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Original Article

Divergent Phenotypes, Actionable Genotypes, and Phenoconversion in a German Psychiatric Inpatient Population: Results from the FACT-PGx Study

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Abstract

Background and objectives: Genetic polymorphisms of CYP2D6 and CYP2C19 affect both the effectiveness and the occurrence of side effects of many antidepressants. By drug-drug-gene interactions (also referred to as phenoconversion), the phenotype of the patient can be changed. Both pharmacogenetic testing, drug-drug, and drug-drug-gene interaction checks are essential to individualize the dose of the antidepressant or start an alternative drug in accordance with the pharmacogenetic guidelines. The aim of this study was to analyze the frequency of divergent phenotypes (i.e. divergent from the common phenotypes considered normal), of phenoconversion (a genotype–phenotype mismatch), and of actionable genotypes (genotypes where a prescribing change may be indicated) in psychiatric inpatients with a depressive disorder.

Methods: Genotyping of CYP2D6 and CYP2C19 was performed in 104 patients 18 years of age or older who received inpatient treatment in a German psychiatric university hospital for a depressive disorder. Representation of the frequencies of divergent phenotypes, of phenoconversion, and of actionable genotypes were analyzed.

Results: A divergent phenotype in one or both CYP enzymes was seen in 83.5% of the patients. The rate of CYP2D6 poor metabolizers increased by 142.4% (from 5.9% to 14.3%, $p = 0.013$) at admission and by 183.1% (from 5.9% to 16.7%, $p = 0.004$) at discharge because of phenoconversion. At discharge, 22% of the patients ($n = 104$) received an antidepressant with a dosing recommendation based on their CYP2D6 phenotype and 15.4% on their CYP2C19 phenotype. When considering phenoconversion, the rate increased by 17.4 to 26.0% ($p = 0.221$) for patients with the CYP2D6 genotype.

Conclusions: The clinical relevance of the results of the study is that phenotype conversion is common in patients treated for depression with medication. The discrepancy between the clinically observed phenotype and the phenotype expected based on the patient genotype underscores the need for greater consideration of both genetic and nongenetic factors.

Keywords: Pharmacogenetics; Pharmacogenetic testing (PGx testing); Actionable genotypes; Phenoconversion; Antidepressants.

Abbreviations: CNV, copy number variation; CPIC, clinical pharmacogenetics implementation consortium; CYP, cytochrome p450; DPWG, Dutch pharmacogenetic working group; EM, extensive metabolizer; EMA, European Medicine Agency; FDA, Food and Drug Administration; IM, intermediate metabolizer; NM, normal metabolizer; PGx, pharmacogenetic; PM, poor metabolizer; RM, rapid metabolizer; SNP, single nucleotide polymorphism; TCA, tricyclic antidepressant; TGA, therapeutic goods administration; UM, ultra-rapid metabolizer.

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Introduction

Antidepressants have been used since the 1950s to treat depression. Tricyclics were the first on the market. Many other antidepressants became available in the following decades. They all have in common, that they are mainly metabolized by CYP (cytochrome P450) enzymes in the liver.[1] Some antidepressants are inhibitors of CYP enzymes, causing an increase in serum concentrations of a victim drug. Therefore, antidepressants are considered red flag

medications in regard to drug interactions that can result in adverse outcomes for the patient. Interestingly these drug interactions do not result in adverse outcomes in every patient, which was only understood, when the genetics were taken into account. Over the last decades, research on pharmacogenetics (PGx) has intensified and many guidelines were released for psychotropic drugs and others. Patients suffering from psychiatric disorders may benefit from PGx testing, as polymorphisms of CYP2D6 and CYP2C19 are associated with decreased or increased metabolism of many psychotropic drugs and may result in increased side effects or inefficacy that lead to an unsatisfactory remission rate and low adherence rates owing to intolerable side effects.[2–4] Approximately 40% of the patients taking antidepressants suffer from adverse drug reactions.[5] In the STAR*D trial, the largest, and most consequential antidepressant study, the response rate to the first antidepressant was only 47%.[2]

The genes coding for isoenzymes CYP2D6 and CYP2C19 have been most thoroughly studied as they are relevant for many psychotropic drugs, proton pump inhibitors, clopidogrel, beta blockers, and many others.[6] The enzyme activity defines five metabolizer types: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM) or normal metabolizer (NM), rapid metabolizer (RM, for CYP2C19 only) and ultra-rapid metabolizer (UM) can be distinguished.[7,8] Besides genetic factors, there are many other factors affecting drug metabolism, such as age, sex, medical conditions, and drug interactions.[9] Therefore, the genotype does not always reflect the observed phenotype. Among experts, this is referred to as phenoconversion: a genotype-phenotype mismatch.

Guidelines for PGx testing of SSRIs and tricyclics have been available for many years, for instance by the CPIC (Clinical Pharmacogenetics Implementation Consortium) and the DPWG (Dutch Pharmacogenetics Working Group), which may help the practitioner to implement genotyping results into clinical practice.[7,8,10] Roughly one-third of all PGx guidelines are on psychotropic drugs. Nevertheless, PGx testing in psychiatry is not yet commonly used in clinical practice, even though warnings were issued by the FDA (Food and Drug Administration) and TGA (Therapeutic Goods Administration) about QTc prolongation in CYP2C19 poor metabolizers who receive citalopram.[11] Due to this risk, the CPIC guidelines recommend reducing the recommended starting dose for citalopram by 50% of the starting dose in patients with this genetic variant.[10] The German Summary of Product Characteristics also includes this information, which, however, is not implemented in the absence of available genotyping results.[12]

The term actionable genotype is used if the drug gene interaction results in a clinically significant increase or decrease in drug serum concentration.[13] The first German PGx study in psychiatry dates from 2020.[14] In 108 hospitalized patients suffering from depression, genotyping was performed on a routine basis. Even though the study revealed a high percentage of non-NMs and a shorter length of stay in preemptively genotyped patients, the introduction of PGx to routine clinical care in Germany, is still in its early stages. Further research on the question of how both the application and implementation of PGx can be optimized is of utmost importance.[15]

The present data is part of a larger-scale study entitled "Acceptance, Use, and Feasibility of Pharmacogenetic Testing in Psychiatry" (FACT-PGx), which aimed to demonstrate how to overcome potential obstacles for comprehensive implementation of PGx in daily clinical practice in psychiatry. Most CYP enzymes, alleles, genotypes, and phenotype frequencies have been analyzed and published. To date, only limited data is available for inpatients in psychiatry, which prompted us to carry out this study, where we analyzed the two crucial polymorphic enzymes of drug metabolism, CYP2D6, and CYP2C19, determined in 104 hospitalized psychiatric patients of predominantly European ancestry. In addition to genotype and phenotype frequencies, we also analyzed the number of actionable genotypes and phenoconversion.

This study aimed to analyze the frequency of genetic polymorphisms of the CYP2D6 and CYP2C19 types in hospitalized patients with depressive disorders. Further, phenoconversion (i.e. a genotype–phenotype mismatch) was statistically analyzed. We expected an increase in divergent phenotypes and actionable genotypes because of phenoconversion effects. By using the patient PGx results and conduction of a drug-drug-gene interaction check the drug therapy safety can be increased, especially in settings where therapeutic drug monitoring is not established.[1] This would further emphasize the importance of PGx in routine patient care.

Materials and methods

All patients over 18 years of age who were electively admitted to the two openly managed depression units of the Department of Psychiatry, Psychosomatics, and Psychotherapy of Frankfurt University Hospital of Goethe University for a depressive disorder (F32.x and F33.x) between July 2021 and January 2022 were offered genotyping for CYP2D6 and CYP2C19. A total of 104 patients consented to participate in the study. PGx testing was offered on a routine basis. Polymorphisms of the genetic disposition for the CYP2D6 (*1, *2, *3, *4, *6, *9, *10, *14, *17, *34, *35, *39, *41, *46, *58, *64, *69, *71, *82, *88, and *114) and CYP2C19 (*1, *2, *3, *4, and *17) were analyzed. Genotyping for CYP2D6 and CYP2C19 was performed at the Department of Psychiatry, Psychosomatics, and Psychotherapy of the University Hospital of Würzburg. This required collecting a single EDTA blood sample of 2 mL. The PharmVar website (https://www.pharmvar.org/genes) was used to define haplotypes for each SNP (single nucleotide polymorphism). Phenotypes of CYP2D6 and CYP2C19 were determined based on the specifications of the CPIC ([https://cpicpgx.org]).[16] Comedication, kidney and liver function and smoking status were assessed in clinical interviews, routine laboratory examination, and from the patient chart. Details of the laboratory analysis can be obtained from the first author's correspondence address. The study was approved by the local Ethics Committee of the University of Frankfurt (2021-138) and carried out in line with the ethical principles of the Declaration of Helsinki 2013. Written informed consent was obtained from each patient.

Phenoconversion effects

We assessed the phenoconversion effects for CYP2D6 according to Cicali *et al*.[17] In patients who received a moderate or strong CYP2D6 inhibitor, we multiplied the activity score for CYP2D6 by 0.5 or 0, respectively, and determined the adjusted phenotype using the adjusted activity factor in line with CPIC specifications.[16,17] Phenoconversion for CYP2C19 was calculated as described by Hahn *et al*.[18] in a 2021 publication, based on studies by Klieber *et al*.[19] and Hägg *et al*.[20] Comedications that could lead to phenoconversion owing to their inhibiting or inducing effects on CYP2D6 and CYP2C19 were derived from the Flockhart table.[21] In this study, actionable genotypes refer to medications or certain genotypes or phenotypes for which dose recommendations according to the guidelines of the CPIC or DPWG are available, thus deviating from standard dose in a clinically relevant manner. We compared our cohort to a cohort studied by Hahn *et al*.[14] to see whether the high number of divergent phenotypes was an exception or could be assumed to be representative of Germany. Data

Table 1. Overview of the antidepressants taken by the 104 German patients at admission and discharge

Antidepressant	Admission		Discharge	
	n	%	*n*	%
Agomelatine	2	1.9	1	1
Amitriptyline	0	0	16	15.4
Bupropion	4	3.8	7	6.7
Citalopram	2	1.9	0	0
Clomipramine	2	1.9	1	1
Duloxetine	4	3.8	3	2.9
Escitalopram	12	11.5	9	8.7
Fluoxetine	4	3.8	1	1
Maprotiline	0	0	1	1
Milnacipran	0	0	2	1.9
Mirtazapine	0	0	17	16.3
Paroxetine	1	1	1	1
Sertraline	13	12.5	20	19.2
Tranylcypromine	1	1	0	0
Trimipramine	1	1	2	1.9
Venlafaxine	17	16.3	40	38.5

analysis was performed using R statistical software (version 4.1.2). The independence of two categorical parameters was tested by the chi-squared test. To evaluate changes in the proportions of a categorical parameter between admission and discharge, the McNemar's test (in case of two categories) and the Stuart-Maxwell test (in case of at least three categories) were used. Chi-square tests were used to compare the two cohorts.

Results

Patient characteristics

A total of 104 patients with major depressive disorder were genotyped, 50% of whom were women. The average age was 42.6 ± 15.2 years. In the sample, 44.7 % were smokers. The ethnic background of the patients was not recorded. However, it can be assumed that the patients were predominantly of European descent. No patient refused genotyping. Antidepressants were administered orally and dose adjustments were made by therapeutic drug monitoring (TDM). It should be noted that the genotyping results were available only after the patients had been discharged and had no impact on treatment.[22] Table 1 includes a summary of the antidepressants taken by the 104 patients at admission and discharge.

CYP2D6 and CYPC19 test results

The frequencies of the CYP2D6 and CYP2C19 phenotypes are summarized in Table 2, which shows that 83.5% of the patients had a divergent phenotype (i.e. divergent from the common phenotypes considered normal, such as an NM) in at least one and/or both enzymes: in 66 (63.5%) of our patients, CYP2C19 was of a divergent phenotype. In CYP2D6, 47 patients (46.5%) had a divergent phenotype. Only 16.5% of the patients had an NM status for both CYP2D6 and CYP2C19.

We compared the frequencies of divergent phenotypes present in our study with data from 2021, the first German genotyping study in psychiatry to record the frequencies of genetic polymorphisms of CYP2D6 and CYP2C19 in 108 hospitalized patients with depressive disorders on a routine basis.[14] The distribution of the metabolizer types between the two groups showed no significant difference (see Table 3)[14]; therefore, the phenotypic frequen-

Table 2. Genotype-predicted phenotype frequencies for CYP2D6 and CYP2C19 in 104 German patients

Predicted phenotype	CYP2D6		CYP2C19	
	n	%	*n*	%
UM	5	5	5	4.8
RM	–	–	32	30.8
NM	54	53.5	38	36.5
IM	36	35.6	28	26.9
PM	6	5.9	1	1

IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UM, ultra-rapid metabolizer. –, No rapid metabolizer phenotype exists for CYP2D6.

Table 3. Comparison of phenotype frequencies with a German study from 2021[14]

Author and Date of Study	CYP2D6, %				CYP2C19, %				
	UM	NM	IM	PM	UM	RM	NM	IM	PM
Hahn *et al*. 2021[14] (*n* = 108)	1 (+3 UM/PM)	53	35	7	9	31	32	27	2
Eckert *et al*. 2023 (*n* = 104)	5	53	36	6	5	31	37	27	1
Chi-squared test		*p* = 0.381					*p* = 0.703		

IM, intermediate metabolizer; NM, normal metabolizer; PGx, pharmacogenetic; PM, poor metabolizer; RM, rapid metabolizer; UM, ultra-rapid metabolizer.

cies determined in both studies may be rated as characteristic of inpatients in psychiatry in Germany.

Phenoconversion frequencies for the CYP2D6 and CYP2C19 enzymes

Table 4 shows the phenotypic frequencies for the CYP2D6 and CYP2C19 types, before and after phenoconversion, at the moment of admission and discharge, and the drugs prescribed, which may act as both inhibitors and/or inducers. The prescribed CYP2D6 inhibitors causing phenoconversion (following the Flockhart table) included bupropion, paroxetine, fluoxetine, duloxetine, sertraline, escitalopram, and citalopram. Paroxetine, fluoxetine, duloxetine, and bupropion are potent CYP2D6 inhibitors. There were no known moderate or strong inducers of CYP2D6. Prescribed CYP2C19 inhibitors causing phenoconversion (based on the Flockhart table) included fluoxetine and citalopram. CYP2C19 inducers were not prescribed.

In our study, the most commonly prescribed CYP2D6 inhibitors causing phenoconversion (following the Flockhart table) included escitalopram (n = 12 at admission and n = 9 at discharge), citalopram (n = 2 at admission and n = 0 at discharge), sertraline (n = 13 at admission and n = 20 at discharge), paroxetine (n = 1 at admission and n = 1 at discharge), fluoxetine (n = 4 at admission and n = 1 at discharge), duloxetine (n = 4 at admission and n = 3 at discharge), and bupropion (n = 4 at admission and n = 7 at discharge). Antidepressants that are potent CYP2D6 inhibitors include paroxetine, fluoxetine, duloxetine, and bupropion.

The prescribed CYP2C19 inhibitors of the 104 patients that caused phenoconversion (based on the Flockhart table) were fluoxetine and citalopram. CYP2C19 inducers were not prescribed. Because of phenoconversion, CYP2D6-IM had an increase of 37.6% (35.6–49%, p = 0.001) at admission and 23.0% (from 35.6% to 43.8%, p = 0.044) at discharge. The rate of CYP2D6-PM increased by 142.4% (from 5.9% to 14.3%, p = 0.013) at admission and by 183.1% (from 5.9% to 16.7%, p = 0.004) at discharge owing to phenoconversion. Before phenoconversion, 53.5% of the patients were classified as CYP2D6 NM. After considering phenoconversion effects, the rates were 32.7% and 35.4%, respectively. Considering phenoconversion effects for CYP2C19, the number of CYP2C19-PM increased by 380% from 1% to 4.8% (p = 0.133) at admission and by 90% to 1.9% (p = 1) at discharge. However, the results were not statistically significant. The other CYP2C19 phenotypes had only marginal changes. There were quite small differences related to the time of admission and discharge for phenoconversion of the enzymes CYP2D6 and CYP2C19. In the statistical calculation using the Stuart-Maxwell test, there were no statistically significant differences for CYP2D6 (p = 0.667) and CYPC19 (p = 0.3425) with regard to a change in phenoconversion related to the time of admission and discharge.

Medications with actionable PGx guideline recommendations

The frequencies calculated for the actionable genotypes of the 104 patients are summarized in Table 5. A total of 14.4% of the patients carried at least one actionable genotype for either CYP2D6 or CYP2C19 at admission, which may have had an impact on one or several currently prescribed medications. At discharge, 31.7% of the patients had at least one actionable PGx variant in one of both enzymes. Of the 104 patients, 1% or 2.9%, respectively, carried an actionable genotype in both investigated enzymes (CYP2D6 and CYP2C19). Figure 1 shows the number of patients receiving antidepressants at admission and discharge before and after phenoconversion based on the presence or absence of medications with actionable PGx guideline recommendations.

At admission, 7.7% of the 104 patients with the CYP2D6 genotype and 8.7% with the CYP2C19 genotype received antidepressants with actionable genotypes based on the phenotype results. Due to phenoconversion, the rate increased to 10.6% in patients with the CYP2D6 genotype, for whom there was only one actionable genotype. A total of 83.5% of the patients par-

Table 4. Calculated phenoconversion frequencies for CYP2D6 and CYP2C19 in 104 German patients at admission and discharge

Type	CYP2D6, %			CYP2C19, %		
	Genetic phenotype	Phenoconversion admission	Phenoconversion discharge	Genetic phenotype	Phenoconversion admission	Phenoconversion discharge
UM	5	4.1	4.2	4.8	4.8	4.8
RM	–	–	–	30.8	30.8	30.8
NM	53.5	32.7	35.4	36.5	33.7	37.5
IM	35.6	49	43.8	26.9	26	25
PM	5.9	14.3	16.7	1	4.8	1.9
	Stuart-Maxwell: *p* = 0.667			Stuart-Maxwell: *p* = 0.343		

IM, intermediate metabolizer; NM, normal metabolizer; RM, rapid metabolizer; PM, poor metabolizer; UM, ultra-rapid metabolizer.

Table 5. Frequencies of actionable genotypes in CYP2D6 and CYP2C19 genes predictive of altered response to substrate drugs in 104 German patients

Test findings	Admission		Discharge		*p*-value
	n	%	*n*	%	
Non-normal metabolizer with no actionable genotype	37	35.6	51	49	0.035
Actionable genotype[a]	15	14.4	33	31.7	0.0005
Actionable genotypes[b]	1	1	3	2.9	0.617

[a]Patients with an actionable genotype in exactly one of the tested enzymes, in either CYP2D6 or CYP2C19. [b]Patients with an actionable genotype for both enzymes, once for CYP2D6 and once for CYP2C19.

ticipating in our study had a divergent phenotype in at least one enzyme. CYP2D6 polymorphisms were present in 46.5% of the patients. In 26 patients on admission, phenoconversion for CYP2D6 occurred. Four patients had a phenoconversion in CYP2C19. At discharge, the numbers did not change significantly in 26 patients and CYP2D6 and CYP2C19 phenoconversion occurred in three patients.

Discussion

Our findings suggest that the recommended standard dose of CYP2D6 substrates according to the recommendations of the CPIC and DWPG guidelines needed to be adjusted and/or alternative medications needed to be selected in almost half the study population. CYP2C19 polymorphisms were present in 63.5% of our patients. Of those, 35.6% were UM and RM and therefore had a high risk of not responding to CYP2C19 substrates. For example, citalopram, escitalopram, and some tricyclic antidepressants needed a higher dosage than the one included in the prescribing information. Furthermore, CYP2C19 PMs carry an increased risk of suffering undesirable side effects from standard dosages of CYP2C19 substrate medications. The PM frequency of 1% in our sample roughly

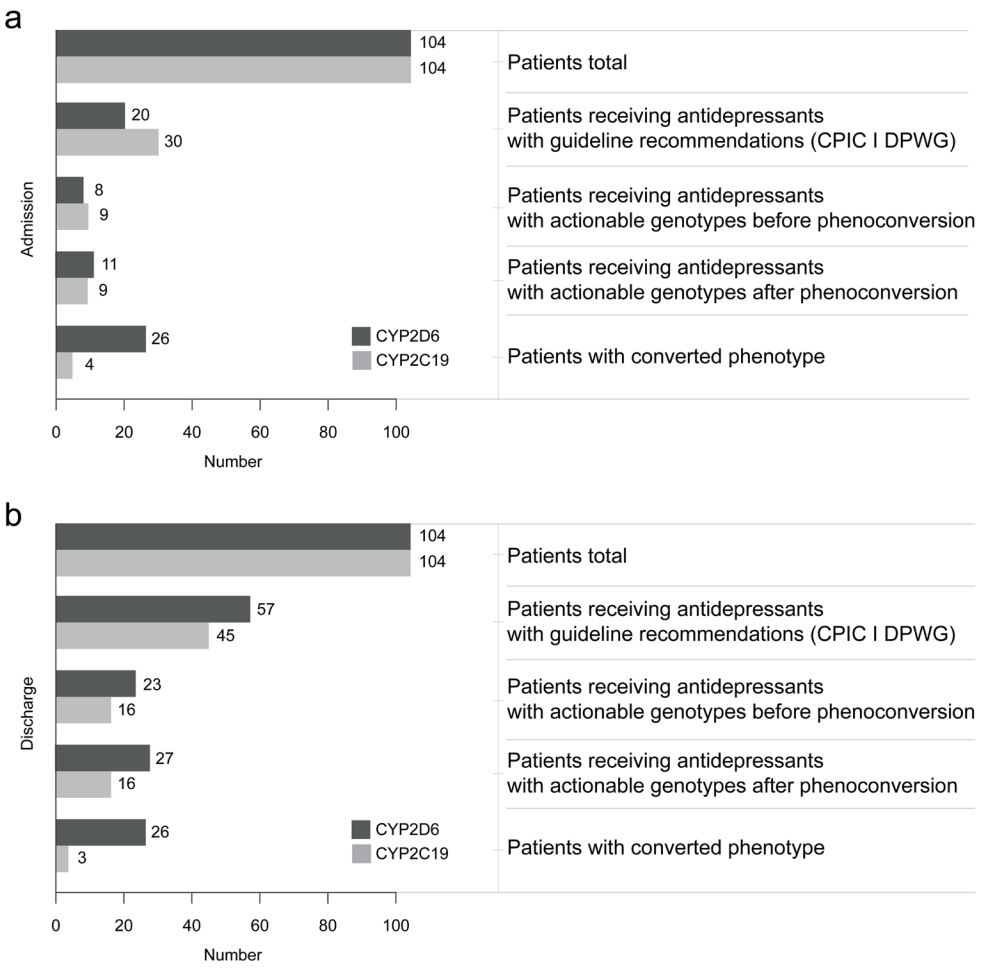

Fig. 1. Patients receiving antidepressants with actionable PGx guideline recommendations at admission and discharge before and after phenoconversion. CPIC, clinical pharmacogenetics implementation consortium; CYP, cytochrome p450; DPWG, Dutch pharmacogenetic working group.

corresponded to the frequency in Europeans (2%) and was lower than in other ethnic groups, such as the Japanese (15.2–24%), Native Americans (3.3–7.0%), and African-Americans (7.0%).[23] Finally, we compared the frequencies of divergent genotypes of our study with the data from the 2021 study.[14] The differences between the two groups were not statistically significant, so the phenotypic frequencies determined in both studies may be rated as characteristic of inpatients in psychiatry in Germany.

Our findings suggest that when prescribing antidepressants, it is essential to consider not only the genetic influence on drug metabolism but also the effects of drugs on an individual patient's metabolic status, especially drug-drug interactions, although we were able to demonstrate statistically significant results only with respect to CYP2D6. Even though this phenomenon is unlikely to pose an increased risk to the general population, patients treated with antidepressants who are also taking other medications may experience high rates of phenoconversion, which can significantly increase the risk of adverse drug reactions.

In our study, the rate of CYP2D6 poor metabolizers showed a 2.4-fold increase at admission and a 2.8-fold increase at discharge owing to phenoconversion. In a naturalistic study on depression published in 2013, it was reported that phenoconversion led to a seven-fold increase in CYP2D6 poor metabolizers.[24] In patients with a CYP2D6 poor metabolizer status, standard dosing of CYP2D6 substrates (e.g., metoprolol, atomoxetine, or nortriptyline) may lead to adverse drug reactions, and prodrugs such as codeine or tamoxifen cannot be converted into active substance. An Australian study conducted in 2019 reported a five-fold increase in the frequency of CYP2D6 and CYP2C19 poor metabolizers when phenoconversion was considered.[25]

Because of phenoconversion, CYP2D6-IM had an increase of 37.6% (from 35.6% to 49%, $p = 0.001$) at admission and 23.0% (from 35.6% to 43.8%, $p = 0.044$) at discharge in our study. Before phenoconversion, 53.5% of the patients were CYP2D6 NM. After taking phenoconversion effects into account, the rates were only 32.7% or 35.4%, respectively. Considering phenoconversion effects for CYP2C19, the number of CYP2C19-PM increased by 380% from 1% to 4.8% ($p = 0.133$) at admission and by 90% to 1.9% ($p = 1$) at discharge. This finding, although not statistically significant, may impact CYP2C19 substrates (e.g., sertraline or clopidogrel) and be associated with treatment failure.[10,26]

Drug-drug interactions in psychiatry are very common.[27] To evaluate the clinical relevance of pharmacokinetic drug-drug interactions, the phenotype is important. For example, duloxetine–ciprofloxacin drug interactions depend upon the CYP2D6 genotype. While not relevant in CYP2D6 NMs, duloxetine levels increase by 400% in CYP2D6 poor metabolizers.[28] As TDM is only established in psychiatry, neurology, and antimicrobial therapy, the concentrations of the involved drugs can only be measured in certain cases. Also, laboratory methods only allow the measurement of parent drugs and a few active metabolites. Nevertheless, it is known that the accumulation of metabolites that are not measured can affect the tolerability and adherence of the patient.[29] The study results are limited in several ways: The PGx test panel used in the study did not include any other important pharmacogenes (e.g., CYP1A2, CYP3A4, CYP2C9, ABCB1 gene, and HTR2A gene). Therefore, the number of medications with actionable genotypes was probably underestimated. In addition, future studies should also consider clinical data, such as treatment duration, side effects, comedication, and remission at discharge.

Future directions

The use of PGx testing in psychiatry in Germany is currently limited because of differing opinions about its clinical benefits, doubts about the evidence, and a lack of knowledge. Nonetheless, recent developments in the field of PGx and published data showing that PGx testing improves remission rates in depressed patients[30–32] suggest that these obstacles may soon be overcome. PGx testing could become an established tool in psychiatry in Germany. A well-coordinated interprofessional collaboration between physicians and clinical pharmacists could help overcome the current hesitancy toward PGx testing.

Conclusions

Many previous studies neglected the effect of phenoconversion, potentially leading to a failure to find a correlation between genotype and plasma drug concentration. The relevance of pharmacokinetic drug interactions depends on the patient's genotype, which explains why interactions may lead to clinically significant changes in some patients but not in others. This is also reflected in the different assessments of interactions in interaction databases. An evaluation of pharmacokinetic interactions is only possible when the genotype is known, which underscores the importance of PGx testing in clinical practice. In psychopharmacotherapy, agents that induce phenoconversion are frequently used, such as paroxetine, fluoxetine, duloxetine, and bupropion, and can lead to CYP inhibition and consequently to toxic effects due to the enrichment of substrates.

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Conflict of interest

The authors declare that they have no conflict of interests related to this publication.

Author contributions

Study design (AE, AF, MSC, HW, SU, AR, MH), performance of experiments (AE, AF, MSC, HW, SU, AR, MH), analysis and interpretation of the data (AE), manuscript writing (AE), critical revision (AE, AF, MSC, HW, SU, AR, MH), and statistical analysis (AE). All authors made significant contributions to the study and have approved the final manuscript.

Ethical statement

The study was approved by the local Ethics Committee of the University of Frankfurt (2021-138) and carried out in line with the ethical principles of the Declaration of Helsinki 2013. A written informed consent was obtained from each patient.

Data sharing statement

The data set is available upon reasonable request from the corresponding author at Andreas.Eckert@kgu.de.

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