CYP2D6 Genotyping and Inhibition as Predictors of Adverse Drug Reactions in Depressive Disorders

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Abstract

Objective: The primary aim of this study was to examine the association between the different predicted phenotypes of the polymorphic *CYP2D6* gene and the prevalence of adverse drug reactions in patients suffering from depressive disorders. The secondary aim was to investigate if comedication with CYP2D6 inhibitors resulted in more adverse drug reactions due to phenoconversion.

Methods: Between January 2012 and December 2021, 415 patients with a depressive disorder and insufficient treatment response in secondary psychiatric care were included in the naturalistic observational study Genes, Depression, and Suicidality (GENDS). The patients were subjected to a semistructured interview and diagnosed according to *DSM-IV*. Patients were also required to complete the self-rating version of the UKU Side Effect Rating Scale. All patients were genotyped for *CYP2D6* and assigned a corresponding predicted CYP2D6 phenotype.

Results: Out of the 415 patients, 147 patients with available genotyping and UKU scale results were also prescribed 1 or more drugs metabolized by CYP2D6. We did not find any evidence of an effect of the predicted CYP2D6 phenotype on the total burden of adverse drug reactions or in any of the specific symptom domains as measured with the UKU scale among these patients. We also investigated if comedication with 1 or more substances that inhibited the effect of the CYP2D6 enzyme resulted in more reported adverse drug reactions due to phenoconversion. Even though the rate of phenotypic PMs increased from 13 to 38 patients, we did not find any support for increased adverse drug reactions in this group.

Conclusions: We did not find that CYP2D6 phenotype could predict the occurrence of adverse drug reactions in patients with depressive disorders in this naturalistic setting. However, information about *CYP2D6* genotype may still be important in antidepressant treatment for the selection of appropriate drugs, for dosing recommendations of certain medications, or when the patient is suffering from severe adverse reactions.

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Depressive disorders are ranked as the single largest contributor to non-fatal health loss globally,[1] and 13.2% of adult Americans reported antidepressant use in the past 30 days during 2015–2018.[2] Adverse drug reactions (ADRs) with antidepressant treatment are common, with 16.7% of the patients in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project discontinuing first line therapy due to drug intolerance.[3] Associations have been made between the occurrence of ADRs and high overall cost of illness.[4]

One possible important contributor to the interindividual variability in drug response and drug intolerance is the inherited differences in drug metabolism mediated by the genes of the cytochrome P450 (CYP) family.[5] A high proportion of drugs commonly used in the treatment of depressive disorders are CYP2D6 substrates.[6] The combined *CYP2D6* alleles in an individual can be categorized into 4 different predicted phenotypes with varying enzymatic activity: poor metabolizer (PM), intermediate metabolizer (IM), normal metabolizer (NM), and ultrarapid metabolizer (UM).[7] More than 130 different *CYP2D6* genes have been identified.[8–11]

A decreased metabolism of CYP2D6 substrates implicates an increased serum concentration of the drugs. Consequently, genotypes that predict a decreased metabolism of CYP2D6 have been suggested to increase ADRs,[5,12] even though study results are not consistent. Some, but not all, suggest that taking the CYP2D6 phenotype into consideration when prescribing

Clinical Points

- Adverse drug reactions are common in antidepressant treatment and may lead to decreased quality of life and discontinuation of treatment. Pharmacogenetic testing has been suggested as one way to address this issue.
- Genetic testing of CYP2D6 did not show that predicted poor drug metabolism led to increased adverse drug reactions in patients treated for depressive disorders.

antidepressant drugs may lead to improved outcomes or fewer adverse reactions. One possible reason for the inconsistency of previous findings is the phenomenon of phenoconversion. This occurs when concurrent treatment with a CYP2D6 inhibitor decreases the enzymatic activity, thus mimicking the genetic defect and converting the subject into a PM phenotype regardless of genotype.[13] IMs are likely to be more susceptible to phenoconversion than NMs since they already have a somewhat compromised metabolizing capacity.[13]

The primary aim of this study was to examine the association between the genetic variation of *CYP2D6* and the prevalence of ADRs in patients with depressive disorders and insufficient treatment response in a naturalistic observational setting. The secondary aim was to investigate if comedication with CYP2D6 inhibitors resulted in more ADRs due to phenoconversion. We hypothesized that IMs would show an increased incidence of ADRs compared to NMs.

METHODS

Ethics Statement

The project was approved by the Regional Ethical Review Board in Lund, Sweden, dnr 2011/673. Participants signed an informed consent form.

Recruitment Procedures and Study Participants

This study is part of the research project GEN-DS (Genes, Depression, and Suicidality). The material and methods have been described previously.[14] Patients aged 18 years or above with a preliminary diagnosis of major depressive disorder, dysthymia, or bipolar disorder with a current or recent depressive episode were included in the study. The patients were referred to the study from several psychiatric clinics in Region Skåne, Sweden, because of insufficient treatment response. The preliminary diagnosis was based on clinical assessment by the patient's referring psychiatrist. Exclusion criteria were ongoing pregnancy, liver disease, and body mass index < 15. The data were collected between January 2012 and December 2021.

Interview and Assessment Scales

A consultant or resident in psychiatry performed a semistructured interview including the Mini-International Neuropsychiatric Interview,[15] the Structured Clinical Interview for *DSM-IV* Axis II Disorders,[16] and the Comprehensive Psychopathological Rating Scale (CPRS).[17] Reevaluated diagnoses were set according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (*DSM-IV*).[18] The Montgomery-Asberg Depression Rating Scale (MADRS)[19] was extracted from the CPRS. The research protocol included questions on current medication and current somatic illness.

UKU Scale

Patients were asked to complete the self-rating version of the UKU Side Effect Rating Scale (Udvalg før Kliniske Undersøgelser)[20] to rate ADRs from ongoing medication in the last 2 weeks. The UKU scale is validated in psychiatric samples,[21] and it encompasses 42 questions for males and 45 questions for females. ADRs are rated as none, mild, moderate, or severe (corresponding to a score of 0, 1, 2, or 3). The UKU scale covers the 4 domains psychological, neurologic, autonomic, and other adverse reactions (9 common items for males and females; 3 sex-specific items for males and 6 sex-specific items for females).

To adjust for the different sex-specific items, they were omitted in a first step and the total score (0–117) was calculated for males and females. Finally, the sex-specific items were analyzed separately.

Blood Sampling, Analysis, and Genotyping

Blood samples for *CYP2D6* genotyping were drawn at 8:00 AM on the day of the study visit. Patients were instructed to fast for 4 hours before the blood draw and to avoid nicotine use and medications in the morning.

Genotyping analyses were performed at the Department of Forensic Genetics and Forensic Toxicology, Linköping, Sweden. DNA was isolated from whole blood using a NorDiag Arrow and the Blood DNA500 v2.0 kit from Hain Lifescience (Nehren, Germany). The *CYP2D6* single nucleotide polymorphisms **3* (NM_000106.6(*CYP2D6*):c.775del, *rs35742686*), **4* (NM_000106.6(*CYP2D6*):c.506−1G > A, *rs3892097*), and **6* (NM_000106.6(*CYP2D6*):c.454del, *rs5030655*), as well as CYP2D6 copy number variation, were analyzed using Pyrosequencing as previously described.[22,23] *CYP2D6*41* (NM_000106.6(*CYP2D6*):c.985+39G > A, *rs28371725*) were determined using TaqMan Drug Metabolism Genotyping (Assay ID: C__34816116_20) according to the manufacturer's protocol. 10 ng of genomic DNA was used along with 2 × TaqMan Genotyping Master Mix (Life Technologies) per reaction. The PCR conditions were initiation at 95 °C for 10 min and 40 cycles of 95 °C for 15 s and 60 °C for 60 s and run on a 7500 Fast Real-Time PCR system (Applied Biosystems).

Table 1.

Demographic Characteristics of All Subjects and Divided by Medication Status

	All subjects (n = 415)	Subjects receiving CYP2D6 substrate/s (n = 164)	Subjects only receiving drug/s with other pharmacokinetic profiles (n = 229)	Subjects receiving no drugs (n = 22)
Age, y				
Mean (SD)	37.6 (13.4)	39.1 (14.5)	36.7 (12.6)	36.4 (12.6)
Range	18–77	18–76	18–77	22–65
Sex, n (%)				
Female	273 (65.8)	108 (65.9)	158 (69.0)	7 (31.8)
Male	142 (34.2)	56 (34.1)	71 (31.0)	15 (68.2)
MADRS score, mean (± SD)[a]	21.4 (8.5)	22.0 (8.0)	21.0 (8.9)	19.9 (8.8)
Personality syndrome, n (%)	170 (41.0)	62 (37.8)	98 (42.8)	10 (45.5)
Anxiety disorder,[b] n (%)	247 (59.5)	97 (59.1)	137 (59.8)	13 (59.1)
Somatic comorbidity, n (%)	270 (65.1)	105 (64.0)	156 (68.1)	9 (40.9)
Bipolar depression, n (%)	35 (8.4)	14 (8.5)	20 (8.7)	1 (4.5)
Dysthymia/chronic depression, n (%)	206 (49.6)	84 (51.2)	118 (51.5)	4 (18.2)
Number of current medications,[c] mean (± SD)	3.0 (2.1)	3.6 (2.1)	2.9 (1.9)	...

[a]MADRS score was available for 397 subjects.
[b]Anxiety disorder includes social phobia, panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder.
[c]Only medications taken regularly are included. Includes both psychiatric drugs and other drugs.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Table 2.

Frequency of Reported Medications That Are Substrates[a] or Inhibitors of CYP2D6

Medication	Number of patients (%)	Substrate CYP2D6	Strength of CYP2D6 inhibition
Venlafaxine	84 (57.1)	Level 1A	...
Mirtazapine	46 (31.3)	Level 2A	...
Bupropion	20 (13.6)	...	Strong
Metoprolol	14 (9.5)	Level 1A	...
Aripiprazole	10 (6.8)	Level 1A	...
Paroxetine	9 (6.1)	Level 1A	Strong
Duloxetine	8 (5.4)	...	Moderate
Clomipramine	8 (5.4)	Level 1A	...
Amitriptyline	4 (2.7)	Level 1A	...
Risperidone	3 (2.0)	Level 1A	...
Tramadol	3 (2.0)	Level 1A	...
Fluoxetine	2 (1.4)	...	Strong
Atomoxetine	1 (0.7)	Level 1A	...
Nortriptyline	1 (0.7)	Level 1A	...
Codeine	1 (0.7)	Level 1A	...
Tamoxifen	1 (0.7)	Level 1A	...

[a]Only medications with a clinical annotation level of evidence of 1 or 2 are included (Whirl-Carrillo et al[26]).

The wild-type allele (**1*) was assigned when none of the alleles were detected. The copy number variation of *CYP2D6* was determined to identify gene deletion (**5*) or multiple gene copies (*CYP2D6xN*). Genotype to phenotype conversion was performed using activity scores according to current guidelines.[24]

Drug Selection

Information about which drugs were metabolized by CYP2D6 was retrieved from PharmGKB.org.[25–27] Classification as CYP2D6 substrate was limited to drugs with a clinical annotation level of evidence of 1 or 2. Drugs with moderate or strong level of inhibition of CYP2D6 according to the Flockhart Cytochrome P450 Drug-Drug Interaction Table[28] were reported as CYP2D6 inhibitors.

Adjustment of Predicted CYP2D6 Phenotype According to Phenoconversion by Comedication With CYP2D6 Inhibitor

To investigate the effect of phenoconversion by CYP2D6 inhibitors, we used the inhibition factor model proposed in previous studies.[29,30] Moderate inhibitors were assigned an inhibitor factor of 0.5, and strong inhibitors were assigned an inhibitor factor of 0. Activity scores[24] were multiplied by the inhibitor factor if the patient was prescribed a CYP2D6 inhibitor; individuals taking no CYP2D6 inhibitory medication kept their unchanged activity score. Predicted CYP2D6 phenotypes (henceforth denoted phenotypes) were adjusted accordingly (for example, a previous NM with an activity score of 2 who received a moderate inhibitor would be assigned the adjusted activity score of $2 \times 0.5 = 1$ and the adjusted CYP2D6 phenotype of IM).

Statistics

All statistical analyses were performed using IBM SPSS Statistics for Windows version 28 (IBM Corp). The total UKU scores and the UKU scores in the different domains were compared between CYP2D6 phenotypes using the Kruskal-Wallis *H* test. Means between two groups were compared using the Student *t* test. A linear regression model was created to investigate what other factors were associated with a higher UKU score. A P value of $< .05$ was considered statistically significant. Reported P values are 2-sided.

When the response to 1 or 2 items on the UKU scale was missing for a patient, a value was imputed based on the patient's mean item value. The UKU scale result was excluded from analyses if more than 2 UKU items were missing. A sensitivity analysis was performed to ensure that the imputed values did not affect the outcome of the analyses.

RESULTS

Demographic Characteristics

The cohort consisted of 415 subjects. Baseline data are presented in Table 1. Somatic comorbidity and chronic depression/dysthymia were less common among patients who did not receive any medication. Patients receiving CYP2D6 substrates were taking more concomitant medications than patients in the other groups.

CYP2D6 genotype test results were available in 407 patients. The phenotype distribution was as follows: PM 33 (8.0%), IM 165 (39.8%), NM 198 (47.7%), and UM 11 (2.7%).

UKU Scores and CYP2D6 Phenotypes

Out of the 415 patients, 164 were prescribed 1 or more drugs metabolized by CYP2D6. UKU scale and genotyping results were available in 147 of these patients. Medications that are metabolized by or inhibit the CYP2D6 enzyme are reported in Table 2 in order of frequency as reported by the patients.

UKU scores in relation to CYP2D6 phenotype are shown in Table 3. No statistically significant differences were found between the CYP2D6 phenotypes in overall ADR burden or in any of the specific symptom domains. Two patients did not identify as their biological sex; these were omitted from the analyses of sex-specific ADRs. There were no apparent differences in UKU scores in the sex-specific items between CYP2D6 phenotypes.

Table 3.

Median Values of UKU Score in the CYP2D6 Phenotypes (n = 147) for Patients Receiving CYP2D6 Substrates

	PM (n = 13)	IM (n = 51)	NM (n = 78)	UM (n = 5)	*P*
Total number[a] median (min–max)	35 (20–62)	35 (4–59)	32 (4–79)	50 (4–54)	.86
Psychological median (min–max)	16 (7–28)	15 (1–26)	15 (0–27)	8 (2–22)	.72
Neurologic median (min–max)	6 (2–16)	6 (0–18)	7 (0–22)	11 (0–20)	.99
Autonomic median (min–max)	8 (3–15)	7 (0–18)	6.5 (0–20)	9 (0–16)	.55
Other[a] median (min–max)	5 (1–11)	4 (0–10)	4 (0–11)	6 (0–13)	.74

[a]Sex-specific adverse drug reactions not included.
Abbreviations: IM = intermediate metabolizer, NM = normal metabolizer, PM = poor metabolizer, UM = ultrarapid metabolizer.

Table 4.

Median Values of UKU Score in the Adjusted CYP2D6 Phenotypes (n = 147) for Patients Receiving CYP2D6 Substrates

	PM (n = 38)	IM (n = 40)	NM (n = 67)	UM (n = 2)	*P*
Total number[a] median (min–max)	34 (10–62)	35.5 (4–59)	32 (4–79)	7.5 (4–11)	.076
Psychological median (min–max)	16 (4–28)	15 (1–24)	14 (0–27)	5 (2–8)	.12
Neurologic median (min–max)	6 (0–21)	7 (0–18)	7 (0–22)	1 (0–2)	.20
Autonomic median (min–max)	7.5 (0–16)	7.5 (1–18)	6 (0–20)	1 (0–2)	.081
Other[a] median (min–max)	5 (0–11)	4 (0–11)	4 (0–13)	0.5 (0–1)	.044

[a]Sex-specific adverse drug reactions not included.
Abbreviations: IM = intermediate metabolizer, NM = normal metabolizer, PM = poor metabolizer, UM = ultrarapid metabolizer.

Effect of CYP2D6 Inhibitors

Out of the 147 patients that received CYP2D6 substrates, 34 patients also received at least 1 moderate or strong CYP2D6 inhibitor. There was no statistically significant difference in total UKU score between the patients that received CYP2D6 inhibitors (mean = 35.9, SD = 15.0) and the ones that did not (mean = 32.5, SD = 14.9, $P = .27$).

No statistically significant difference of the total UKU score or in any of the specific domains was found between the CYP2D6 phenotypes when the analysis was restricted to patients receiving both CYP2D6 substrates and inhibitors. The median value of the total UKU score varied from 33 (min–max 20–47) in PMs (n = 4), 36 (10–48) in IMs (n = 13), 31 (12–59) in NMs (n = 15) to 52.5 (51–54) in UMs (n = 2), $P = .24$.

For the patients receiving CYP2D6 inhibitors, adjusted activity scores were calculated and converted into adjusted CYP2D6 phenotypes. Twenty-seven patients (18.4%) had a changed phenotype when phenoconversion was considered. The rate of PMs increased from 13 (8.8%) to 38 (25.9%) among the 147 patients.

No statistically significant difference of the total UKU score was found between the CYP2D6 phenotypes when the analysis was repeated using the adjusted CYP2D6 phenotype. There was a significant difference among the phenotypes in the score of "other" ADRs on the UKU scale ($P = .044$) with UMs reporting lower median values than the other phenotypes (Table 4); however, this result did not reach statistical significance when the sensitivity analysis was performed ($P = .076$). There were no apparent differences between the adjusted CYP2D6 phenotypes in the sex-specific UKU items.

Table 5.

Linear Regression Model of Total UKU Score[a]

	B	95% CI	β	*P*
Sex[b]	4.63	[1.77 to 7.49]	0.148	.002
Number of medications	0.832	[0.110 to 1.55]	0.114	.024
Age (y)	0.072	[−0.037 to 0.181]	0.064	.19
Somatic illness	4.50	[1.49 to 7.51]	0.144	.004
MADRS score	0.724	[0.556 to 0.892]	0.417	< .001
Any anxiety disorder	1.15	[−1.70 to 3.99]	0.038	.43
Any personality disorder	1.02	[−1.85 to 3.89]	0.034	.49

[a]$R^2 = 0.30$.
[b]0 = male; 1 = female.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Explanatory Model

To estimate an explorative linear regression model for predicting total UKU score, we used the following variables: sex, number of medications, age, somatic illness, MADRS score, and occurrence of any anxiety disorder and/or personality disorder (Table 5). The model was based on 339 of the patients that were receiving at least 1 medication and where information of all these variables were available.

MADRS score made the most significant contribution to the model, followed by female sex, somatic illness, and to a lesser degree number of medications.

Sensitivity Analysis

UKU items were imputed for 23 patients (10 patients that received CYP2D6 substrates). Sensitivity analyses excluding these patients were consistent with the main results presented except when otherwise specified.

DISCUSSION

We did not find evidence of an effect of the CYP2D6 phenotype on reported ADRs in patients with depressive disorders in a naturalistic setting. We also investigated if comedication with CYP2D6 inhibitors resulted in more ADRs due to phenoconversion, but we did not find any support for this. In summary, we could not support our hypothesis that IMs would report more ADRs than NMs. Furthermore, no difference in ADRs was seen between the other CYP2D6 phenotypes. However, the PM and UM groups were small, and the study may lack power to discover differences between these groups.

It is likely that the varying effect of the CYP2D6 enzyme was only one of many factors that affected the occurrence of ADRs in the study. Many patients received several drugs, whereof some may cause ADRs unconnected to the *CYP2D6* genotype. Additionally, though the patients were instructed to report possible ADRs connected to ongoing medication, patients may have mistaken symptoms of depression, psychiatric comorbidity, or somatic illness for ADRs.

Our results are mainly in line with previous studies on the impact of CYP2D6 phenotype on ADRs in treatment of depression. Ng et al[31] allocated patients to treatment with escitalopram or venlafaxine. They found no difference in UKU score with regard to the combined CYP2D6 PM/IM versus NM/UM groups after 1 week in the venlafaxine group. Roberts et al[32] randomized patients to treatment with fluoxetine or nortriptyline. After 3 and 6 weeks of treatment, PMs were not more likely than EMs (extensive metabolizers; in newer studies commonly referred to as normal metabolizers) to have developed ADRs. In another study, patients were allocated to treatment with nortriptyline or escitalopram.[33] The authors found that *CYP2D6* (and *CYP2C19*) genotype did not predict ADRs after 8 weeks treatment and was unrelated to study discontinuation.

Other studies have found that the *CYP2D6* genotype did predict the occurrence of ADRs. In one study where patients were treated with fixed doses of amitriptyline, the authors found that carriers of a non-functioning allele had a higher risk for ADRs.[34]

In a pilot study, Rau et al[35] found that when physicians at psychiatric clinics in Germany were asked to refer patients who had marked ADRs or were nonresponders to treatment with CYP2D6-dependent antidepressants, 29% were PMs, ie, 4 times higher than the 7% frequency in the German population. Another study included patients with varying psychiatric diagnoses that started treatment with antidepressants or antipsychotics; they found no associations between CYP2D6 phenotype and ADRs.[36]

Several possible explanations have been proposed to explain the conflicting results of earlier studies. The proportions of PMs and UMs tend to be small, making many samples underpowered. Study designs are heterogenous, and there is a significant variability between classification of phenotype based on genotype; the assessed alleles vary among studies; and many studies do not take comedication into account.[5] In our study, we did not find that *CYP2D6* genetic information predicted ADRs even when adjusted for CYP2D6 inhibition, even though the number of phenotypic PMs increased from 13 to 38 patients.

There are a few other studies that have investigated the effect of CYP2D6 inhibition. Walden et al[30] provided physicians of treatment-resistant patients with varying psychiatric diagnoses with a report with treatment recommendations based on *CYP2D6* and *CYP2C19* genotype. They also adjusted activity scores for CYP2D6 inhibition and correlated the activity score to ADRs, but no statistically significant correlation was observed. In a study of venlafaxine treatment where comedication was allowed, almost 1 of 4 patients with a CYP2D6 non-PM predicted phenotype was converted to phenotypic PM status as a result of the other medications.[37] Another study investigated the effect of the interaction between CYP2D6 substrates and the CYP2D6 inhibitors duloxetine and paroxetine on the CYP2D6 substrate plasma drug levels.[38] The authors found that the interaction was higher in carriers of 1 nonfunctional *CYP2D6* allele than in patients with 2 fully functional alleles, suggesting that the former group was more susceptible to phenoconversion.[38] When reading these seemingly discrepant results, it should be considered that there is not reliable evidence that ADRs are concentration-dependent in antidepressant treatment.[39]

Since we did not find evidence that CYP2D6 expression or inhibition predicted reported ADRs, we performed an exploratory regression model. Depression severity, somatic comorbidity, and female sex were associated with more reported ADRs in our sample. This is in line with previous findings that ADRs seem to be more positively related to severity of depressed mood than to antidepressant dose.[40] Somatic comorbidity can lead to symptoms that may mistakenly be reported as side effects. It has also been shown previously that women have a nearly 2-fold greater risk than men for exhibiting ADRs across all drug classes.[41]

In contrast to most other studies that have investigated the predictive value of CYP2D6 in ADRs, we allowed

concomitant medications and investigated the effect of phenoconversion due to CYP2D6 inhibitors. This is a strength in our study. As the UKU scale is constructed to include more question for women, we also excluded sex-specific items when comparing overall UKU scores. Interestingly, most other studies do not take this into account, which may influence their results.

The present study was carried out in a naturalistic setting, leading to certain limitations. The ADRs were analyzed by a single measure of the UKU scale, and most subjects had been treated with 1 or several drugs for varying amounts of time. Therefore, the results do not tell us anything about the initial ADRs when starting on a new drug regimen. Drugs that can induce CYP2D6-dependent ADRs may already have been dose adjusted or discontinued before referral to the study. In addition, the reported ADRs depended on self-report, and we did not measure ADRs that would be unknown to the patient such as QTc prolongation. Furthermore, about half of the included patients were diagnosed with chronic depression or dysthymia, and comorbidity with anxiety disorder or personality disorder was common; thus, the results may not be representative of uncomplicated major depressive disorder. The GEN-DS project was originally designed to include 516 patients; however, primarily due to the COVID pandemic, we were unable to recruit as many patients as planned, leading to a limited sample size in this study.

The subjects were genotyped for the alleles that were deemed most relevant at the time of the study. As in previous studies, not all possible alleles were tested for, and new variants are continuously discovered. It is important to keep this in mind when interpreting the results. The inherent risk when analyzing too few allelic variants is an overestimation of *CYP2D6*1* (and/or *2).[42] The frequencies of the alleles also vary between different ethnic groups, with some alleles being more represented in non-European groups[43]; however, our sample consisted mostly of subjects with European lineage. Also, not all cited studies may be directly comparable to our results, as different classifications of CYP2D6 phenotypes are sometimes used.

In conclusion, we did not find that *CYP2D6* genotype could predict the occurrence of ADRs in depressive patients with insufficient treatment response in this naturalistic setting. However, *CYP2D6* genotyping may still be important in this clinical group for selection of antidepressive treatment, for dosing of certain medications or when the patient is suffering from severe ADRs. Also, even though we did not find evidence that phenoconversion predicted ADRs, the risk of drug interaction should always be considered. Future studies should investigate the effect of comedication and phenoconversion in prospective study designs in order to further elucidate the impact of phenoconversion and *CYP2D6* genetic variation.

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References

1. Depression and Other Common Mental Disorders: Global Health Estimates. World Health Organization. Licence: CC BY-NC-SA 3.0 IGO; 2017. https://www.who.int/publications/i/item/depression-global-health-estimates/
2. Brody DJ, Gu Q. Antidepressant use among adults: United States, 2015-2018. *NCHS Data Brief.* 2020;(377):1–8.
3. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006;163(11):1905–1917.
4. Gyllensten H, Rehnberg C, Jönsson AK, et al. Cost of illness of patient-reported adverse drug events: a population-based cross-sectional survey. *BMJ Open.* 2013;3(6):e002574.
5. Solomon HV, Cates KW, Li KJ. Does obtaining CYP2D6 and CYP2C19 pharmacogenetic testing predict antidepressant response or adverse drug reactions? *Psychiatry Res.* 2019;271:604–613.
6. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry.* 2018;51(1-02):e1.
7. Ingelman-Sundberg M, Sim SC, Gomez A, et al. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. *Pharmacol Ther.* 2007;116(3):496–526.
8. Pharmacogene Variation Consortium (PharmVar). Updated December 20, 2022. Accessed Jan 20, 2023. www.PharmVar.org/genes
9. Gaedigk A, Casey ST, Whirl-Carrillo M, et al; Pharmacogene Variation Consortium. Pharmacogene Variation Consortium: a global resource and repository for pharmacogene variation. *Clin Pharmacol Ther.* 2021;110(3):542–545.
10. Gaedigk A, Ingelman-Sundberg M, Miller NA, et al; PharmVar Steering Committee. The Pharmacogene Variation (PharmVar) consortium: incorporation of the human cytochrome P450 (CYP) allele nomenclature database. *Clin Pharmacol Ther.* 2018;103(3):399–401.
11. Gaedigk A, Whirl-Carrillo M, Pratt VM, et al. PharmVar and the landscape of pharmacogenetic resources. *Clin Pharmacol Ther.* 2020;107(1):43–46.
12. Altar CA, Hornberger J, Shewade A, et al. Clinical validity of cytochrome P450

metabolism and serotonin gene variants in psychiatric pharmacotherapy. *Int Rev Psychiatry*. 2013;25(5):509–533.
13. Shah RR, Smith RL. Addressing phenoconversion: the Achilles' heel of personalized medicine. *Br J Clin Pharmacol*. 2015;79(2):222–240.
14. Asp M, Lindqvist D, Fernström J, et al. Recognition of personality disorder and anxiety disorder comorbidity in patients treated for depression in secondary psychiatric care. *PLoS One*. 2020;15(1):e0227364.
15. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22–33, quiz 34–57.
16. First M, Gibbon M, Spitzer RL, et al. *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)*. American Psychiatric Press, Inc; 1997.
17. Åsberg M, Montgomery SA, Perris C, et al. A comprehensive psychopathological rating scale. *Acta Psychiatr Scand suppl*. 1978;57(S271):5–27.
18. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition. American Psychiatric Association; 2000.
19. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
20. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale: new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand suppl*. 1987;76(s334):1–100.
21. Lindström E, Lewander T, Malm U, et al. Patient-rated versus clinician-rated side effects of drug treatment in schizophrenia: clinical validation of a self-rating version of the UKU Side Effect Rating Scale (UKU-SERS-Pat). *Nord J Psychiatry*. 2001;55(suppl 44):5–69.
22. Söderbäck E, Zackrisson AL, Lindblom B, et al. Determination of CYP2D6 gene copy number by pyrosequencing. *Clin Chem*. 2005;51(3):522–531.
23. Zackrisson AL, Lindblom B. Identification of CYP2D6 alleles by single nucleotide polymorphism analysis using pyrosequencing. *Eur J Clin Pharmacol*. 2003;59(7):521–526.
24. Caudle KE, Sangkuhl K, Whirl-Carrillo M, et al. Standardizing CYP2D6 genotype to phenotype translation: consensus recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group. *Clin Transl Sci*. 2020;13(1):116–124.
25. Pharm GKB. Accessed Nov 1, 2022. https://www.PharmGKB.org/
26. Whirl-Carrillo M, Huddart R, Gong L, et al. An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther*. 2021;110(3):563–572.
27. Whirl-Carrillo M, McDonagh EM, Hebert JM, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther*. 2012;92(4):414–417.
28. Flockhart DA, McDonald C, Desta Z. The Flockhart Cytochrome P450 Drug-Drug Interaction Table. Division of Clinical Pharmacology, Indiana University School of Medicine. Updated 2021. Accessed Aug 27, 2023. https://drug-interactions.medicine.iu.edu
29. Borges S, Desta Z, Jin Y, et al. Composite functional genetic and comedication CYP2D6 activity score in predicting tamoxifen drug exposure among breast cancer patients. *J Clin Pharmacol*. 2010;50(4):450–458.
30. Walden LM, Brandl EJ, Tiwari AK, et al. Genetic testing for CYP2D6 and CYP2C19 suggests improved outcome for antidepressant and antipsychotic medication. *Psychiatry Res*. 2019;279:111–115.
31. Ng C, Sarris J, Singh A, et al. Pharmacogenetic polymorphisms and response to escitalopram and venlafaxine over 8 weeks in major depression. *Hum Psychopharmacol*. 2013;28(5):516–522.
32. Roberts RL, Mulder RT, Joyce PR, et al. No evidence of increased adverse drug reactions in cytochrome P450 CYP2D6 poor metabolizers treated with fluoxetine or nortriptyline. *Hum Psychopharmacol*. 2004;19(1):17–23.
33. Hodgson K, Tansey KE, Uher R, et al. Exploring the role of drug-metabolising enzymes in antidepressant side effects. *Psychopharmacology (Berl)*. 2015;232(14):2609–2617.
34. Steimer W, Zöpf K, von Amelunxen S, et al. Amitriptyline or not, that is the question: pharmacogenetic testing of CYP2D6 and CYP2C19 identifies patients with low or high risk for side effects in amitriptyline therapy. *Clin Chem*. 2005;51(2):376–385.
35. Rau T, Wohlleben G, Wuttke H, et al. CYP2D6 genotype: impact on adverse effects and nonresponse during treatment with antidepressants-a pilot study. *Clin Pharmacol Ther*. 2004;75(5):386–393.
36. Sánchez-Iglesias S, García-Solaesa V, García-Berrocal B, et al. Role of pharmacogenetics in improving the safety of psychiatric care by predicting the potential risks of mania in CYP2D6 poor metabolizers diagnosed with bipolar disorder. *Medicine (Baltimore)*. 2016;95(6):e2473.
37. Preskorn SH, Kane CP, Lobello K, et al. Cytochrome P450 2D6 phenoconversion is common in patients being treated for depression: implications for personalized medicine. *J Clin Psychiatry*. 2013;74(6):614–621.
38. Storelli F, Matthey A, Lenglet S, et al. Impact of CYP2D6 functional allelic variations on phenoconversion and drug-drug interactions. *Clin Pharmacol Ther*. 2018;104(1):148–157.
39. Funk CSM, Hart XM, Gründer G, et al. Is therapeutic drug monitoring relevant for antidepressant drug therapy? implications from a systematic review and meta-analysis with focus on moderating factors. *Front Psychiatry*. 2022;13:826138.
40. Uher R, Farmer A, Henigsberg N, et al. Adverse reactions to antidepressants. *Br J Psychiatry*. 2009;195(3):202–210.
41. Zucker I, Prendergast BJ. Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biol Sex Differ*. 2020;11(1):32.
42. Gaedigk A, Sangkuhl K, Whirl-Carrillo M, et al. Prediction of CYP2D6 phenotype from genotype across world populations. *Genet Med*. 2017;19(1):69–76.
43. Zhou Y, Ingelman-Sundberg M, Lauschke VM. Worldwide distribution of cytochrome P450 alleles: a meta-analysis of population-scale sequencing projects. *Clin Pharmacol Ther*. 2017;102(4):688–700.