Pharmacogenomic Characterization of Childbearing-Aged Individuals With Mood Disorders in a Tertiary Care Perinatal Mental Health Clinic

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Abstract

Objective: The effectiveness of antidepressant treatment for mood disorders is often limited by either a poor response or the emergence of adverse effects. These complications often necessitate multiple drug trials. This clinical challenge intensifies during pregnancy, when medications must be selected to improve the likelihood of response and optimize reproductive outcomes. We determined the distribution of common pharmacogenetic variants, metabolizer phenotypes, past medication responses, and side effects in childbearing-aged individuals seeking treatment in a tertiary care perinatal mental health clinic.

Methods: Sixty treatment-seeking women (based on sex at birth) with *DSM-5*–defined bipolar disorder (n = 28) or major depressive disorder (n = 32) provided DNA samples and completed psychiatric diagnostic and severity assessments between April 2014 and December 2017. Samples were genotyped for single-nucleotide variants in drug-metabolizing enzyme genes of commonly prescribed antidepressants (cytochrome P450 [CYP] 1A2, 2B6, 2C9, 2C19, 2D6, 3A4, and 3A5), and the frequency of normative metabolizer status was compared to reference populations data from Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines. The Antidepressant Treatment History Form was used to record historic medication trials and side effects.

Results: A significantly greater proportion of extensive metabolizers for CYP2B6 was observed in the study population when compared to CPIC population frequency databases in Caucasians (0.64 vs 0.43 [95% CI: 0.49–0.76]; *P* value = .006) and African Americans (0.71 vs 0.33 [95% CI: 0.29–0.96]; *P* value = .045). No significant association was found between metabolizer phenotype and the likelihood of a medication side effect.

Conclusion: Pharmacogenomic testing may have value for personalized prescribing in individuals capable of or considering pregnancy.

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Depression and bipolar disorder are commonly occurring disorders associated with a high level of disability, lost productivity, and financial burden.[1] Despite various treatment options, patients often do not fully recover. Only half of patients with depression report a response with selective serotonin reuptake inhibitors, and less than a third will achieve remission.[2] There is some evidence that pharmacogenomic variation contributes to the challenge of achieving remission through pharmacologic treatment.[3] In pharmacogenomic studies, differential drug responses based on genetic variants contributing to drug metabolism have been explored. Differences in metabolic phenotypes have also been identified between races/ethnicities. Pharmacogenomic interindividual differences contribute to the large variability in plasma concentrations and thereby response and tolerability among individuals.[4] Adverse effects increase the risk of drug discontinuation and failing to achieve a therapeutic response. An individual's response, both in terms of benefit and adverse effects, is mediated in part by differences in pharmacogenomic variants.

The goal of personalized therapy using pharmacogenomics is to improve the likelihood that a treatment will both be effective and tolerable and is one of many variables to consider when

Editor's Note

We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

Clinical Points

- The routine use of pharmacogenomic testing has been debated, and yet there are no consistent recommendations for its use in persons of childbearing capacity.
- In patients of childbearing capacity who have had atypical responses or side effects to antidepressants, the use of pharmacogenomic testing should be considered to guide dose or choice of agent on an individual basis.
- Dose adjustments to antidepressants may be needed during pregnancy due to metabolic changes attributable to metabolic phenotype and physiological changes during pregnancy.

determining treatment options. Both the Food and Drug Administration (FDA) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) provide drug-specific recommendations regarding dosing and side effects related to pharmacogenomic variations.[5,6] The FDA drug labeling includes information about potential interindividual responses based on pharmacogenomic differences for several antidepressants. Pharmacogenomic testing identifies these variations in an individual's metabolic phenotype based on the activity of each cytochrome P450 (CYP) enzyme evaluated. While the nomenclature varies for each CYP enzyme, individuals with extensive metabolic phenotypes demonstrate normal enzyme activity, rapid, ultrarapid, and hyperinducer phenotypes demonstrate increased activity, and intermediate and poor phenotypes demonstrate reduced or nonfunctional enzyme activity. The FDA includes language on prescribing some medications where genetic variability is known due to increased risk of adverse drug reactions or subtherapeutic response—specifically citing citalopram for poor CYP2C19 metabolizers and venlafaxine for poor CYP2D6 metabolizers.[7] The CPIC provides guidelines about tailoring prescription dosing, titration schedule, and maintenance dosage for specific CYP2D6 genotypes for paroxetine and CYP2B6 and CYP2C19 genotypes for sertraline.[8]

Evidence suggesting a benefit from pharmacogenomic testing in the treatment of mood disorders is limited. In one large, randomized controlled trial, the impact of pharmacogenomic testing on remission of a major depressive disorder (MDD) was investigated in over 1,000 participants who had not responded to at least one trial of an antidepressant.[9] Participants who received testing and pharmacogenomic-guided treatment had a greater response (26.0% vs 19.9%, $P = .013$) and remission (15.3% vs 10.1%, $P = .007$) rates compared to those who did not. Other studies have failed to demonstrate a differential benefit of antidepressant treatment directed by the determination of pharmacogenomic variants.[10–12] Some authors have described a role for pharmacogenomic testing in individuals with multiple failed treatment trials or in patients with a higher side effect symptom burden.[13,14] Despite these studies, there is no consensus approach for deciding when to use pharmacogenetic testing in the general population, and even less consideration to the perinatal period.[15]

Childbearing is an especially high-risk time for the onset and recurrence of mental illness. The period prevalence of MDD is 12.7% during pregnancy (with 7.5% having a new episode) and 21.9% the year after parturition[16]; therefore, MDD is among the most common complications of childbearing.[17] The onset of depressive symptoms frequently begins postpartum (40.1%), with 33.4% of individuals reporting initial symptoms during pregnancy and the remaining 26.5% reporting symptoms that predated pregnancy.[17] Antidepressant use is increasingly common in perinatal patients, and approximately 8% of all pregnancies have some exposure to antidepressants. An estimated 2%–2.5% of pregnant patients continue an antidepressant throughout pregnancy.[18]

Pregnant persons who continue antidepressants may be less likely to experience a relapse of depression symptoms compared to those who discontinue their antidepressants prior to pregnancy, especially in those with an earlier age of onset of first depressive episode, more severe depression, or more than 4 lifetime episodes of depression.[19,20] Despite metabolic phenotypes remaining stable throughout the lifespan, changes to phase I metabolism that occur during pregnancy could meaningfully impact medication response and tolerability for patients (essentially a "double hit" for pregnant persons). A contributor to the risk for relapse during continued treatment is the effect of pregnancy on the absorption, distribution, metabolism, and/or excretion of the drug. Plasma volume expands, cardiac output and renal filtration increase, and hepatic metabolism changes. Changes in enzymatic activity during pregnancy vary by enzyme: CYP2C9, CYP3A4, and CYP3A5 have higher enzymatic activity,[21] CYP1A2 and CYP2C19 have lower activity,[22–24] CYP2D6 varies based on genotype, and the activity of CYP2B6 appears to be unchanged.[25,26] Given the metabolic changes during pregnancy, medication adjustment may be required to keep the pregnant person's mood stable. Also, the secondary metabolic pathways of some prescribed psychotropics contribute to predicting medication response, guiding dose adjustments, and avoiding drug interactions. Given these factors, it may be warranted to consider pharmacogenomic testing for patients of childbearing capacity as one factor in guiding medication selection and dosage expectations. For commonly prescribed

Table 1.
CYP Enzymatic Changes in Pregnancy for Commonly Prescribed Antidepressants

Enzyme	Enzyme activity in pregnancy				Psychotropics identified by primary metabolic pathway	Psychotropics identified by secondary metabolic pathways
	Increases	Varies	Decreases	No change		
CYP1A2			X		Duloxetine[27] Mirtazapine[a,28,29]	Paroxetine[30,31]
CYP2B6				X	Bupropion[32]	Sertraline[33]
CYP2C9	X[34]					Sertraline[33]
CYP2C19			X		Es/citalopram[35] Sertraline[33]	Paroxetine[30,31] Fluoxetine[36] Venlafaxine[37] Bupropion[32]
CYP2D6		X			Paroxetine[30,31] Fluoxetine[36] Venlafaxine[37] Mirtazapine[a,28,29]	Es/citalopram[35] Sertraline[33] Duloxetine[27] Trazodone/vilazodone[38]
CYP3A4	X[39]				Trazodone/vilazodone[38,40]	Es/citalopram[35] Sertraline[33] Paroxetine[30,31] Fluoxetine[36] Venlafaxine[37] Mirtazapine[a,28,29]
CYP3A5	X[41]					Paroxetine[30,31] Fluoxetine[36] Trazodone/vilazodone[38]

[a]Metabolism complex, CYP2D6 and CYP1A2 majority with additional contribution CYP3A4.

antidepressants, we identified primary and secondary metabolic pathways through a review of the primary literature on drug metabolism and detailed changes in their metabolism in pregnancy (Table 1).

We investigated pharmacogenomic variants in a group of childbearing-aged patients with mood disorders and analyzed their prior medication trials. We hypothesized that our participants would have a disproportionate representation of less common CYP enzyme metabolizer phenotypes due to the primarily consultative nature of our perinatal mental health program in which we evaluate individuals with difficult-to-treat mood disorders. If more differences in metabolic phenotypes were found, we hypothesized that this may support the consideration of pharmacogenomic testing in populations capable of or considering pregnancy.

METHODS

All patients who sought care at Northwestern's Asher Center for the Study and Treatment of Depressive Disorders perinatal mental health clinic were invited to enroll in a research database from April 2014 through December 2017. No patients were excluded based on gender identification. Data were collected from all 60 patients who enrolled and were between ages 18 and 45 years with a diagnosis of either current MDD or bipolar disorder. Patients with bipolar disorder were included since often these patients are treated with antidepressants in combination with mood stabilizers or antipsychotic drugs. Participants provided a DNA sample for pharmacogenetic testing and completed diagnostic evaluation by a psychiatrist or PhD-level psychologist using the structured Mini International Neuropsychiatric Interview,[42] the Antidepressant Treatment History Form[43] to collect data about numbers of prior medication trials and side effects or intolerability, the Inventory of Depressive Symptomatology (IDS)[44] to classify severity of depressive symptoms, and the Generalized Anxiety Disorder 7-item (GAD-7) questionnaire[45] to classify comorbid anxiety symptom severity. Patients received monetary compensation of $50 for their participation.

Pharmacogenetic testing was completed by Genelex (now Invitae, which no longer offers this panel [San Francisco, CA]) with a panel including variants in CYP1A2, 2B6, 2C9, 2C19, 2D6, 3A4, and 3A5. In addition to the 60 participant samples, 6 redundant, blinded samples were also genotyped as internal controls to cross-check the accuracy of the pharmacogenomic testing. CYP metabolizer phenotypes were assigned based on genotypes using CPIC guidelines.[46,47] For each gene, the CPIC frequency tables—based on allele frequencies synthesized by PharmGKB—were referenced for each phenotype as stratified by race.[48–51] If phenotypes

presented as activity scores, the clinical decision support tables were referenced to translate activity score into metabolizer status.[52,53] As there were no CPIC guidelines with associated phenotype frequencies for CYP1A2 and CYP3A4, these were excluded from the analysis due to the lack of a consistent broader population for comparison.

Statistical Methods

We used descriptive statistics to summarize patient characteristics including frequency (percent) for categorical variables, mean (standard deviation), and median (minimum, maximum) for numeric variables. Analyses were stratified by self-reported race. We performed Pearson χ^2 tests and binomial exact tests to examine the extent to which the sample proportion of normal metabolizers of a given race and CYP gene was statistically different from the larger reference population as defined by CPIC. To assess whether metabolizer status was associated with experiencing at least one side effect of a specified drug, we used generalized linear regression using a binomial distribution and log link. All analyses were performed using R (version 3.5.3, 2019, The R Foundation) and assumed a two-sided 5% level of significance. No adjustment for multiple hypothesis testing was performed due to the exploratory nature of the study.

RESULTS

We studied 60 treatment-seeking patients in a perinatal mental health clinic with bipolar disorder (n = 28) or MDD (n = 32) (Table 2). All participants were female based on birth sex. No data on gender, diet, or other exposures were collected. All 60 patients completed pharmacogenomic testing, diagnostic interviews, and questionnaires. Of the participants, 73% were Caucasian, 11% were African American, and the average age was 33 years. During the study period, 25 participants (41.7%) reported a pregnancy. No significant difference existed between groups with unipolar vs bipolar depression regarding ethnicity, race, body mass index, treatment with electroconvulsive therapy or transcranial magnetic stimulation, anxiety symptom severity as reported on the GAD-7, or severity of depression or anxiety based on the IDS and GAD-7, respectively. The only difference between groups was a higher rate of pregnancy in the patients with bipolar vs unipolar disorder (57.1% vs 28.1%, $P = .044$). The groups were consolidated and assessed for CYP metabolizer phenotype frequency. The number of past medication trials is reported in Table 3.

The study population and CPIC comparative population proportions of normal metabolizers stratified by self-identified race and CYP pathway are presented in

Table 2.
Participant Characteristics

Population characteristics	Overall (n = 60)
Age	
Mean (SD), y	33.4 (5.41)
Median [min, max], y	33.5 [20.0, 44.0]
Missing	14 (23.3%)
Race	
American Indian/Alaska Native	1 (1.7%)
Asian	3 (5.0%)
Black or African American	7 (11.7%)
Native Hawaiian/other Pacific Islander	0 (0%)
White or Caucasian	44 (73.3%)
Other	3 (5.0%)
Missing	2 (3.3%)
Ethnicity	
Hispanic	10 (16.7%)
Pregnant	25 (41.7%)
ECT or TMS	3 (5.0%)
GAD-7 total score	
Mean (SD)	6.07 (5.26)
Median [min, max]	5.00 [0.00, 21.0]
Missing	1 (1.7%)
GAD-7 groupings	
None	29 (48.3%)
Mild	18 (30.0%)
Moderate	7 (11.7%)
Severe	5 (8.3%)
Missing	1 (1.7%)
IDS total score	
Mean (SD)	23.6 (14.4)
Median [min, max]	19.0 [5.00, 72.0]
Missing	4 (6.7%)
IDS groupings	
None	17 (28.3%)
Mild	17 (28.3%)
Moderate	13 (21.7%)
Severe	7 (11.7%)
Very severe	2 (3.3%)
Missing	4 (6.7%)

Abbreviations: ECT = electroconvulsive therapy, GAD-7 = Generalized Anxiety Disorder 7-item, IDS = Inventory of Depressive Symptomatology, TMS = transcranial magnetic stimulation.

Table 4. The proportions of extensive metabolizers for CYP2C9, CYP2C19, and CYP2D6 in our study populations were comparable to previously published population allele frequencies. In contrast, the proportion of extensive metabolizers of CYP2B6 in our study population differed from the population allele frequencies. Interestingly, the proportion of both Caucasian and African American CYP2B6 extensive or normative metabolizers in our study population was significantly greater than population estimates (0.64 vs 0.43 [95% CI: 0.49–0.76], $P = .006$; and 0.71 vs 0.334 [95% CI: 0.29–0.96], $P = .045$, respectively).

Table 5 describes the summary of the number of past medication trials reported by individuals,

Table 3.

Study Population's Past Medication Trials by Medication Class

Medication class and number of past medication trials	Overall (n = 60)	Mean (SD)	Median [min, max]
Benzodiazepines			
0	22 (36.7%)	1.11 (1.18)	1.00 [0.00, 4.00]
1	13 (21.7%)		
2	13 (21.7%)		
3+	6 (10.0%)		
Missing	6 (10.0%)		
Antipsychotics			
0	36 (60.0%)	0.722 (1.25)	0.00 [0.00, 5.00]
1	7 (11.7%)		
2	5 (8.3%)		
3+	6 (10.0%)		
Missing	6 (10.0%)		
Mood stabilizers			
0	31 (51.7%)	0.778 (1.04)	0.00 [0.00, 3.00]
1	9 (15.0%)		
2	9 (15.0%)		
3	5 (8.3%)		
Missing	6 (10.0%)		
Stimulants			
0	41 (68.3%)	0.370 (0.784)	0.00 [0.00, 3.00]
1	9 (15.0%)		
2	1 (1.7%)		
3	3 (5.0%)		
Missing	6 (10.0%)		
Antidepressants			
0	2 (3.3%)	3.63 (2.18)	3.00 [0.00, 10.0]
1	6 (10.0%)		
2	11 (18.3%)		
3	9 (15.0%)		
4	11 (18.3%)		
5+	15 (25.0%)		
Missing	6 (10.0%)		

stratified by metabolizer phenotype. Only patients with CYP1A2 hyperinducer phenotype had significantly more past medication trials (median [interquartile range] = 4.0 [2.0; 5.0] vs 2.0 [0.75; 3.0], P = .041 for hyperinducers vs extensive/normative metabolizers). No significant association between metabolizer phenotype and likelihood of experiencing a side effect was observed (Table 6). Descriptive statistics are reported by individual drug and metabolizer phenotypes.

DISCUSSION

Our study did not suggest that patients presenting to care in a specialty care perinatal mental health clinic have higher frequencies of atypical metabolic phenotypes. In fact, the only difference in phenotypic frequencies demonstrated was a higher proportion of normative metabolizers for CYP2B6 which would not be expected to have a clinically significant impact on drug selection, dosing, or titration. In our study, those patients with atypical metabolic phenotypes also did not report more adverse side effects from antidepressant medications. Only those with an atypical CYP1A2 metabolic phenotype reported statistically more past medication trials, theoretically due to reduced medication response. Therefore, there may be other factors besides pharmacogenetic differences, which lead patients to a perinatal specialty care center. These findings raise the question of the utility of widespread pharmacogenomic testing including in subspecialty perinatal populations.

Despite these findings, from the literature and our clinical work here with perinatal populations, there are scenarios where knowing a patient's metabolizer status for specific medications could change the treatment course, plan, and discussion with a patient. For example, poor and intermediate CYP2C19 metabolizers treated with sertraline (n = 6 in our study sample) in pregnancy experience a drop in drug concentration which can lead to subtherapeutic concentrations and risk of recurrence and morbidity for the pregnant person and fetus.[54] Patients with extensive or ultrarapid CYP2D6 metabolic phenotypes may also have significant concentration reductions of paroxetine (n = 5 in our study population) or fluoxetine (n = 17 in our study population) in pregnancy which can contribute to recurrence of illness.[30] In contrast, drug concentrations increase across pregnancy for intermediate or poor CYP2D6 metabolizers (paroxetine, n = 9; fluoxetine, n = 6, in our study population), potentially increasing side effects. Clinically, pregnant patients with ultrarapid CYP2D6 metabolic phenotype treated with fluoxetine (n = 1 in our study population) may require dose titrations beyond the comfort of most patients or clinicians. In these cases, pharmacogenetic testing may remain clinically appropriate for the peace of mind of both the patient and the clinician, who may be reluctant to increase medication dosage to sustain the plasma concentration. The discussion should remain focused on the goal of maintaining maternal euthymia and recognizing the risks of exposure of un- or undertreated mental illness to maternal-fetal health. Considering the clinical presentation of perinatal patients, prepregnancy pharmacogenetic testing may be valuable, especially if patients have a higher number of past medication trials or frequent side effects, but this decision should be made on a person-to-person basis given the lack of consistent clinical guidelines across populations.

Finally, while our study looked primarily at antidepressants given existing guidelines on pharmacogenomics and common antidepressants, there are potential dosing implications for benzodiazepines[55] and mood stabilizers in patients with bipolar disorder as several of these CYP enzymes are implicated (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5).[56]

Table 4.

Study and Comparative Population Proportions of Normal Metabolizers by Race and CYP Metabolic Pathway[a]

Normative metabolizer phenotype by CYP	Race	CPIC reference population phenotype frequency[46]	Study population phenotype frequency	95% Confidence interval	*P* value[b]
CYP2B6[48]	Caucasian	0.430	0.64	(0.49–0.76)	.006*
	African American	0.334	0.71	(0.29–0.96)	.045*
CYP2C9[50,52]	Caucasian	0.628	0.75	(0.61–0.85)	.095
	African American	0.759	0.57	(0.18–0.9)	.371
CYP2C19[49]	Caucasian	0.396	0.36	(0.24–0.51)	.660
	African American	0.328	0.43	(0.1–0.82)	.690
CYP2D6[51,53]	Caucasian	0.492	0.53	(0.39–0.67)	.573
	African American	0.538	0.57	(0.18–0.9)	>.999
CYP3A5[41]	Caucasian	0.005	0	(0–0.08)	.622
	African American	0.205	0.29	(0.04–0.71)	.638

[a]CYP1A2 and CYP3A4 are intentionally excluded as no comparative population frequency data are available from CPIC. CYP3A5 and CYP2C9 are included here as they have population frequency data from CPIC and their significance as secondary metabolic pathways may have more implications in pregnancy.
[b]Asterisk (*) indicates significance.
Abbreviation: CPIC = Clinical Pharmacogenetics Implementation Consortium.

Table 5.

Study Population Drug Trials by CYP Phenotype

CYP phenotypes		Study population (n = 60)	Number of drug trials, median [interquartile range]	*P* value
CYP1A2 phenotype				
Normal	Extensive	16 (26.7%)	2.00 [0.75; 3.00]	.041*
Other	Hyperinducer	44 (73.3%)	4.00 [2.00; 5.00]	
CYP2B6 phenotype				
Normal	Extensive	37 (61.7%)	3.00 [1.00; 5.00]	.759
Other	Poor	5 (8.3%)	2.00 [2.00; 4.00]	
	Intermediate	18 (30.0%)		
CYP2C9 phenotype				
Normal	Extensive	45 (75.0%)	3.00 [2.00; 5.00]	.361
Other	Poor	1 (1.7%)	3.00 [0.50; 4.00]	
	Intermediate	14 (23.3%)		
CYP2C19 phenotype				
Normal	Extensive	25 (41.7%)	3.00 [1.00; 5.00]	.401
Other	Intermediate	16 (26.7%)	3.00 [1.50; 4.00]	
	Rapid	18 (30.0%)		
	Ultrarapid	1 (1.7%)		
CYP2D6 phenotype				
Normal	Extensive	34 (56.7%)	4.00 [2.00; 5.00]	.083
Other	Poor	4 (6.7%)	3.00 [1.00; 4.00]	
	Intermediate	20 (33.3%)		
	Ultrarapid	1 (1.7%)		
Missing		1 (1.7%)		
CYP3A4 phenotype				
Normal	Extensive	43 (71.7%)	3.00 [2.00; 5.00]	.217
Other	Intermediate	17 (28.3%)	2.00 [1.00; 4.00]	
CYP3A5 phenotype				
Normal	Extensive	2 (3.3%)	1.50 [0.75; 2.25]	.289
Other	Poor	51 (85.0%)	3.00 [1.25; 4.75]	
	Intermediate	7 (11.7%)		

*Indicates significance.

Table 6.

Study Population Drug Side Effects by CYP Phenotype Classified by Primary Metabolic Pathway

Study population metabolizer phenotype		Drug name	Number of patients with past trial	Total number of trials	Number of patients with reported adverse side effect from at least 1 trial
CYP1A2 phenotype					
Normal	Extensive	Duloxetine	0	0	0 (0)
		Mirtazapine	0	0	0 (0)
Other	Hyperinducer	Duloxetine	7	7	1 (0.14)
		Mirtazapine	4	4	2 (0.5)
CYP2B6 phenotype					
Normal	Extensive	Bupropion	16	19	1 (0.06)
Other	Poor	Bupropion	2	2	0 (0)
	Intermediate	Bupropion	5	6	0 (0)
CYP2C19 phenotype					
Normal	Extensive	Sertraline	17	21	3 (0.18)
		Es/citalopram	12	17	5 (0.42)
Other	Intermediate	Sertraline	6	6	4 (0.67)
		Es/citalopram	4	5	1 (0.25)
	Rapid	Sertraline	11	15	3 (0.27)
		Es/citalopram	10	15	4 (0.4)
	Ultrarapid	Sertraline	1	1	1 (1)
		Es/citalopram	1	2	1 (1)
CYP2D6 phenotype					
Normal	Extensive	Fluoxetine	16	18	4 (0.25)
		Paroxetine	5	5	2 (0.4)
		Venlafaxine	7	9	4 (0.57)
		Mirtazapine	1	1	0 (0)
Other	Poor	Fluoxetine	0	0	0 (0)
		Paroxetine	1	1	1 (1)
		Venlafaxine	1	1	0 (0)
		Mirtazapine	0	0	0 (0)
	Intermediate	Fluoxetine	6	6	1 (0.17)
		Paroxetine	8	8	3 (0.38)
		Venlafaxine	2	2	0 (0)
		Mirtazapine	3	3	2 (0.67)
	Ultrarapid	Fluoxetine	1	2	1 (1)
		Paroxetine	0	0	0 (0)
		Venlafaxine	1	1	0 (0)
		Mirtazapine	0	0	0 (0)
CYP3A4 phenotype					
Normal	Extensive	Vilazodone/ trazodone	14	15	3 (0.21)
Other	Intermediate	Vilazodone/ trazodone	2	2	1 (0.5)

Limitations

Though men and women are usually included in pharmacogenetic studies, the study population consisted of all females (based on sex at birth) likely due to the nature of recruiting from a perinatal mental health clinic. With the relatively small population size, analysis regarding comparison of medication trials and side effects was likely underpowered. Additionally, while retrospective recall of numbers of prior medication trials and subjective self-report of side effects was reported, data on treatment response were not available. Another potential limitation is using a single CYP enzyme analysis.

While the primary metabolic pathway was identified for each medication, the secondary pathways also contribute to outcomes which may have significant impacts in pregnancy given the changes in CYP enzyme activity. Lastly, the study sample comprised mainly Caucasian, non-Hispanic individuals, limiting further evaluation on race-related pharmacogenomic differences.

Conclusion

The use of pharmacogenomic testing in the treatment of psychiatric disorders is a growing field and is driven by clinician and patient interest in personalized medicine. Pharmacogenomic liability may be of particular interest at time periods where differences in interindividual metabolism of medications are accentuated, such as during pregnancy. This study adds to a growing literature debating the utility of pharmacogenetic testing and continues the debate about the clinical utility for a population capable of pregnancy. While no consensus on the routine use of pharmacogenomic testing exists, it may be considered on an individual basis and should be considered as one of many factors in medication selection and dosing. Finally, when pharmacogenomic results are available, they may provide additional guidance[6] for medication selection and dosing adjustments that may be particularly of use in pregnancy.

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