymes (Rautio et al., 2018). Interethnic variation of *CYP* genes has been revealed using whole-genome and exome sequencing (Zhou et al., 2017), though additional research is vital to ensure pharmacogenomic testing has

equal utility across populations. Metabolizer status is broken down into four groups, including ultrarapid metabolizers, normal metabolizers, intermediate metabolizers, and poor metabolizers. The impact that one's metabolizer status has on individual drug response is illustrated in Figure 1. (Rautio et al., 2018; Weinshilboum et al., 2003).

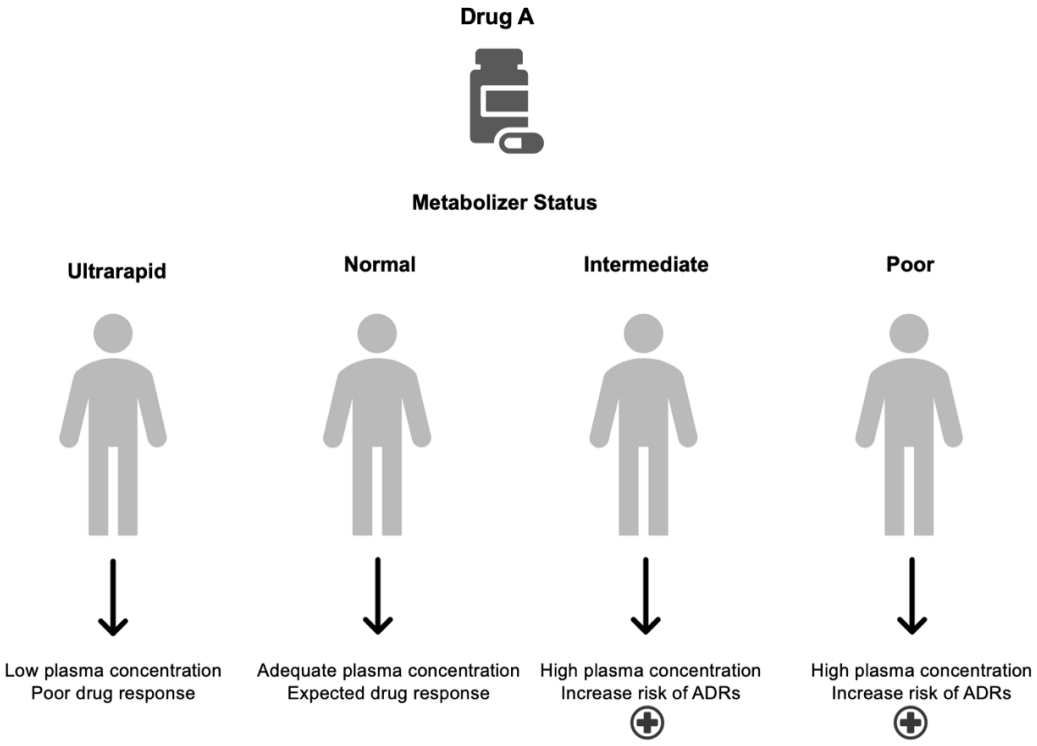

Figure 1 Metabolizer Status

For example, active drugs, which are immediately biologically available, may result in intermediate and poor metabolizers to experience ADRs due to high drug plasma concentration. An ultrarapid metabolizer taking the same active drug may experience poor drug response due to low drug plasma concertation. In the case of a prodrug, which is inactive until converted by CYP450 enzymes, intermediate and poor metabolizers may have no response to therapy, which

results from the inability to convert the drug into an active metabolite (Rautio et al., 2018; Weinshilboum et al., 2003).

2.1.3 FDA Approved Drugs with Pharmacogenomic Information in the Drug Label

The FDA's Table of Pharmacogenomic Biomarkers in Drug Labeling lists FDA approved drugs that contain pharmacogenomic information within the drug label (FDA Table of Pharmacogenomic Biomarkers in Drug Labeling, 2022). Per Title 21 of the Code of Federal Regulations, the FDA is obligated to include information on clinically significant ADRs (FDA Code of Federal Regulations Title 21, 2022). Specific actions are recommended for drug prescribers in some, but not all drug labels, such as stating genetic testing should be performed prior to prescription; the labeling sections in which pharmacogenomic information appears varies according to the implications of the biomarker (variant). The table below compares the current available CPIC guidelines and whether or not these drugs contain any pharmacogenomic information within the FDA drug label. Drugs that are bolded have the recommendation that patients receive pharmacogenomic testing prior to prescription on the drug label (Kapoor et al., 2016).

Table 2 Comparison of CPIC Guidelines and FDA Pharmacogenomic (PGx) Labeling

Drug or Drug Class	Gene(s)	FDA PGx Labeling
Abacavir	*HLA-B*	*Yes*
Allopurinol	*HLA-B*	*Yes*
Atazanavir	*UGT1A1*	*No*
Atomoxetine	*CYP2D6*	*Yes*
Carbamazepine	*HLA-B*	*Yes*

Codeine	*P4502D6*	*Yes*
Clopidogrel	*CYP2C19*	*Yes*
Efavirenz	*CYP2B6*	*Yes*
Ivacaftor	*CFTR*	*Yes*
Ondansetron	*CYP2D6*	*Yes*
Oxcarbazepine	*HLA-B*	*Yes*
Ondansetron	*CYP2D6*	*Yes*
Peginterferon-alpha-based regimens peginterferon alfa-2a peginterferon alfa-2b ribavirin	*IFNL3*	 *No* *Yes* *No*
Phenytoin	*CYP2C9* *HLA-B*	*No*
SSRIs citalopram escitalopram fluvoxamine paroxetine sertraline	*CYP2C19* *CYP2D6*	 *Yes* *Yes* *Yes* *Yes* *No*
Simvastatin	*SLCO1B1*	*No*
Tacrolimus	*CYP3A5*	*No*
Tamoxifen	*CYP2D6*	*Yes*
Thiopurines azathioprine mercaptopurine thioguanine	*NUDT15* *TPMT*	 *Yes* *Yes* *Yes*
Volatile anesthetic agents and succinylcholine	*CACNA1S* *RYR1*	

desflurane enflurane halothane isoflurane methoxyflurane sevoflurane succinylcholine		 *Yes* *Yes* *No* *Yes* *No* *Yes* *Yes*
Voriconazole	*CYP2C19*	*Yes*
Warfarin	*CYP2C9* *VKORC*	*Yes*

2.1.4 Examples of Pharmacogenomic Testing in Practice

The majority of FDA approved drugs that recommend pharmacogenomic testing within the drug label are anticancer agents and do not have available CPIC guidelines. These act to predict therapy response according to biomarker status, such as human epidermal growth factor receptor (Mallal et al., 2008). The screening of patients prior to prescription of abacavir (Ziagen) and ivacaftor (Kalydeco) are examples of routine pharmacogenomic testing in therapeutic areas other than oncology.

Abacavir is an anti-human immunodeficiency virus (HIV) drug that is one of several preferred combination regimens for HIV. Patients with the *HLA* gene variant *HLA-B*B7:01* are at an increased risk of a hypersensitivity reaction to abacavir and require alternative antiretroviral therapy. Death can occur within hours of administration of the drug and 5-8% of patients experience a hypersensitivity reaction within the first six weeks due to this high-risk variant. Symptoms include fever, rash, multiorgan failure, and anaphylaxis. The efficacy of *HLA-B*B7:01* screening is represented by a 100% negative predictive value and 47.9% positive predictive value.

(Mallal et al., 2008). The current CPIC guideline and FDA drug label are in agreement of recommending screening for the *HLA-B*B7:01* variant prior to prescription of abacavir for all individuals with HIV (Martin et al., 2014).

Treatment for cystic fibrosis varies according to the causative mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Ivacaftor is a drug specifically indicated for 38 *CFTR* variants. Screening for *CFTR* variants is warranted from the perspective of appropriate therapy selection; only patients with the mentioned variants have a high probability of response and are therefore eligible for ivacaftor treatment. In addition, from the perspective of cost, ivacaftor is expensive, exceeding $300,000 a year per patient. Screening also ensures that patients who are not eligible for ivacaftor treatment due to low likelihood of response can receive alternative therapy and supportive care (e.g. *F508del*). The current CPIC guideline and FDA drug label are in agreement of recommending screening for the *CFTR* variants prior to prescription of ivacaftor for all individuals with cystic fibrosis (Clancy et al., 2014).

2.2 Public Health and Pharmacogenomic Guidelines

The role of public health in the implementation of pharmacogenomic guidelines is extensive. This includes educating healthcare professionals and the public, developing tools for clinicians to apply guidelines in clinical practice, informing insurance companies of potential savings, and addressing barriers and inequities related to pharmacogenomic testing. Identifying guidelines that are acceptable for routine implementation, particularly for vulnerable populations, is essential to positively impact public health (Kapoor et al., 2016). Vulnerable populations include individuals with a chronic health condition(s), defined as a physical or mental condition that

persists longer than one year and requires continuous monitoring and treatment (Raghupathi et al., 2018). Among the diseases and conditions included in the CPIC guidelines, a large portion are related to chronic health conditions such as heart disease, cancer, autoimmune disease, and depression, all of which are significant to public health. Genetically informed drug prescribing may reduce the burden of chronic disease on the individual and the healthcare system.

In review of the CPIC pharmacogenomic guidelines, two guidelines were identified that provide dosage recommendations for drugs used to treat depression. These guidelines included two classes of antidepressants: tricyclic antidepressants (atypical agent) and selective serotonin reuptake inhibitors (SSRIs). SSRIs are used as a first line therapy for major depressive disorder (MDD) and anxiety disorders. The mechanism of SSRIs is to selectively increase the activity of serotonin by inhibiting its uptake (Preskorn, 1997; Xue et al., 2016). The monoamine hypothesis suggests that reduced neurotransmitter activity, including serotonin, is critical to the pathophysiology of MDD (Feighner et al., 1999). Recent studies suggest a continued increase in the prevalence of depressive disorders, especially for adolescents and young adults (Mojtabai et al., 2016). Given that SSRIs are prescribed as first line therapy for MDD and have established pharmacokinetics evidence, investigation of reported ADRs in the FAERS database is warranted to determine if the SSRI CPIC guideline, titled the CPIC Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of SSRIs, might act to prevent certain ADRs.

2.2.1 Major Depressive Disorder

Major depressive disorder (MDD) remains the leading cause of disability worldwide (Wang et al., 2017). Approximately 7% of the United States population is affected with this condition. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) states

the essential feature of a major depressive episode is a depressed mood or loss of interest or pleasure for at least two consecutive weeks. At least four additional symptoms are also requited for an individual to be diagnosed with MDD, including a change in sleep, appetite, or energy; decreased concentration and difficulty thinking or making decisions; or recurrent thoughts of death or suicide. These symptoms can present as mild, moderate, or severe.

The standard treatment for MDD is pharmacotherapy and psychotherapy (APA, 2019; Malhi et al., 2013). SSRIs are one of four classes of antidepressants; they are the most frequently prescribed class of antidepressant and typically used as a first line therapy based on their efficacy and tolerability (Anderson, 1998; Hicks et al., 2015). Practice guidelines for SSRIs recommend starting at the lowest suggested dose possible. It is not uncommon for patients to not respond to their initial prescription; this ADR is referred to as therapeutic failure or incomplete symptom remission (Malhi et al., 2013). Identifying a dose or alternative antidepressant that is efficacious is often challenging for patients; some studies suggest up to 50% of individuals with MDD will experience therapeutic failure with their initial SSRI dose (Barak et al., 2011). Thirty percent of individuals with MDD will experience treatment resistant depression, which is therapeutic failure after two or more antidepressants (Souery et al., 1999; Zhdanava et al., 2021).

A study that investigated emergency department visits for psychiatric medication ADRs determined that over approximately two years more than 25,000 patients were admitted to the emergency department for an ADR caused by an antidepressant (Hampton et al., 2014). Common reported ADRs for SSRIs include therapeutic failure, mood alteration, gastrointestinal distress (nausea and vomiting), sexual dysfunction, somnolence, and weight increase. ADRs are also associated with poor adherence and discontinuation of antidepressants, which can worsen depressive symptoms (Fabbri et al., 2020). Though the International Society of Psychiatric

Genetics recommends that pharmacogenomic testing should be performed for antidepressants, its recommendation is limited to patients with MDD who have already experienced therapeutic failure or an ADR after initiating treatment (ISPG, 2019). Because the efficacy of an antidepressant can take up to two months evaluate, this may result in the worsening of depressive symptoms (Erb et al., 2016). Given the available evidence, it is possible that increasing the use of pharmacogenomic testing for SSRIs may assist in identifying MDD patients who are at an increased risk of experiencing common ADRs and potentially improve patient outcomes.

2.2.2 Barriers to Implementation and Inequity

One of the largest barriers to implementing pharmacogenomic testing for antidepressants is the lack of knowledge among mental healthcare providers who prescribe antidepressants, such as psychiatrists and primary care physicians (Laplace et al., 2021). Several studies have determined low levels of competence and pharmacogenomic training for prescribing providers (Jameson et al., 2021). Additionally, the infrastructure and personnel to successfully implement pharmacogenomic testing is lacking. Ideally, a pharmacogenomic test consultation would be performed by a genetic counselor, however, due to the shortage of genetic counselors, this is not a scalable option at this time (Fabbri et al., 2020; Laplace et al., 2020). Cost and insurance coverage is also a concern for providers and patients. A pharmacogenomic test has an average cost of $2,000 and most private insurers are unlikely to cover pharmacogenomic testing for MDD (Fabbri et al., 2020). This may reflect the need to collect additional data on the benefits of pharmacogenomic guidelines when applied in a clinic setting overtime.

Inequities in genetic testing are well established in all areas, including pharmacogenomics. There is significant need diversify the participants in pharmacogenomic studies to ensure equal

utility of predicting drug response across racial and ethnic minority groups. Nearly 90% of the data used to inform pharmacogenomic research and pharmacogenomic guidelines are from individuals of European ancestry (Fabbri et al., 2020). Due to this lack of representation, racial and ethnic minorities are more likely to receive a variant of uncertain significance (Caswell-Jin et al., 2017). Multiple studies have also identified that racial and ethnic minorities are less likely to be offered genetic testing in all clinical settings, even when established guidelines are available (Ademuyiwa et al., 2021; Cragun et al., 2019).

2.2.3 CPIC Guideline for Selective Serotonin Reuptake Inhibitors

The CPIC guideline for SSRIs, titled CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of SSRIs, includes recommendations for five commonly prescribed SSRIs according to metabolizer status. These drugs are primarily metabolized by genes *CYP2D6* and *CYP2C19*. The recommendations for each drug, fluvoxamine (Luvox), paroxetine (Paxil), citalopram (Celexa), escitalopram (Lexapro), and sertraline (Zoloft), have been summarized below. Given that citalopram, escitalopram, and sertraline are commonly prescribed SSRIs and metabolized by the same gene, *CYP2C19*, this exploratory study will focus on these three drugs.

Table 3 Summary of SSRI CPIC Guideline

PAROXETINE	
***CYP2D6* Metabolizer Status**	**Therapeutic Recommendation**
Ultrarapid	Select alternative drug
Normal	Initiate recommended starting dose
Intermediate	Initiate recommended starting dose
Poor	Select alternative drug or

	Consider 50% reduction in starting dose
FLUVOXAMINE	
***CYP2D6* Metabolizer Status**	**Therapeutic Recommendation**
Ultrarapid	No recommendation (lack of evidence)
Normal	Initiate recommended starting dose
Intermediate	Initiate recommended starting dose
Poor	Consider 25-50% reduction in starting dose Or Select alternative drug
CITALOPRAM	
***CYP2C19* Metabolizer Status**	**Therapeutic Recommendation**
Ultrarapid	Select alternative drug
Normal	Initiate recommended starting dose
Intermediate	Initiate recommended starting dose
Poor	Consider 50% reduction in starting dose Or Select alternative drug
ESCITALOPRAM	
***CYP2C19* Metabolizer Status**	**Therapeutic Recommendation**
Ultrarapid	Select alternative drug
Normal	Initiate recommended starting dose
Intermediate	Initiate recommended starting dose
Poor	Consider 50% reduction in starting dose Or Select alternative drug
SERTRALINE	
***CYP2C19* Metabolizer Status**	**Therapeutic Recommendation**
Ultrarapid	Initiate recommended starting dose *Consider alternative drug if not responsive
Normal	Initiate recommended starting dose
Intermediate	Initiate recommended starting dose
Poor	Consider 50% reduction in starting dose Or

	Select alternative drug

3.0 Specific Aims

3.1 Specific Aims I: Published 2019 CPIC Guidelines

1. Assess the percentage of therapeutic areas for the 47 individual drugs within all CPIC guidelines and their associated gene role or function as of December 2019.
2. Assess the percentage of individual drugs within all CPIC guidelines that have a corresponding FDA drug label with pharmacogenomic information as of December 2019.

3.2 Specific Aims II: FAERS Reports for Citalopram, Escitalopram, and Sertraline

1. Assess the percentage of reporter types and percentage of serious ADR case reports between January 2018 and December 2019.
2. Assess the percentage of hospitalizations and estimated cost for serious ADRs between January 2018 and December 2019.
3. Assess the percentage of case reports by sex and determine the mean age of case reports between January 2018 and December 2019.
4. Assess the frequency of common ADRs that occurred between January 2018 and December 2019.

4.0 Methods

4.1 Description of Dataset

The FDA Adverse Event Reporting System (FAERS) was enacted in 1968 to detect ADRs post drug approval process. ADRs are voluntarily reported to FAERS by healthcare professionals, consumers, and drug manufacturers. Each case report is anonymous and has a unique case identification number; case report information includes the individual's age, sex, reason for drug use, type of adverse reaction, seriousness of the adverse reaction, reporter type, and outcome (hospitalization and death). The Center for Drug Evaluation and Research monitors this database and informs the FDA if a drug requires regulatory actions such as updating drug label information, contacting healthcare professionals, or re-evaluating the approval status of the drug to protect public health. The continued storage and analysis of reports has enabled the identification of adverse events that did not appear during the drug approval process (FDA Post-marketing Surveillance Programs, 2020). FAERS raw data is reported on a quarterly basis and available for download by the public for further analysis. Though this data is sourced from the FDA, this study is not representative of any opinion of the FDA.

4.2 Data Collection and Analysis

The 23 published guidelines were manually collected from the CPIC website and input into Microsoft Excel for coding and subsequent analysis in the Statistical Package for the Social

Sciences (SPSS). All 47 drugs and their associated genes were coded according to FDA recommendations (FDA Spectrum of Diseases/Conditions, 2020). This includes the therapeutic area of each drug (10 categories: infectious disease, neurology, pulmonary, oncology, cardiology, hematology, anesthesiology, psychiatry, immunology, and rheumatology) and the role or function of the 32 drug-associated genes appreciated in Table 2 (9 categories: anion transport, drug metabolism, immune system, ion transport, metabolite production, reduced nicotinamide adenine dinucleotide phosphate (NADPH production), pyrimidine metabolism, thiopurine metabolism, and vitamin K production). Coding was also performed to determine the presence or absence of pharmacogenomic information within the FDA drug labels.

Raw data files containing case reports made during January 2018 through December 2019 were downloaded from FAERS for citalopram, escitalopram, and sertraline; due to the public availability of this data, this study did not require Intuitional Review Board approval. These extensible markup language files (XMLs) were imported to Microsoft Excel. All case reports were included regardless of sex, reason for drug use, type of adverse reaction, seriousness of the adverse reaction, reporter type, and outcome. These files contain 18,530 total case reports and were exported to SPSS software for analysis. Additional analysis of these case reports was performed using Microsoft Excel to determine the frequency of common ADRs for each drug. Common ADRs were broken down into 8 categories: therapeutic failure, mood alteration or worsened depression, gastrointestinal distress, sexual dysfunction, somnolence or sleep disorder, weight increase, headache or migraine, and long QT syndrome. A set of phrases was input to detect the frequency of each category (24 phrases: therapeutic failure, ineffective, unresponsive, therapeutic response unexpected, therapeutic response decreased; depression, mood alteration; gastrointestinal distress, nausea, vomiting; sexual dysfunction, erectile dysfunction, arousal disorder; somnolence,

drowsiness, malaise, sleep disorder; weight gain, weight increase; headache, migraine; QT prolongation, long qt syndrome, electrocardiogram prolonged QT). All figures and tables were generated in Microsoft Excel and Microsoft Word.

4.3 Results

4.3.1 CPIC Therapeutic Areas and Gene Role or Function

The most common therapeutic areas identified in the CPIC guidelines were psychiatry (25.5%), oncology (21.3%), and infectious disease (17.0%). Results for all 10 therapeutic areas are illustrated in Figure 2. Fifty percent of the genes with a CPIC guideline have a role or function in drug metabolism, followed by 18.8% of genes with a role or function in immune system activity, appreciated in Figure 3.

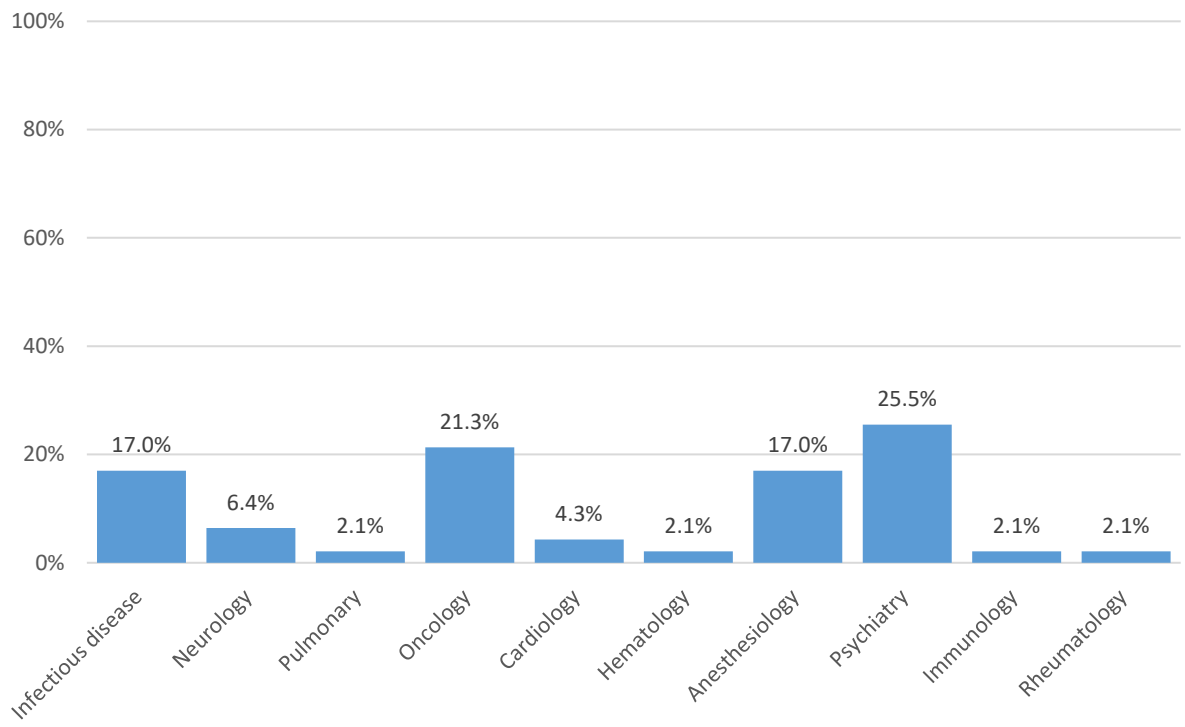

Figure 2 Theraputic Area

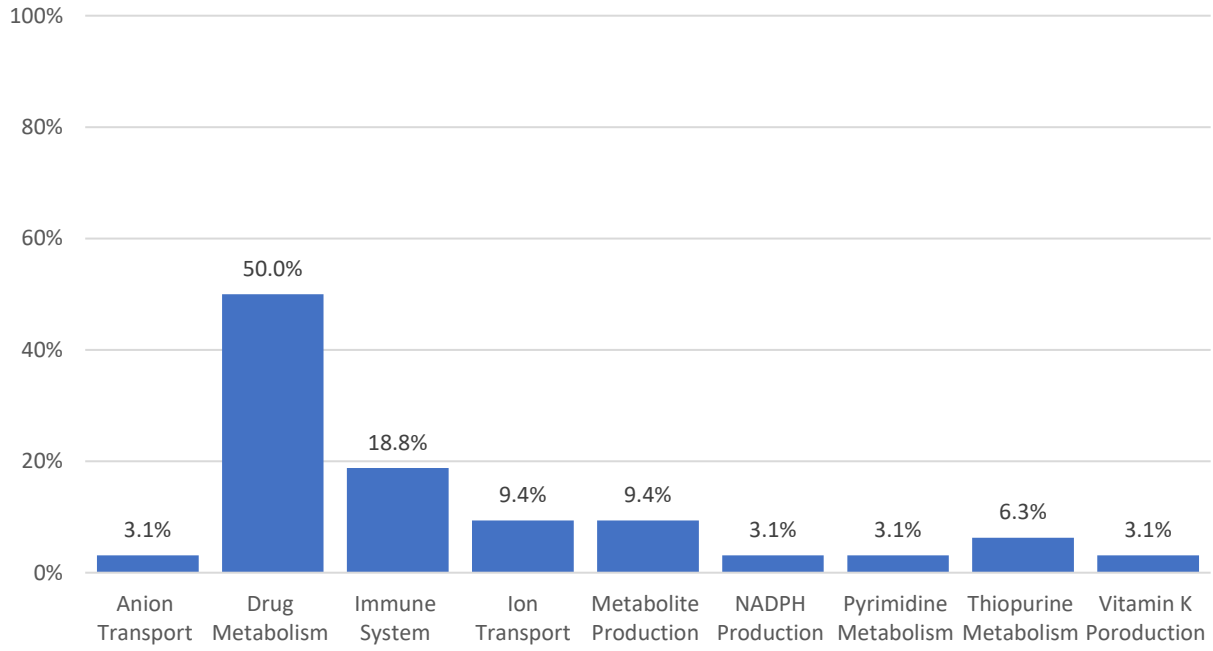

Figure 3 Gene Role or Function

4.3.2 Presence of Pharmacogenomic Information within FDA Labeling

Of the individual drugs within all CPIC guidelines analyzed, 74.5% were identified as having an FDA drug label with some pharmacogenomic information present (Figure 4). No specific therapeutic areas were found to be more or less likely to have pharmacogenomic information in the drug label.

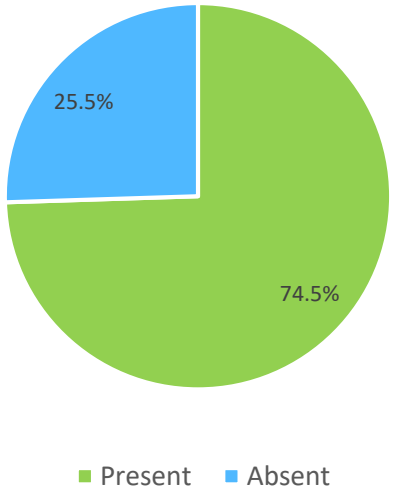

Figure 4 Presence of Pharmacogenomic information within FDA Labeling

4.3.3 FAERS Case Report Demographics by Sex and Age

The total number of case reports for each drug was identified as: citalopram 3,379, escitalopram 4,940, and sertraline 10,211. For all drugs, the majority of case reports were female (average of 56.4%), as seen in Figure 5. The mean age of all case reports was 53 years.

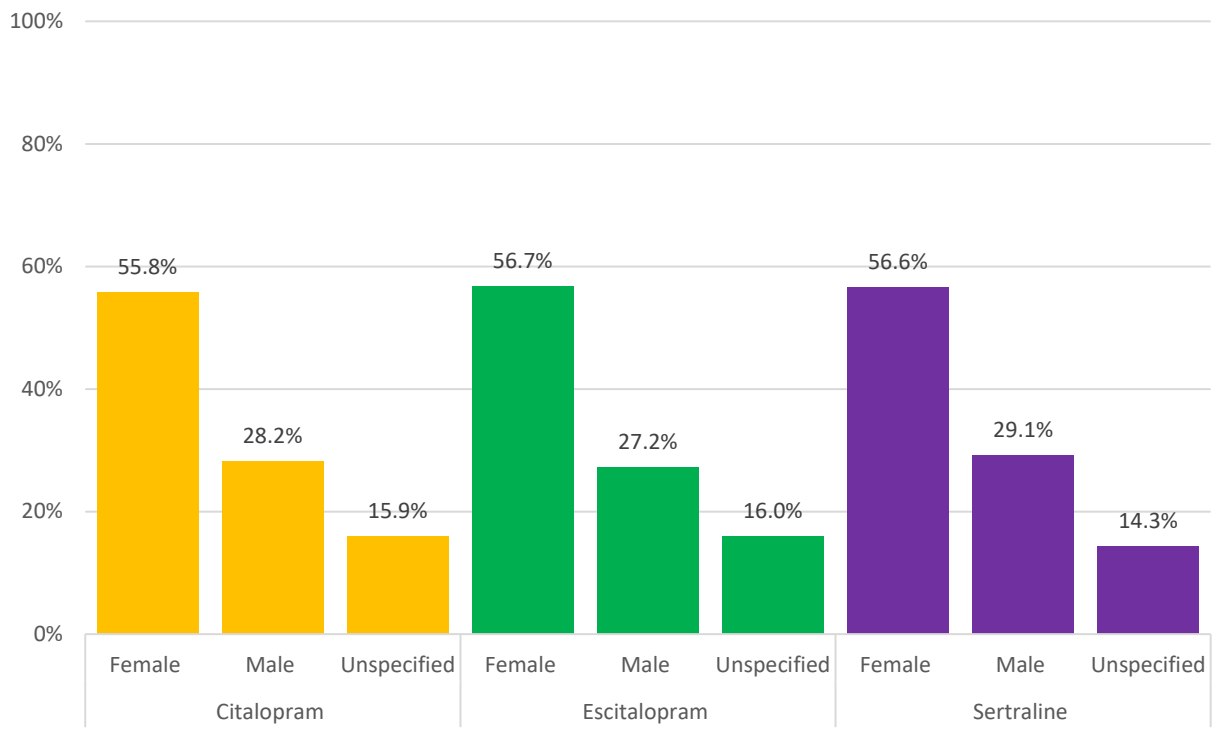

Figure 5 Case Reports by Sex

4.3.4 FAERS Reporter Type and Serious Adverse Drug Reactions

The majority of individuals reporting ADRs to the FAERS database were healthcare professionals, who reported 76.4% of all cases; consumers reported 22.5% of all cases. Nearly all cases were serious ADRs, an average of 84.9% for all three drugs; a serious ADR may indicate that these individuals required at minimum additional outpatient visits if not hospitalization. Reporter type and serious ADRs for each drug can be appreciated in Figure 6 and Figure 7.

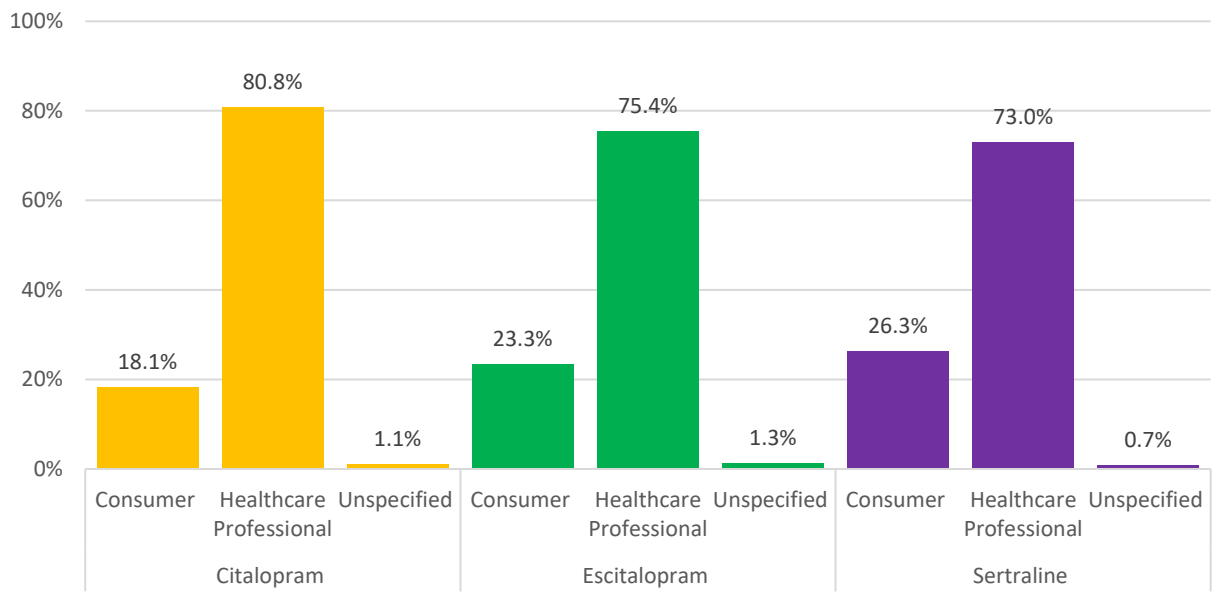

Figure 6 Case Reporter Type

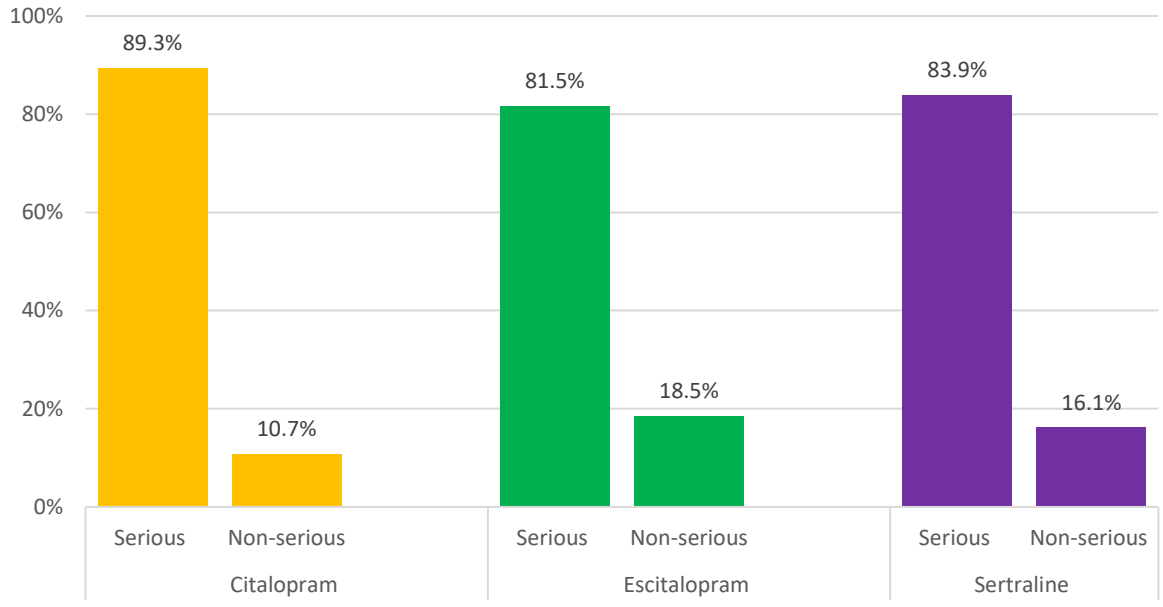

Figure 7 Serious Adverse Drug Reactions

4.3.5 Hospitalization, Death, and Cost

Of all cases, 26.2% required hospitalization. Escitalopram had the highest percentage of hospitalized cases at 28.6%. The average percent of reported deaths is 10.3%, with citalopram accounting for the highest percentage of deaths at 18.4%. Hospitalization and death for each drug can be appreciated in Figure 8.

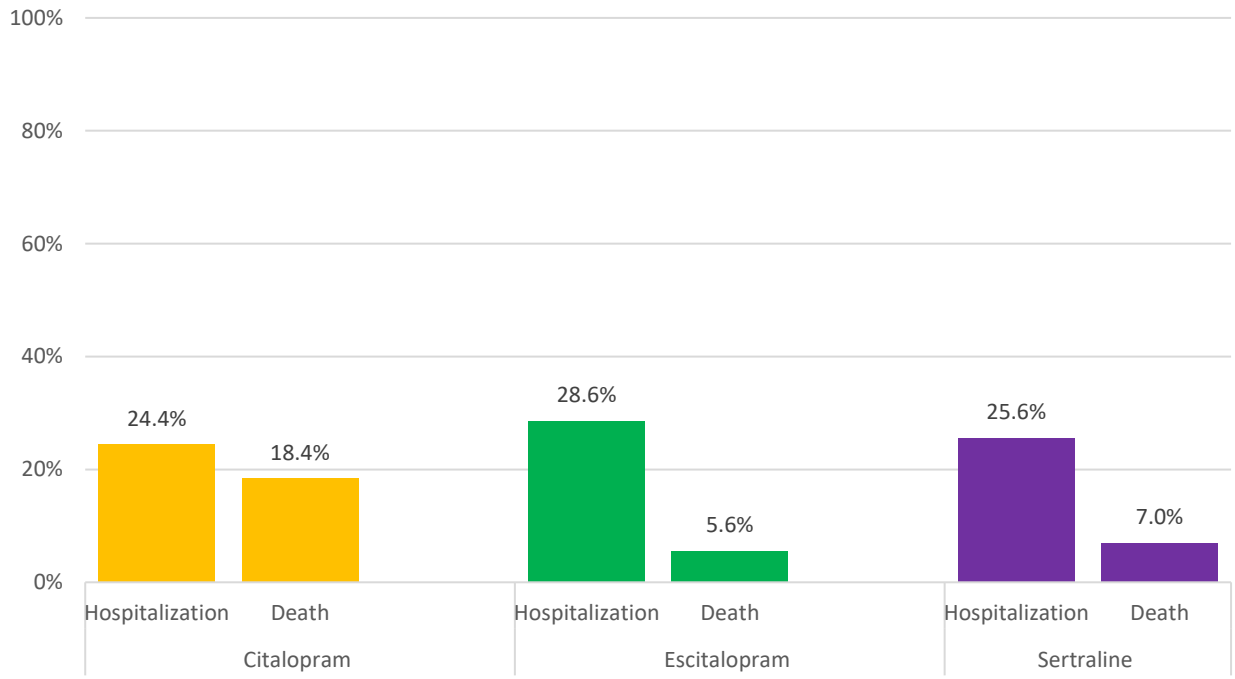

Figure 8 Hospitalization and Death

To estimate the cost of reported ADRs to the healthcare system, the number of serious ADRs for each drug was multiplied by $3,000, which is recognized as the average cost per serious ADR in the United States (Hug et al., 2012). The average estimated cost of serious ADRs for all three drugs between January 2018 and December 2019 is $46,848,000 or approximately $23,423,500 per year. Estimated costs of individual drugs can be seen in Table 4.

Table 4 Estimated Cost Per Year for Individual Drugs

Drug	Estimated Cost Per Year
Citalopram	$4,528,000
Escitalopram	$6,037,500
Sertraline	$12,858,000
Total: $23,423,500	

4.3.6 Frequency of Common Adverse Drug Reactions

The frequency of common ADRs for citalopram, escitalopram, and sertraline are provided in Table 5. Some of these ADRs are classified as serious ADRs as they might have resulted in additional outpatient visits or hospitalization. The ADRs with the highest frequency across all drugs include gastrointestinal distress, therapeutic failure, and somnolence or sleep disorder. These ADRs consist of 58.7% of all analyzed categories of common ADRs (therapeutic failure, mood alteration or worsened depression, gastrointestinal distress, sexual dysfunction, somnolence or sleep disorder, weight increase, headache or migraine, and long QT syndrome). Escitalopram had the highest proportion of common ADRs at 51.5%.

Table 5 Frequency of Common Adverse Drug Reactions between January 2018 and December 2019

CITALOPRAM	
ADR	**Frequency (n=1,481)**
Therapeutic Failure	297 (20.1%)
Mood Alteration	170 (11.5%)

or Worsened Depression	
Gastrointestinal Distress	354 (24.0%)
Sexual Dysfunction	60 (4.1%)
Somnolence or Sleep Disorder	186 (12.6%)
Weight Increase	101 (6.8%)
Headache or Migraine	159 (10.7%)
Long QT Syndrome	154 (10.4%)
ESCITALOPRAM	
ADR	**Frequency** **(n=2,543)**
Therapeutic Failure	542 (21.3%)
Mood Alteration or Worsened Depression	342 (13.5%)
Gastrointestinal Distress	459 (18.1%)
Sexual Dysfunction	92 (3.6%)
Somnolence or Sleep Disorder	471 (18.5%)
Weight Increase	99 (3.9%)

Headache or Migraine	232 (9.1%)
Long QT Syndrome	306 (12.0%)
SERTRALINE	
ADR	**Frequency (n=4,577)**
Therapeutic Failure	926 (20.2%)
Mood Alteration or Worsened Depression	687 (15.0%)
Gastrointestinal Distress	1094 (23.9%)
Sexual Dysfunction	165 (3.6%)
Somnolence or Sleep Disorder	722 (15.8%)
Weight Increase	241 (5.3%)
Headache or Migraine	499 (10.9%)
Long QT Syndrome	243 (5.3%)
ALL THREE DRUGS	
ADR	**Frequency (n=8,601)**
Therapeutic Failure	1,765 (20.5%)

Mood Alteration or Worsened Depression	1,199 (13.9%)
Gastrointestinal Distress	1,907 (22.2%)
Sexual Dysfunction	317 (3.7%)
Somnolence or Sleep Disorder	1,379 (16.0%)
Weight Increase	441 (5.1%)
Headache or Migraine	890 (10.4%)
Long QT Syndrome	703 (8.2%)

5.0 Discussion

5.1 Published 2019 CPIC Guidelines

Analysis of the available 2019 CPIC guidelines identified that the therapeutic areas of psychiatry, oncology, and infectious disease comprised 80.8% of all guidelines. Due to the mechanism of these drugs and the well-known ADRs associated with them, this was not surprising (Relling et al., 2021). Though nearly 75% of CPIC drugs were identified to have some mention of pharmacogenomic information within the FDA drug label, there was no mention of the availability of genetic testing or pharmacogenomic guidelines for any of the SSRIs analyzed in this study. Though both citalopram and escitalopram drug labels include information about drug metabolism and *CYP2C19,* only citalopram recommends specific dosage for poor metabolizers, without appropriate guidance to determine a patient's metabolizer status. Currently, sertraline does not have pharmacogenomic information in its FDA labeling (FDA Table of Pharmacogenomic Biomarkers in Drug Labeling, 2022). Given the availability of genetic testing and CPIC pharmacogenomic guidelines for SSRIs, the consideration of more detailed pharmacogenomic information and guidance within the FDA drug labels is warranted.

5.2 FAERS Case Reports for Citalopram, Escitalopram, and Sertraline

5.2.1 Demographics and Reporter Type

To our knowledge, this study is the first to investigate FAERS case reports for citalopram, escitalopram, and sertraline. Of all case reports, 56.4% were female, which is consistent with previous research that suggests cisgender females are more likely to experience an ADR across all drug classes than cisgender males (Zucker et al., 2020). The mean age of case reports, age 53, aligns with previous studies that show an individual's risk of experiencing an ADR increases after age 50 (Aronson et al., 2005; Evans et al., 2003). Healthcare professionals were most likely to report ADRs to FAERS and account for 76.4% of all case reporters. Contextualizing this finding with the low health literacy levels of the United States, it appears that individuals who experience an ADR are likely seeking the advice of their healthcare provider, who subsequently reports the ADR to FAERS.

5.2.2 Serious ADRs and Associated Outcomes

The average percent of serious ADRs was 84.5% for all three drugs. This high percentage may be a result of individuals with a serious ADR being more likely to seek medical care, resulting in their healthcare provider reporting the ADR. An average of 26.2% of serious ADRs required hospitalization and 10.3% resulted in death, though the cause of death was not specified. Interestingly, citalopram was identified to have the highest proportion of serious ADRs accounting for 89.5% of its total case reports, despite being the only drug to include recommendations for

drug dosage based on poor metabolizer status. This is especially concerning with citalopram's percent of reported deaths of 18.4%.

The personal and economic impacts of serious ADRs is a significant concern. These safety findings support the need for continued investigation of pharmacogenomic testing for SSRIs in a clinical setting. Evaluation in a clinical setting is necessary to prove that pharmacogenomic testing can prevent the number of serious ADRs for SSRIs, which have significant impacts to the individual prescribed them, including psychosocial distress, financial burden, and physical harm. Impacts to the healthcare system are notable in the estimated cost of the serious ADRs identified in this study. The calculations in this study estimate the yearly cost of serious ADRs for citalopram, escitalopram, and sertraline is approximately $23.4 million. This calculation is certainly less than the actual yearly cost, as ADRs for all pharmaceutical products are historically underreported and there is no requirement for healthcare providers or consumers to report them (Gahr et al., 2017; Hazell et al., 2006).

5.2.3 Frequency of Common ADRs

This study identified the most frequently reported common ADRs for citalopram, escitalopram, and sertraline were gastrointestinal distress, therapeutic failure, and somnolence or sleep disorder. Again, I hypothesize that these and other common ADRs for said SSRIs may be prevented using pharmacogenomic testing prior to treatment initiation. Regarding therapeutic failure, approximately 20% of case reports indicated therapeutic failure. It is possible that pharmacogenomic testing might have prevented this ADR through appropriate drug dosage or the prescription of an alternative drug. From the perspective of cost, pharmacogenomic testing for MDD has been shown to be more cost effective than repeated outpatient visits for therapeutic

failure. A recent study by Maciel et. al, which focused on the economic impact of pharmacogenomic testing for MDD using a cost analysis model, determined an estimated savings of $3,962 annually per patient (Maciel et al., 2018).

Together, these results suggest that there is a need for more informed drug prescribing for MDD, particularly for citalopram, escitalopram, and sertraline. The utilization of pharmacogenomic testing for SSRIs might improve patient outcomes, increase adherence, and reduce costs to the healthcare system through more precise drug prescribing. As mentioned, ADRs are underreported in all drug classes (Gahr et al., 2017; Hazell et al., 2006); efforts to increase reporting of ADRs to FAERS and other public databases is essential to constructing, evaluating, and implementing strategies to prevent ADRs known to be caused by high-risk variants. Additionally, to achieve the potential of pharmacogenomic testing, prescribing providers must be made aware of pharmacogenomic testing, when it is indicated, and how interpret test results in the absence of a genetic counselor. These complicating factors require attention to provide scalable solutions. Integrative software that can indicate when pharmacogenomic testing is available for SSRIs, pharmacogenomic test results that are more easily interpretable by non-genetics providers, and increased pharmacogenomic information in drug labeling should be considered. Approaches to increase clinical application and awareness might include electronic alerts for healthcare professionals when prescribing drugs with an actionable variant or when reporting an ADR for drugs that have an actionable variant. Finally, action from regulatory bodies, professional organizations, and public health professionals is critical to successfully implement pharmacogenomic testing into the clinical setting for MDD.

5.3 Future Directions

Future directions include investigating FAERS case reports for SSRIs on a larger scale and within a clinical setting. Public health initiatives related to this effort are also of interest, such as creating tools to increase prescribing provider awareness and understanding of pharmacogenomic testing for MDD and available resources. Electronic distribution of tools like pharmacogenomic flowsheets for antidepressants could benefit a wide spectrum of providers including psychiatrists, primary care physicians, and obstetrician-gynecologists, all of which routinely prescribe antidepressants (Mark et al., 2009). Additionally, a similar approach could be applied to increase awareness and understanding among the general public to assist patients in self advocating for personalized therapy. Assessing the general public's perception of pharmacogenomic testing for antidepressants may better inform these efforts.

5.4 Study Limitations

The data used to inform this study results has several limitations due to the nature of the FAERS. First, though this public database is one of the largest sources of ADR data, it is not an account of all reported ADRs. Further, this study was limited to case reports between January 2018 and December 2019, and there is no definitive method to determine whether each case report is indeed a true ADR. Duplicate case reports, human error, and missing information are also limitations of this dataset; to reduce this occurrence, the raw data collected from FAERS was manually reviewed to avoid the inclusion of duplicate reports. Bias from the reporter should also be considered in completing the case reports that were used in this study, this may include

exempting information or including information in the case report that is not accurate to the patient experience. Additionally, since there is no genotyping information for this study population, there is not a definitive method to determine which reported ADRs might have been caused by a genetic predisposition.

6.0 Conclusion

The goal of this study was to better understand which therapeutic areas might be underutilizing pharmacogenomic guidelines and how it may be affecting public health and healthcare costs. Overall, this study determined that though there is pharmacogenomic information available on drug labels across all therapeutic areas, it is lacking in detail and actionability, which is further complicated by reduced awareness and understanding of prescribing providers. When analyzing the individual drugs within CPIC guidelines, psychiatry was identified as the most frequent therapeutic area. Further, most of these psychiatric drugs are prescribed to treat MDD, a significant public health concern affecting 7% of the United States population. To our knowledge, this study is the first to investigate FAERS case reports for first line therapies for MDD. This already vulnerable population continues to face undue morbidities as a result of drugs that are intended to improve their condition. It is possible that genetically informed drug prescribing can prevent morbidities that are caused by ADRs, like the ones analyzed in this study. Although additional research is necessary, such as evaluation in a clinical setting, the preliminary data from this study indicates that there might be value in implementing pharmacogenomic guidelines for first line SSRIs to prevent common and serious ADRs by identifying high-risk variants. Though it is clear that pharmacogenomic-based personalized medicine can improve public health and reduce healthcare costs, in order to achieve its full potential, the field of public health must take an active role in evaluating its utility and educating healthcare professionals and the general public.

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