mhc MENTAL HEALTH CLINICIAN

ORIGINAL RESEARCH Open Access

Impact of sex on antidepressant discontinuation in groups of similar cytochrome P450 phenotypes

Dylan L. Kosaski, PharmD[1]; Kristin C. Cole[2]; Jessica A. Wright, PharmD[3]; Razan M. El Melik, PharmD[4]; Simon Kung, MD[5]; Wayne T. Nicholson, MD, PharmD[6]; Jonathan G. Leung, PharmD[7]

How to cite: Kosaski DL, Cole KC, Wright JA, El Melik RM, Kung S, Nicholson WT, Leung JG. Impact of sex on antidepressant discontinuation in groups of similar cytochrome P450 phenotypes. Ment Health Clin [Internet]. 2023;13(6):303-310. DOI: 10.9740/mhc.2023.12.303.

Submitted for Publication: March 28, 2023; **Accepted for Publication:** September 25, 2023

Abstract

Introduction: Although there are studies assessing reasons for antidepressant discontinuation, little is known about the impact of sex differences or cytochrome P450 phenotypes. Our objective is to assess discontinuation rates between males and females and whether CYP450 phenotype influences discontinuation.

Methods: This is a retrospective review of patients previously enrolled in the Right Drug, Right Dose, Right Time: Using Genomic Data to Individualize Treatment database with major depressive disorder. Patients were evaluated for antidepressants trialed between January 1, 2009, and September 30, 2019. Survival analyses with competing risks were used to analyze discontinuation reasons. A Kaplan-Meier estimation method was used to assess the time to discontinuation and discontinuation rates. Analyses were also completed to assess discontinuation between men and women by phenotypic groups. All tests were two-sided, and p-values $\leq .05$ were considered statistically significant.

Results: There were 620 antidepressant discontinuation events discovered from 1015 antidepressant trials included. Overall, the median time to discontinuation for males was 2.6 years and 1.9 years for females (hazard ratio [HR] 0.97 [95% confidence interval (CI): 0.80, 1.19], $p = .77$). The risk of discontinuation was not different between males and females in any of the phenotype groups, which was consistent in the multivariable analyses. Concomitant use of medications that inhibited or induced antidepressant metabolism increased the overall risk of discontinuation (HR 1.45, 95% CI [1.06, 1.99], $p = .020$) in a time-dependent analysis.

Discussion: We did not detect a significant difference in risk of antidepressant discontinuation rates between males and females even when accounting for cytochrome P450 phenotype. Future studies should account for whether medications that inhibit or induce antidepressant metabolism may be a crucial factor in antidepressant discontinuation.

Keywords: antidepressants, depression, drug interactions, pharmacogenomics, pharmacokinetics, cytochrome P450, sex, gender

[1] Pharmacist, Department of Pharmacy, Mayo Clinic, Rochester, Minnesota, ORCID: https://orcid.org/0000-0002-2036-0965; [2] Statistician, Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota, ORCID: https://orcid.org/0000-0002-8783-0191; [3] Pharmacist, Department of Pharmacy, Mayo Clinic, Rochester, Minnesota, ORCID: https://orcid.org/0000-0001-9659-4875; [4] Pharmacist, Department of Pharmacy, Mayo Clinic, Rochester, Minnesota, ORCID: https://orcid.org/0000-0003-0970-8374; [5] Psychiatrist, Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota, ORCID: https://orcid.org/0000-0002-2959-8312; [6] Physician, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota, ORCID: https://orcid.org/0000-0002-3418-4253; [7] (Corresponding author) Pharmacist, Department of Pharmacy, Mayo Clinic, Rochester, Minnesota, leung.jonathan@Mayo.edu, ORCID: https://orcid.org/0000-0003-3836-9375

Disclosures: JGL has spoken/consulted (unpaid) for Saladax Biomedical. None of the other authors have any conflicts of interest to disclose.

Introduction

According to the World Health Organization, MDD is a leading cause of disability and estimated to affect 280

million people worldwide.[1] MDD effects an estimated 7.1% of all U.S. adults with half receiving medication treatment.[2] A 2021 study reported that the economic burden of MDD from unemployment, lost productivity, and health care in the United States exceeded $90 billion.[2] Due to the high prevalence and economic impact of MDD, understanding factors that negatively impact the success of pharmacotherapy is crucial as only 30% to 40% of patients achieve remission after a treatment trial.[3] This includes understanding genetic factors such as sex, pharmacodynamic genetic polymorphisms, and pharmacokinetic genetic polymorphisms. Prior reports suggest that females may experience greater antidepressant-related adverse drug events but that treatment response may not differ based on sex.[4–8] Whereas pharmacokinetic parameters are known to be different between males and females, less is known about the influence of CYP450 phenotype on antidepressant discontinuation between males and females.

Methods

The Right Drug, Right Dose, Right Time: Using Data to Individualize Treatment (RIGHT10K) database is a research database containing Cytochrome P450 (CYP450) phenotypes for more than 10,000 patients.[9] In this study, the coding regions of each pharmacogene were sequenced. Translation from genotype to phenotype was performed by the clinical pharmacogenomics laboratory using their standard processes, including PharmVar allele definitions, Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, and the American College of Medical Genetics and Genomics Guidelines for Variant Interpretation with modifications as described in prior publications.[10–12] The data from subjects recruited into phase 2 of the RIGHT10K study were available for secondary analysis following approval from the Mayo Clinic institutional review board. Using the RIGHT10K database, a retrospective study was conducted to assess discontinuation rates between males and females and whether CYP450 phenotype influenced discontinuation.

Patients with a diagnosis of MDD, aged 18 and older, who consented to research and had pharmacogenomics results through the Mayo-Baylor RIGHT10K study database were included if they started a new antidepressant of interest between January 2009 and September 2019.[9] Antidepressant trials started prior to January 2009, patients with a history of liver or bone marrow transplant, and those who did not consent to research were excluded. Patients were categorized into 1 of 3 groups based on phenotypic data with respect to the major metabolism pathways of their prescribed antidepressant. This included those categorized as "fast," combining phenotypes of normal to ultrarapid, rapid, rapid to ultrarapid, and ultrarapid; "middle," including phenotypes of intermediate to rapid, intermediate, intermediate to normal, and normal; and "slow" with phenotypes of poor, poor to intermediate, and poor to normal. Drug-gene pairings were based on known CYP450 routes of metabolism with relevance to pharmacogenomic testing, FDA-approved prescribing information, and available pharmacogenomic-based medication recommendations via the CPIC or WebPharmGKB.[13,14] Drug-gene pairs were reviewed and agreed upon by authors WTN, JW, and RE (Table 1).

For the primary analysis, information regarding antidepressant initiation and discontinuation dates were collected via chart review along with reason for discontinuation. Patients with more than 1 antidepressant trial were included. Information on maximum dose achieved was collected and standardized to sertraline based on the World Health Organization defined daily dose index. Other data elements collected included patient age, race and ethnicity as reported within the electronic health record, comorbidities based on a calculated Charlson comorbidity index (CCI), and concomitant medications known to be moderate or strong CYP450 inhibitors and inducers based on the Drug Interactions Flockhart™ table.[15]

Statistical Analysis

The second phase of the Mayo-Baylor RIGHT10K Study database had recruited 10 077 participants with an estimated 10% on an antidepressant for depression. Of those on an antidepressant for MDD, we expected 60% to have a discontinuation. Thus, with an expected 605 discontinuations with a two-sided test and an alpha of 0.05, we would have 80% power to be able to detect a hazard ratio (HR) between males and females of 1.5 or more.

Baseline characteristics were summarized using mean (SD) for continuous data, whereas frequencies and percentages were used for categorical data. Characteristics were compared between males and females (the reference group) using generalized estimating equations to account for antidepressant retrials in the same patient. Cox proportional hazards modeling with a robust variance to account for antidepressant retrials in the same patient was used to evaluate the possible effect of covariates on time to discontinuation. Analyses were also stratified by drug phenotypic groups. Survival analyses with competing risks were used to analyze the influence of different discontinuation reasons. A Kaplan-Meier product limit estimation method was used to assess the median time to medication discontinuation and discontinuation rates. All tests were two-sided, and p-values $\leq .05$ were considered statistically significant. All analyses were performed using SAS version 9.4 software (SAS Institute, Inc.; Cary, NC) and R version 3.6.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

In the Mayo-Baylor RIGHT10K study database, 1750 patients had a diagnosis of MDD, accounting for 3821 unique patient

TABLE 1: Baseline characteristics based on individual trials

	Female ($n = 758$)	Male ($n = 257$)	Total ($n = 1015$)	p value
Age, mean (SD)	52.4 (16.1)	56.4 (16.9)	53.4 (16.4)	.047
Race, *n* (%)				.054
White	748 (98.7)	255 (99.2)	1003 (98.8)	
African	0	2 (0.8)	2 (0.2)	
American Indian/Alaskan Native	6 (0.8)	0	6 (0.6)	
Asian	2 (0.3)	0	2 (0.2)	
Unknown/not disclosed	2 (0.3)	0	2 (0.2)	
Ethnicity, *n* (%)				.15
Not Hispanic or Latino	737 (97.2)	255 (99.2)	992 (97.7)	
Hispanic or Latino	7 (0.9)	0	7 (0.7)	
Unknown/not disclosed	14 (1.8)	2 (0.8)	16 (1.6)	
Charlson comorbidity index, median (IQR)	2 (1, 3)	2 (1, 4)	2 (1, 3)	.46
Phenotype category without phenotypic conversion, *n* (%)				.039
Fast	193 (25.5)	89 (34.6)	282 (27.8)	
Middle	528 (69.7)	156 (60.7)	684 (67.4)	
Slow	37 (4.9)	12 (4.7)	49 (4.8)	
Maximum dose per day achieved, median (IQR)	120 (40, 200)	80 (40, 200)	120 (40, 200)	.12
Antidepressant (target gene), *n* (%)				
Sertraline (CYP450 2C19)	170 (22.4)	57 (22.2)	227 (22.4)	
Citalopram (CYP450 2C19, 3A4)	134 (17.7)	44 (17.1)	178 (17.5)	
Venlafaxine (CYP450 2D6)	101 (13.3)	22 (8.6)	123 (12.1)	
Fluoxetine (CYP450 2D6)	100 (13.2)	21 (8.2)	121 (11.9)	
Duloxetine (CYP450 1A2)	81 (10.7)	33 (12.8)	114 (11.2)	
Escitalopram (CYP450 2C19, 3A4)	82 (10.8)	28 (10.9)	110 (10.8)	
Mirtazapine (CYP450 2D6, 1A2, 3A4)	47 (6.2)	32 (12.5)	79 (7.8)	
Nortriptyline (CYP450 2D6)	22 (2.9)	14 (5.4)	36 (3.5)	
Paroxetine (CYP450 2D6)	11 (1.5)	5 (1.9)	16 (1.6)	
Amitriptyline (CYP450 2C19, 2D6)	7 (0.9)	1 (0.4)	8 (0.8)	
Vortioxetine (CYP450 2D6, 2C19, 3A4)	2 (0.3)	0	2 (0.2)	
Imipramine (CYP450 2D6)	1 (0.1)	0	1 (0.1)	

IQR = interquartile range.

and antidepressant combinations for these patients. From a random sample of 1599 antidepressant trials, 584 patient trials were excluded after chart review due to having a start date outside of the study period or unknown discontinuation dates. Of the remaining 1015 antidepressant trials included in the analysis, there were 620 discontinuation events and 395 trials without discontinuation. Baseline characteristics were similar for males and females except for age, which may not be clinically significant (56.4 ± 16.9 vs 52.4 ± 16.1 years, $p = .047$), and the greater distribution of male patients in the fast phenotypic category without consideration for phenotypic conversion than females (Table 1). The genotype information used to characterize phenotypes in the RIGHT10K study group and corresponding phenotypic category for this study (i.e., fast, middle, slow) is provided in Table 2.

Overall, the median time to discontinuation for males was 2.6 years and 1.9 years for females. A survival analysis showed no difference in discontinuation rates between males and females, (HR 0.97 [95% confidence interval (CI): 0.79, 1.19], $p = .77$). The most common cause of antidepressant discontinuation was due to adverse effects, which accounted for 51.5% of all discontinuation events (Table 3). Based on median time to discontinuation, we analyzed intervals of 2 and 4 years from the time of antidepressant trial start, which also revealed no significant sex-based findings. The antidepressant discontinuation rate for males and females at 2 years was 45.7% and 50.9%, respectively (HR 0.90, 95% CI [0.74, 1.13], $p = .36$). The antidepressant discontinuation rate for males and females at 4 years was 57.2% and 59.0%, respectively (HR 0.94, 95% CI [0.76, 1.17], $p = .59$). There was also no difference between males and females when stratified by phenotypic group (fast phenotype: HR 1.09, 95% CI [0.79,1.50]; middle phenotype: HR 0.89, 95% CI [0.70, 1.12]; slow phenotype: HR 1.26, 95% CI [0.52, 3.02]).

In a second analysis, middle phenotypes (ie, reference) group, discontinuation events for patients assigned to the fast or slow group were not found to be at increased risk of discontinuation (Table 4). Use of medications that inhibit or induce the associated antidepressant metabolism increased overall risk of discontinuation (HR 1.45, 95% CI [1.06, 1.99], $p = .020$) in a time-dependent analysis. In total there were 121 antidepressant trials in which a concomitant interacting medication was identified, and 100 of these trials were associated with discontinuation. In review of these specific trials,

TABLE 2: Representative genotypes of individual patients

CYP450 Enzyme	Fast Group (Normal to Ultrarapid, Rapid, Rapid to Ultrarapid, and Ultrarapid)[a]	Middle Group (Intermediate to Rapid, Intermediate, Intermediate to Normal, and Normal)[a]	Slow Group (Poor, Poor to Intermediate, and Poor to Normal)[a]
CYP1A2, *N* = (genotypes)	*N* = 529 (*1/*1F; *1F/*1F)	*N* = 47 (*1/*6; *1/*1K; *1F/*1K; *1F/*6)	*N* = 0 (–)
CYP2C19, *N* = (genotypes)	*N* = 179 (*1/*17; *17/*17)	*N* = 376 (*1/*1; *1/*2; *1/*8)	*N* = 21 (*2/*2; *2/*3)
CYP2D6, *N* = (genotypes)	*N* = 12 (*1/*2Ax2; *1x2/*2A; *1x2/*41; *2A/*2Ax2; *2Ax3/*9; *1/*1x2)	*N* = 476 (*1/*1; *1/*15; *1/*3; *1/*4; *1/*4N+*4; *1/*4x2; *1/*5; *1/*6; *1/*68+*4; *1/*68xN+*4; *10/*17; *10/*41; *13+*2A/*5; *2A/*3; *2A/*4; *2A/*4N+*4; *2A/*4x2; *2A/*5; *2A/*68+*4; *3/*35A; *36+*10/*41; *4/*35A; *41/*41; *5/*35A; *6/*35A; *68+*4/*33; *68+*4/*35A; *9/*41; *9/*9; *1/*10; *1/*2; *1/*22; *1/*28; *1/*36+*10; *1/*41; *1/*59; *1/*9; *22/*35A; *28/*35A; *2A/*10; *2A/*17; *2A/*22; *2A/*28; *2A/*2A; *2A/*41; *2A/*9; *2Ax2/*3; *2Ax2/*4; *2Ax2/*68+*4; *33/*41; *35A/*41; *1/*13+*2A; *1/*2A; *1/*33; *1/*35A; *1x2/*4; *1x2/*4N+*4; *1x2/*68+*4; *2A/*33; *2A/*35A; *35A/*35A)	*N* = 88 (*3/*4; *3/*68+*4; *4/*11; *4/*4; *4/*4N+*4; *4/*5; *4/*6; *4/*68+*4; *4/*68x2+*4; *4N+*4/*5; *68+*4/*68+*4; *3/*41; *3/*9; *4/*41; *4/*9; *4N+*4/*41; *5/*22; *5/*41; *5/*9; *68+*4/*22; *68+*4/*28; *68+*4/*41; *68+*4/*59; *68+*4/*9; *68x2+*4/*41)
CYP3A4, *N* = (genotypes)	*N* = 0 (–)	*N* = 576 (*1/*20; *1/*8; *22/*22; *1/*22)	*N* = 0 (–)

[a]Rare variants, not shown in this table, were classified using the ACMG Guidelines for Variant Interpretation with modifications. Variants of uncertain significance (VUS) were considered to have a potential range of activity (eg, if the patient was heterozygous for only a VUS, the phenotype was reported as "intermediate to normal metabolizer" to reflect the uncertainty; similarly, a patient heterozygous for a known nonfunctional star allele and heterozygous for a VUS for which the phase was unknown was reported as a "poor to intermediate metabolizer").

reasons for discontinuation included adverse event ($n = 59$), patient-perceived ineffectiveness ($n = 27$), unknown ($n = 10$), or felt not to be needed ($n = 4$). For every 10 years older a patient was, there was a 7% decreased likelihood of discontinuation. There was no significant difference between comorbidities based on the CCI. In multivariable Cox models, based on phenotype category, the risk of discontinuation events with inhibitor/inducer use was statistically significant for patients in the middle and slow phenotype groups, but not fast phenotype group (Table 5). Age remained significant for the fast and middle phenotype groups, whereas CCI scores lost significance in relevant models. Additionally, when included, the multivariable Cox models did not show sex significant for any of the phenotype groups.

Discussion

This study of 1015 antidepressant trials for MDD compared antidepressant discontinuation events for males and females and considering known CYP450 phenotypes. There

TABLE 3: Rates and cause of discontinuation

	Female ($n = 758$)	Male ($n = 257$)	Total ($n = 1015$)
Discontinuation, *n*			
Yes	466	154	620
No	292	103	395
Reason, *n* (%)			
Adverse effects	243 (52.1)	76 (49.4)	319 (51.5)
Felt it wasn't needed	59 (12.7)	13 (8.4)	72 (11.6)
Patient-perceived ineffectiveness	87 (18.7)	43 (27.9)	130 (21.0)
Other	16 (3.4)	4 (2.6)	20 (3.2)
Unknown	61 (13.1)	18 (11.7)	79 (12.7)

TABLE 4: Univariate analysis: antidepressant discontinuation by age, phenotype category, sex, and inhibitor/inducer use

	Overall		0 to 2 years		0 to 4 years	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age (per decade)	0.93 (0.88, 0.98)	.006[a]	0.93 (0.87, 0.99)	.014[a]	0.93 (0.88, 0.98)	.007[a]
Phenotype						
Fast phenotype group	0.94 (0.79, 1.12)	.47	0.90 (0.74, 1.10)	.31	0.90 (0.75, 1.09)	.28
Middle phenotype group	Reference		Reference		Reference	
Slow phenotype group	0.77 (0.51, 1.16)	.22	0.77 (0.47, 1.26)	.29	0.71 (0.44, 1.13)	.15
Sex (M vs F)	0.97 (0.79, 1.19)	.77	0.90 (0.74, 1.13)	.36	0.94 (0.76, 1.17)	.59
Charlson comorbidity index (per 1 point)	1.02 (0.99, 1.05)	.22	1.02 (0.98, 1.05)	.32	1.02 (0.99, 1.05)	.27
Inhibitor/inducer	1.45 (1.06, 1.99)	.020*	1.35 (0.98, 1.85)	.065	1.36 (0.99, 1.87)	.058

[a]*p*-value < .05.

was not a greater risk of discontinuation between males and females although females numerically discontinued antidepressants on average 1 year before males (1.9 vs 2.6 years). This was also true when accounting for P450 phenotype. When factoring the inclusion of inhibitors and inducers, the risk of antidepressant discontinuation increased for both males and females when antidepressants were taken concomitantly. This has broader implications in that drug-drug interactions, especially in the slow and middle phenotype categories prior to any phenotypic conversion, is an important consideration for the risk of antidepressant discontinuation. Therefore, a fast phenotype prior to any phenotypic conversion may be a protective factor against risk of antidepressant discontinuation. The presence of inducers was rare, and so clinically this may have greater implications for reviewing a patient's medication list for any CYP450 inhibitors. Practically, clinicians should be familiar with common inducers and inhibitors that may influence antidepressants or how to access related resources, including pharmacists. Several antidepressants are inhibitors of various CYP450 isozymes, and interactions also need to be accounted for during cross-tapers. Examples of common inducers include carbamazepine, phenytoin, phenobarbital, rifampin, St John's Wort, and cigarette smoking. Common inhibitors

TABLE 5: Multivariable Cox analyses: discontinuation with age, phenotype category, sex, and inhibitor/inducer use

Multivariable Cox Models – Fast Phenotype Group

	Overall		0 to 2 years		0 to 4 years	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (per decade)	0.87 (0.78, 0.96)	.008[a]	0.87 (0.78, 0.96)	.009[a]	0.87 (0.78, 0.97)	.011[a]
Sex (male vs female)	1.09 (0.80, 1.49)	.58	1.10 (0.81, 1.50)	.54	1.10 (0.81, 1.50)	.56
Charlson comorbidity index	1.06 (1.00, 1.12)	.069	1.06 (1.00, 1.12)	.064	1.06 (1.00, 1.12)	.062
Inducer/inhibitor	0.63 (0.28, 1.43)	.27	0.55 (0.23, 1.33)	.18	0.54 (0.22, 1.33)	.18

Multivariable Cox Models – Middle Phenotype Group

	Overall		0 to 2 years		0 to 4 years	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (per decade)	0.92 (0.85, 0.98)	.014[a]	0.91 (0.85, 0.98)	.009[a]	0.91 (0.85, 0.98)	.011[a]
Sex (male vs female)	0.92 (0.70, 1.21)	.56	0.93 (0.71, 1.22)	0.59	0.92 (0.70, 1.20)	.53
Charlson comorbidity index	1.03 (0.98, 1.08)	.19	1.04 (0.99, 1.09)	.17	1.03 (0.98, 1.09)	.19
Inducer/inhibitor	1.56 (1.09, 2.24)	.014[a]	1.49 (1.04, 2.13)	.030[a]	1.50 (1.05-2.15)	.026[a]

Multivariable Cox Models –Slow Phenotype Group (*n* = 24, so only 2 variables)

	Overall		0 to 2 years		0 to 4 years	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (per decade)	0.93 (0.70, 1.23)	.59	0.92 (0.70, 1.21)	.55	0.93 (0.71, 1.23)	.61
Inhibitor/inducer	6.04 (2.47, 14.80)	<.001[a]	4.85 (2.07, 11.39)	<.001[a]	4.77 (2.05, 11.11)	<.001[a]

[a]*p*-value < .05.

include cimetidine, ciprofloxacin, fluconazole, fluoxetine, fluvoxamine, paroxetine, ritonavir, and verapamil.

Patients had an average of 2.2 medication trials during the study period. The baseline percentage of males and females in the fast, middle, and slow phenotype groups were statistically different with more males in the fast group than females. There is a paucity of literature elsewhere describing such a finding and certainly the need for future studies regarding this sex difference, especially because the CYP450 genes in our analysis are not located on the sex chromosomes. Findings add to the growing body of literature considering the use of pharmacogenomics as a factor to determine optimal treatment regimens for patients. Differences in sex and the rate of adverse events involves many factors, including body mass index, organ function, volume of distribution, body fat percentage, protein binding, and hepatic drug metabolizing capacity.[16] Recent literature also shows sex-related differences in the pharmacokinetics of CYP450. Specifically, females have a higher activity for CYP3A4, CYP2D6, and CYP2B6, whereas males are suggested to have greater activity of CYP2E1, CYP1A2, and CYP2C19.[17–19] Adverse events with SSRIs are more commonly reported in females and may be explained by pharmacokinetic differences.[5] Pharmacokinetic or clinical outcome differences between females and males is not necessarily a consistent phenomenon across all psychiatric medications and a finding of the present study.[20] However, 1 study comparing sertraline and imipramine found that sertraline is more effective and better tolerated than imipramine in females, whereas males responded similarly to both agents.[21] Another study found that females had 35% lower clearance of zolpidem on average compared with males, which was not explained by body weight.[22] Multiple publications also highlight a lower dose requirement of clozapine for females as compared with men.[23–25] These findings identify that there could be sex differences in CYP450 enzymes impacting drug metabolism. Furthermore, alterations in CYP450 enzyme phenotypes may contribute to alterations in drug metabolism that predispose patients to side effects, intolerance, and/or treatment failure.

Unfortunately, it is difficult to isolate sex differences in small studies due to large interpatient variability. Prior studies observing sex differences have failed to assess pharmacogenomics information, which is likely to impact results. Limited studies have identified pharmacogenomic differences but not sex differences. Bradley et al found that pharmacogenetic-guided treatment can be effective in patients diagnosed with depression or anxiety. This prospective, randomized, double-blind control trial assessing 685 patients found that response rates were significantly higher in the pharmacogenetic-guided treatment group as compared with the control group at 12 weeks.[26] Two recent meta-analyses both support the notion of improved remission rates with pharmacogenomic-guided antidepressant selection for MDD.[27,28] Yet pharmacogenomic testing remains controversial with barriers such as access to testing and to clinicians who may correctly interpret results. There are also many practical considerations that influence both antidepressant acceptability and response. Clinicians must be mindful to involve patients in medication selection, describe expectations, follow appropriate antidepressant titration, educate patients on potential side effects, and discuss plans for managing potential side effects. As a part of this, pharmacogenomic testing should be seen as a useful tool although not required for selecting pharmacotherapy for MDD.

There are notable limitations to our study that should be considered. First, we report results from a retrospective chart review, which inherently provides limited information about medication trials. To include only the most accurate information, our data-collection methods validated antidepressant trial periods through individual chart review and were limited to the accuracy of electronic records. Second, recognizing the routes of antidepressant metabolism or drug-gene pairings are based on what was known or reported at the time of study planning. As an example, CPIC recently updated guidelines to call attention to the influence of CYP2B6 polymorphisms on sertraline metabolism whereas in past guidelines only called out CYP2C19 as important.[29] Also, the determination of drug-gene pairings of interest is sometimes "gray" based on recommendations from guidelines or theoretical considerations of drug metabolism. This is highlighted in the 2015 CPIC guideline for SSRIs, available at the development of this study, which described the complexity of fluoxetine metabolism and lack of data to provide specific gene-based recommendations. However, it was stated that it is "reasonable" to monitor more closely or select an alternative agent for CYP2D6 ultrarapid or poor metabolizers. As such, we included fluoxetine-CYP2D6 as a drug-gene pairing based on consensus. Overall, we recognize the limitations when considering route of metabolism as a variable to predict or judge antidepressant tolerability or effectiveness. Third, the exclusion of those already prescribed antidepressants at the start of the study period or those with unknown discontinuation dates is also a limitation. Fourth, although we were able to collect concomitant medications that could affect antidepressant metabolism through inhibition or induction of their primary metabolism pathways, quantifying these effects on CYP450 enzyme activity was not able to be assessed in this study. Also, we did not collect data on the total number of medication or polypharmacy considerations of medications that would not be expected to have impact on the CYP450 system but might be expected to contribute to drug-drug interactions and side effects and influence antidepressant discontinuation (eg, central nervous system depressants, such as gabapentin; other serotonergic medications, such as trazodone or tramadol). Other factors, such as smoking history and diet (eg, consumption

of cruciferous vegetables, caffeine) known to impact CYP1A2 also were not assessed. Another limitation is that the population was relatively healthy as determined by CCI scores and homogenous in terms of reported race (98.8% white) and ethnicity (97.7% not Hispanic or Latino). This was driven by the subjects enrolled in the RIGHT10K study (94% white) and limits the applicability of these results to a real-world or global population.[9] Although beyond the scope of this paper, it is important to recognize the many anticipated differences in the incidence of poor or ultrarapid metabolizer based on biogeographical ancestry.[30] Also, due to the numerous CYP450 phenotypes reported in the Mayo-Baylor RIGHT10K database, this study categorized them into 3 more generalizable categories based on expected enzyme activity for each assigned phenotype. Therefore, we were not able to assess differences between every phenotype possibility for patients, which reduces the external validity of our findings. Finally, there were some patients in our cohort who discontinued antidepressants due to feeling like they were no longer needed, which could have represented remission of MDD instead of adverse effects or inefficacy, thereby potentially decreasing the likelihood of detecting a statistically significant difference in discontinuation rates.

Conclusion

Antidepressants are still prescribed as first-line therapy for MDD and other psychiatric disorders. Patients taking antidepressants are often prescribed concomitant medications that inhibit or induce metabolism of their antidepressants, which increases antidepressant discontinuation events in patients with a phenotypic category prior to phenotypic conversion in this study of middle or slow. Future studies may benefit from investigating the impact of pharmacogenomic testing in larger predictive models that include a wide range of patient factors. Studies should aim to include a process for shared decision making in the context of coprescribed medication, nonpharmacologic treatments, demographic data, and other clinical variables. Particular attention should be paid to the influence of CYP450 inhibitors and inducers or polypharmacy on discontinuation rates in these studies.

Acknowledgments

The Mayo Clinic Center for Individualized Medicine and the Mayo Clinic Robert D. and Patricia E. Kern Center of the Science of Health Care Delivery provided access to the Mayo-Baylor RIGHT10K study data used in this paper.

References

1. World Health Organization. Depression. [cited 2023 Apr 4]. Available from https://www.who.int/news-room/fact-sheets/detail/depression
2. Zhdanava M, Pilon D, Ghelerter I, Chow W, Joshi K, Lefebvre P, et al. The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. J Clin Psychiatry. 2021;82(2). DOI: 10.4088/JCP.20m13699
3. Thase ME. Effectiveness of antidepressants: comparative remission rates. J Clin Psychiatry. 2003;64(SUPPL. 2):3-7. PMID: 12625792
4. Quitkin FM, Stewart JW, McGrath PJ, Taylor BP, Tisminetzky MS, Petkova E, et al. Are there differences between women's and men's antidepressant responses? AJP. 2002;159(11):1848-54. DOI: 10.1176/appi.ajp.159.11.1848
5. Ekhart C, van Hunsel F, Scholl J, de Vries S, van Puijenbroek E. Sex differences in reported adverse drug reactions of selective serotonin reuptake inhibitors. Drug Saf. 2018;41(7):677-83. DOI: 10.1007/s40264-018-0646-2
6. Romanescu M, Buda V, Lombrea A, Andor M, Ledeti I, Suciu M, et al. Sex-related differences in pharmacological response to CNS drugs: a narrative review. JPM. 2022;12(6):907. DOI: 10.3390/jpm12060907
7. Pinto-Meza A, Usall J, Serrano-Blanco A, Suárez D, Haro JM. Gender differences in response to antidepressant treatment prescribed in primary care. Does menopause make a difference? J Affect Disord. 2006;93(1-3):53-60. DOI: 10.1016/j.jad.2006.02.010
8. Khan A, Brodhead AE, Schwartz KA, Kolts RL, Brown WA. Sex differences in antidepressant response in recent antidepressant clinical trials. J Clin Psychopharmacol. 2005;25(4):318-24. DOI: 10.1097/01.jcp.0000168879.03169.ce
9. Bielinski SJ, St Sauver JL, Olson JE, Larson NB, Black, III JL, Scherer SE, et al. Cohort profile: the right drug, right dose, right time: using genomic data to individualize treatment protocol (RIGHT protocol). Int J Epidemiology. 2019;49(1):23-4k. DOI: 10.1093/ije/dyz123
10. Wang L, Scherer SE, Bielinski SJ, Muzny DM, Jones LA, Black, III JL, et al. Implementation of preemptive DNA sequence–based pharmacogenomics testing across a large academic medical center: the Mayo-Baylor RIGHT 10K Study. Genetics Medicine. 2022;24(5):1062-72. DOI: 10.1016/j.gim.2022.01.022
11. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics Medicine. 2015;17(5):405-24. DOI: 10.1038/gim.2015.30
12. Lopes JL, Harris K, Karow MB, Peterson SE, Kluge ML, Kotzer KE, et al. Targeted genotyping in clinical pharmacogenomics. J Mol Diagnostics. 2022;24(3):253-61. DOI: 10.1016/j.jmoldx.2021.11.008
13. PharmGKB. [cited 2022 Dec 23]. Available from https://www.pharmgkb.org/.
14. CPIC. [cited 2022 Dec 23]. Available from https://cpicpgx.org/.
15. Flockhart DA. Drug Interactions Flockhart Table. [cited 2022 Dec 23]. Available from https://medicine.iu.edu/internal-medicine/specialties/clinical-pharmacology/drug-interaction-flockhart-table
16. Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. Annu Rev. Pharmacol. Toxicol. 2004;44(1):499-523. DOI: 10.1146/annurev.pharmtox.44.101802.121453
17. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2009;48(3):143-157. DOI: 10.2165/00003088-200948030-00001
18. Sakuma T, Kawasaki Y, Jarukamjorn K, Nemoto N. Sex differences of drug-metabolizing enzyme: female predominant expression of human and mouse cytochrome P450 3A isoforms. J Heal Sci. 2009;55(3):325-37. DOI: 10.1248/jhs.55.325
19. Tanaka E. Gender-related differences in pharmacokinetics and their clinical significance. J Clin Pharm Ther. 1999;24(5):339-46. DOI: 10.1046/j.1365-2710.1999.00246.x
20. Reis M, Chermá MD, Carlsson B, Bengtsson F. Therapeutic drug monitoring of escitalopram in an outpatient setting. Ther Drug Monit. 2007;29(6):758-66. DOI: 10.1097/FTD.0b013e31815b3f62
21. Baca E, Garcia-Garcia M, Porras-Chavarino A. Gender differences in treatment response to sertraline versus imipramine in patients

with nonmelancholic depressive disorders. Prog Neuro Psychopharmacol Biological Psychiatry. 2004;28(1):57-65. DOI: 10.1016/S0278-5846(03)00177-5
22. Greenblatt DJ, Harmatz JS, Roth T. Zolpidem and gender: are women really at risk? J Clin Psychopharmacol. 2019;39(3):189-99. DOI: 10.1097/JCP.0000000000001026
23. Flanagan RJ, Hunter S, Obee SJ, Reeves S. Clozapine. J Clin Psychopharmacol. 2023;43(2):131-8. DOI: 10.1097/JCP.0000000000001653
24. Reeves S, Bertrand J, Obee SJ, Hunter S, Howard R, Flanagan RJ. A population pharmacokinetic model to guide clozapine dose selection, based on age, sex, ethnicity, body weight and smoking status. Brit J Clin Pharma. 2023;6(3). DOI: 10.1111/bcp.15691
25. de Leon J, Schoretsanitis G, Smith RL, Molden E, Solismaa A, Seppälä N, et al. An international adult guideline for making clozapine titration safer by using six ancestry-based personalized dosing titrations, CRP, and clozapine levels. Pharmacopsychiatry. 2022;55(2):73-86. DOI: 10.1055/a-1625-6388
26. Bradley P, Shiekh M, Mehra V, Vrbicky K, Layle S, Olson MC, et al. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: a randomized clinical trial demonstrating clinical utility. J Psychiatric Res. 2018;96(1):100-7. DOI: 10.1016/j.jpsychires.2017.09.024
27. Brown LC, Stanton JD, Bharthi K, Maruf AA, Müller DJ, Bousman CA. Pharmacogenomic testing and depressive symptom remission: a systematic review. Clin Pharma Ther. 2022;112(6):1303-17. DOI: 10.1002/cpt.2748
28. Wang X, Wang C, Zhang Y, An Z. Effect of pharmacogenomics testing guiding on clinical outcomes in major depressive disorder: a systematic review and meta-analysis of RCT. Bmc Psychiatry. 2023;23(1). DOI: 10.1186/s12888-023-04756-2
29. Bousman CA, Stevenson JM, Ramsey LB, Sangkuhl K, Hicks JK, Strawn JR, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6*, *CYP2C19*, *CYP2B6*, *SLC6A4*, and *HTR2A* genotypes and serotonin R. Clin Pharma Ther. 2023;114(1):51-68. DOI: 10.1002/cpt.2903
30. Zhou Y, Lauschke VM. The genetic landscape of major drug metabolizing cytochrome P450 genes—an updated analysis of population-scale sequencing data. Pharmacogenomics J. 2022;22(5-6):284-93. DOI: 10.1038/s41397-022-00288-2