Original Article

A Collaborative Approach in Pharmacogenetic Testing: Actionable Genotypes of Antidepressants and Their Avoidance in a Retrospective Study

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Abstract

Background and objectives: Pharmacogenetic (PGx) testing could avoid adverse drug events and increase drug response. CYP2D6 and CYP2C19 actionable genotypes are the most important for antidepressants. The study was conducted to analyze the number of actionable genotypes in patients prior and post PGx testing in a naturalistic setting and also to examine the influence of a clinical pharmacist.

Methods: PGx testing was conducted in adult major depressive disorder inpatients (n = 108; 57% female). A retrospective analysis of the medication and actionable genotypes according to the CPIC and DPWG guidelines prior and post PGx testing was made with the t-test. The acceptance rate of the pharmacist´s recommendation was documented.

Results: Forty-seven percent of all patients (n = 108) received antidepressants with dosing recommendations for the CYP2D6 and/or CYP2C19 genotypes. Of the 84 patients that were administered antidepressants prior to PGx testing, 49 patients (58%) received antidepressants and four patients (5%) received antipsychotics with guideline recommendations for the CYP2D6 and CYP2C19 genotypes. Twenty-eight actionable genotypes (55%) were found in 51 patients (53 prescriptions). The acceptance rate of the clinical pharmacist´s recommendation was 88%, and the reduction rate for the actionable genotypes was 93%. Patients had statistically significant lower number of actionable genotypes after PGx (p < 0.001).

Conclusions: A collaboration of psychiatrists and pharmacists seems advisable for the implementation of PGx testing into clinical practice. As 87% of the patients had divergent genotypes for CYP2D6 and/or CYP2C19 and the majority (55%) of patients were receiving antidepressants that were not ideal according to the PGx guidelines, a pre-emptive testing approach should be applied in daily practice to ensure drug therapy safety.

Introduction

Antidepressants are recommended in patients with a major depressive disorder (MDD) according to the treatment guidelines.[1,2] First line therapy often consists of selective serotonin reuptake inhibitors (SSRIs). In particular, the polymorphic enzymes CYP-2D6 and CYP2C19 are involved in the metabolism of SSRIs and

tricyclics, as reviewed in detail by Kirchheiner *et al*. more than 15 years ago.[3] As a result of this and numerous other pharmacogenetic publications over the past 25 years, several prescription guidelines have been published. For psychiatry, guidelines for SSRIs, tricyclics, antipsychotics, and atomoxetine were published and updated.[4–7] The most comprehensive and most prominent expert consensus guidelines and databases were provided by the Clinical Pharmacogenomic Knowledgebase (PharmGKGB; www.pharmGKB.org**)**, the Pharmacogenetic Implementation Consortium (CPIC; www.cipicpgx.org), and the Dutch Pharmacogenetic Working Group (DPWG; http://upgx.eu). Those guidelines have focused on the CYP2D6 and CYP2C19 genotypes and their implications (adverse drug events, inefficacy, etc.) on antidepressant pharmacotherapy. Pharmacogenetic (PGx) testing could also increase the response rate and avoid adverse drug events. In fact, as many as 12% of emergency visits are due to adverse events caused by a new drug.[8] Thus, the Food and Drug Administration (FDA) has released 28 drug label annotations for psychiatric drugs. Despite the guideline and drug label annotations, the implementation of PGx testing has only been slowly progressing globally due to a number of barriers, such as limited knowledge among physicians, pharmacists, and patients and the question of reimbursement.[9] Moreover, the European Medicines Agency (EMA) has been more restrictive with label annotations, which might be a reason for the slow progression in pharmacogenetic testing in European countries.

Additionally, randomized controlled trials (RCTs) have provided evidence to support pharmacogenetic testing in psychiatric patients, but more studies are still needed to confirm the beneficial outcomes.[10,11] Likewise, in Germany, PGx testing is still not conducted routinely in clinical practice, and health insurance companies do not reimburse PGx testing. To the best of our knowledge, our group at the Vitos Klinik Eichberg was one of the first psychiatric hospitals in Germany to apply genetic testing in patients with depression as part of the routine practice. While physicians do not feel comfortable in interpreting the PGx results, pharmacists do;[12,13] therefore, a clinical pharmacist was chosen to implement PGx testing at the Vitos Klinik Eichberg (Eltville, Germany). In addition, some studies have concluded that pharmacists have better knowledge and understanding of pharmacokinetics to be able to interpret the PGx results.[13–15] As such, a clinical pharmacist specializing in PGx testing helped with the implementation and ensured the correct interpretation of the PGx results. This collaboration seemed especially valuable in PGx testing. Notably, our retrospective study revealed that pharmacogenetic testing and collaboration of a pharmacist with physicians in interpreting the PGx results reduced the hospitalization stay for depression patients.[16] This collaboration, especially with a pharmacist that works in-house, was also recommended by Haga *et al*., De Denous *et al*., and Frigon *et al*.[17–19] Hence, PGx-testing could help to reduce the high nonresponse rate of 50% for the first antidepressant in MDD patients in the future.[20]

Aim

Our present retrospective analyses examined the prescribing rate of antidepressants that were affected by the CYP2D6 and/or CYP2C19 polymorphisms according to the guidelines of the DPWG and CPIC in a naturalistic setting. Furthermore, the numbers of actionable genotypes before and after PGx testing were compared. We expected a high number of actionable genotypes before and a lower number after the PGx testing as a result of the interdisciplinary collaboration between a clinical pharmacist and physicians in interpreting the results and after evaluating the drug-drug interactions, history of the antidepressants, and comorbidities to recommend a new antidepressant.

Methods

PGx testing was offered as a part of the standard treatment to adult patients (≥ 18 years; n = 108) suffering from MDD admitted to the Vitos Klinik Eichberg between November 2016 and July 2017 to avoid selection bias. There was no patient with a history of a drug-related genotype. A genetic testing kit was provided by Humatrix AG (Pfungstadt, Germany). The genetic testing kit could test various genes and alleles (Table 1), which were used in the Stratipharm database at the time of testing according to the cumulative evidence of the pharmacokinetic and pharmacodynamics genes (e.g., CYP, ABCB1, 5HT2A receptors, OPRM1, HLA-A, etc. were taken into account for the pharmacist´s recommendation). The results were ready after 4 days. On Day 4 a pharmaceutical recommendation was given to the physician and the patients received counselling on the results.

For our present analysis, we focused on CYP2D6 and CYP2C19, their clinical guideline annotations in CPIC and DPWG (Table 2), and the actionable genotypes. A retrospective analysis of this cohort of patients was conducted in order to test our main hypothesis that actionable genotypes could be avoided.

Using the patients' files, the following data were collected: Patients' demographics, medication prior and after PGx testing, and pharmacist´s recommendation (written into the patient's chart) based on the genotyping results, medication history, comorbidities, and drug interactions.

For the pharmacist´s recommendation, the comedication, medication history, laboratory results from the patient's file, as well as the PGx results from the database were taken into consideration. The data were presented in the way that the new CPIC guideline recommended for genetic testing results.[21] Moreover, the activity scores for CYP2D6 and the phenotypes were reported in accordance with the consensus paper of the CPIC and DPWG.[22]

The data were collated using Microsoft Excel 2010, Version 14.0.7194.5000 (Microsoft Corporation, Redmond, WA, USA).

Statistical analysis

For the t-test for the comparison after actionable genotypes before and after PGX, we used SPSS version 25.

Results

Of the 108 patients, 84 were on psychotropic drugs prior to PGx testing, and 89 after testing (pre-emptive testing was used partially). Furthermore, 24 patients (22%) did not receive any psychotropic drug on admission and prior to the PGx testing (pre-emptive testing was conducted in these cases), and 17 patients refused antidepressants after the PGx testing. Of the 84 patients that received antidepressants prior to the PGx testing, 49 patients (58%) received antidepressants with the CPIC and/or DPWG guideline recommendations based on the genetic polymorphisms of CYP2D6 and CYP2C19. Another four patients (5%) received aripiprazole (augmentation in depression; off label) with guideline recommendations based on the genotype CYP2D6 (Fig. 1).

Overall, 51 patients (47% of all patients) received at least one

Table 1. Testing panel of the stratipharm test; in addition to the mentioned above loci CNV in CYP2D6 *5 was tested for

Locus	Annotation	Locus	Annotation	Locus	Annotation
ABCB1	rs1045642	*CYP2C19*	*rs4244285*	HMGCR	rs17238540
ABCB1	rs1128503	*CYP2C19*	*rs4986893*	HMGCR	rs17244841
ABCB1	rs2032582	*CYP2C19*	*rs12248560*	HTR2A	rs6311
ABCG2	rs2231142	*CYP2C19*	*rs28399504*	HTR2A	rs6313
ABCG2	rs13120400	*CYP2D6*	*rs4986774*	HTR2A	rs7997012
ABCG2	rs17731538	*CYP2D6*	*rs3892097*	HTR2A	rs9316233
ADRB1	rs1801252	*CYP2D6*	*rs5030655*	HTR2A	rs6314
ADRB1	rs1801253	*CYP2D6*	*rs5030867*	IFNL3	rs8099917
ADRB2	rs1042713	*CYP2D6*	*rs5030865*	IFNL3	rs12979860
ADRB2	rs1042714	*CYP2D6*	*rs5030865*	ITPA	rs1127354
COMT	rs4680	*CYP2D6*	*rs28371720*	MT-RNR1	rs267606617
COMT	rs165599	*CYP2D6*	*rs1065852*	NAT2	rs1801280
COMT	rs4646316	*CYP2D6*	*rs5030863*	NAT2	rs1799930
COMT	rs9332377	*CYP2D6*	*rs28371706*	NAT2	rs1799931
COQ2	rs4693075	*CYP2D6*	*rs59421388*	OPRM1	rs1799971
CYP1A2	rs2069514	*CYP2D6*	*rs28371725*	SLC19A1	rs1051266
CYP1A2	rs762551	*CYP3A4*	*rs2740574*	SLCO1B1	rs4149056
CYP2B6	rs8192709	*CYP3A5*	*rs776746*	SLCO1B1	rs11045819
CYP2B6	rs28399499	DPYD	rs3918290	SLCO1B1	rs2306283
CYP2B6	rs3745274	DPYD	rs72549303	SLCO1B1	rs4149015
CYP2C8	rs10509681	DPYD	rs72549309	TPMT	rs1800462
CYP2C8	rs11572080	DPYD	rs55886062	TPMT	rs1800460
CYP2C8	rs1934951	DPYD	rs67376798	TPMT	rs1142345
CYP2C9	*rs1799853*	DPYD	rs2297595	TPMT	rs1800584
CYP2C9	*rs1057910*	GNB3	rs5443	TPMT	rs12201199
CYP2C9	*rs9332131*	HLA-B	*rs3909184*	VKORC1	rs9923231
CYP2C9	*rs7900194*	HLA-B	*rs2395029*	VKORC1	rs7294
CYP2C9	*rs28371685*	HLA-B	*rs2844682*	VKORC1	rs17708472
COQ2	rs6535454	GSTP1	rs1695	VKORC1	rs2359612
CYP3A4	*rs2242480*	HLA-A	*rs1061235*	VKORC1	rs8050894
		HLA-A	*rs1633021*	VKORC1	rs9934438

antidepressant and/or antipsychotic with a CPIC and/or DPWG guideline recommendation for either CYP2C19 or CYP2D6 (Tables 2 and 3). Likewise, 61% of the patients that received an antidepressant prior to the PGx testing received an antidepressant with the guideline annotations.

However, eight patients did not receive medication prior and after the PGx testing. The reasons for refusing the medication were unknown although the clinical pharmacist provided a specific medication recommendation for every patient.

In addition, 28 actionable genotypes were found (e.g., change drug/change dose) for 53 drug prescriptions in 51 patients (55%) that had already been taken prior to the PGx testing according to the recommendations listed in Tables 1 and 2. Two patients re-

ceived doxepin, and one had both actionable genotypes for CYP-2D6 and CYP2C19. All patients with actionable genotypes received a drug without actionable genotypes after the PGx testing, which was based on a recommendation of the clinical pharmacist and the following decision of the prescribing physician. The physician followed the recommendation of the clinical pharmacist for 80 patients, but did not follow the recommendation for nine patients. Of those nine patients, two patients received drugs with actionable genotypes (venlafaxine UM; aripiprazole PM), but the dosing recommendation of the guidelines were used for choosing the starting and final dose. Eighteen patients also refused to take antidepressants; 13 of them had no antidepressant before the PGx testing and kept refusing antidepressants, and the other five refused to take

Table 2. Antidepressants that were prescribed before the PGx testing and the guideline annotation for the different genotypes with recommendations other than "initiate or treat with standard dose"

Antidepressant	CYP2D6 guideline annotation	CYP2C19 guideline annotation
Agomelatine (n = 3)	–	–
Amitriptyline (n = 1)	DPWG (UM, IM, PM) CPIC (UM, IM, PM)	CPIC (UM, RM, PM)
Bupropion (n = 10)	–	–
Citalopram (n = 5)		DPWG (IM, UM, PM), CPIC (UM, PM)
Doxepin (n = 2)	CPIC (IM, UM, PM)	DPWG (UM, IM, PM), CPIC (UM, RM, PM)
Duloxetine (n = 7)	–	–
Escitalopram (n = 4)	–	DPWG (UM, IM, PM), CPIC (UM, PM)
Milnacipran (n = 3)	–	–
Mirtazapine (n = 8)	–	–
Opipramol (n = 3)	–	–
Sertraline (n = 20)	–	DPWG (PM), CPIC (UM, PM)
Tianeptine (n = 2)	–	–
Tranylcypromine (n = 1)	–	–
Trimipramine (n = 1)	DPWG (UM, IM, PM) CPIC (UM, IM, PM)	CPIC (UM, RM, PM)
Venlafaxine (n = 16)	DPWG (UM, IM, PM)	–

The number of antidepressants was higher than 84 because some patients (n = 84) received more than one antidepressant, e.g., a SSRI plus mirtazapine. CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenetic Working Group; IM, intermediate metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer.

another antidepressant even after the PGx testing because of the adverse drug reactions that they endured, so the antidepressants were discontinued. The acceptance rate of the clinical pharmacist´s recommendation was 88%. The reduction rate for the actionable genotypes was 93%: Two patients received new psychotropic drugs with actionable genotypes (dosing recommendations of the clinical annotation were taken into account). Additionally, all 28 patients with actionable genotypes prior to the PGx testing did not receive psychotropics with actionable genotypes after the PGx testing. Only two patients received drugs with the guideline recommendations for a specific genotype after the PGx testing (Fig. 2). In comparison, the number of actionable genotypes before and after PGx testing was significantly reduced (p < 0.001).

Genetic polymorphisms of CYP2D6 with an activity score below 1.25 were present in 28 patients, nine patients had an activity score of zero, and one patient had an activity score >2.25, thus meaning that a large proportion (44%) of this naturalistic inpatient population was non-normal metabolizers. This caused a 50% rate of actionable genotypes per prescription in venlafaxine-treated patients and 100% in doxepin-treated patients (Fig. 2).

For CYP2C19, 73 (68,6%) of our patients were non-normal metabolizers. Forty-two patients (38.9%) were ultrarapid and rapid metabolizers with a high risk of not responding to the CYP2C19 substrates (e.g., citalopram, escitalopram, and some tricyclics) at the recommended dosage in the prescriber's information. In particular for the SSRIs and tricyclics, this caused high rates of actionable genotypes per prescription: 100% in citalopram, doxepin, and trimipramine, 80% in escitalopram, and 40% in sertraline.

Notably, only 14 patients (13 %) were normal metabolizers for CYP2C19 and NM for CYP2D6. Ninety-four patients (87%) also had genetic polymorphisms for either one or both CYP relevant enzymes for the metabolism of the antidepressants and needed dose adaption according to the dosing guidelines, e.g., CPIC.[5,6]

Discussion

Key findings

Sixty-one percent of the patients (n = 108) received antidepressants with the CPIC and/or DPWG guideline recommendations. The high number of actionable genotypes [e.g., 100% in citalopram treated patients (Fig. 2)] resulted in a low tolerability or low efficacy of the drug according to the guideline recommendation that was alarming, as this could have caused the patient to be admitted into the psychiatric hospital. Through the collaboration with a clinical pharmacist, the number of actionable genotypes could be reduced by 93%. The physician did not follow the pharmacist´s recommendation for two patients, which caused two actionable genotypes, consequently emphasizing the importance of a close collaboration between the psychiatrist and the pharmacist. The acceptance rate of the pharmacist´s recommendation was 88%, which was higher compared to other studies, where only 85% of the pharmacist's recommendations were accepted. These were even lower than the recommendations in another study in the same hospital regarding drug selection, drug interactions, and other recommendations, where it was 100%.[23,24] The knowledge about PGx was considered low among physicians, and this might explain why they might not have followed the recommendations.[25]

Strengths and weaknesses

The presented data were the only data for PGx testing in Germany. As PGx testing has still not been conducted routinely in Germany and other European countries, the presented data were still up to date. This was the largest German psychiatric cohort that was
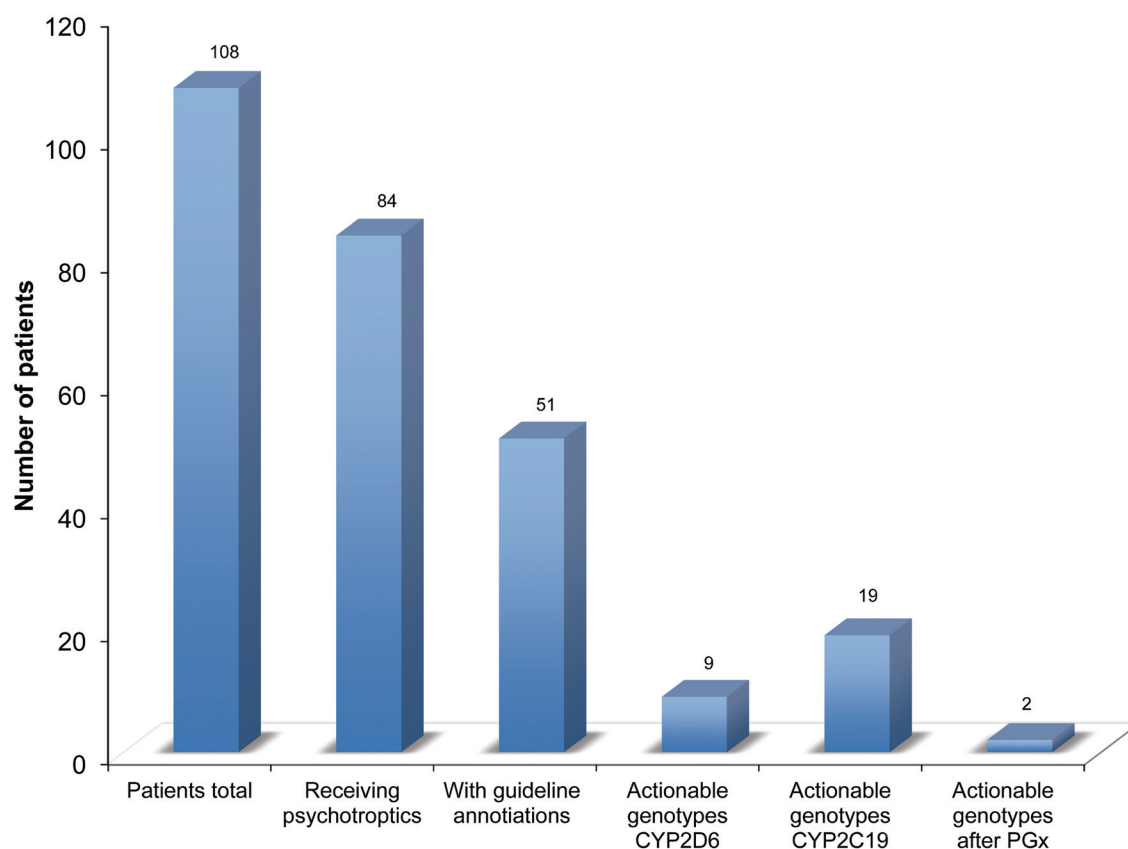
Fig. 1. Results of the retrospective analysis. The figure shows the numbers of patients that were genotyped (n = 108), patients that were receiving antidepressant at the time of PGx testing (n = 84), patients that were taking antidepressants with guideline annotations for CYP2D6 or CYP2C19 at the time of PGx testing. The tree column to the right show the number of patients with actionable genotypes, meaning that they had a genotype that required a change in either dose or drug choice as recommended by the CPIC or DPWG guidelines. CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenetic Working Group.

analyzed and published. Moreover, the guidelines had not been updated since the collection of the data so that the statement of our study remained valid. The naturalistic setting and retrospective design mirrored the magnitude of the problem of the divergent genotypes without any selection bias. However, the randomized controlled trials had a higher validity. Additionally, comedication was not documented, so the potential phenoconversion effects were unknown and could have altered the number of patients with actionable genotypes due to the gene-drug interactions.[23]

Interpretation

Other studies on actionable genotypes showed similar results: 24.2% of the patients had actionable genotypes in another natural-istic study, which was slightly lower than 26% in our study. However, since we were only looking at the drug classes, "antipsychotics" and "antidepressants", and did not analyze the comedication, our rate seemed to be very high in comparison.[24] In sertraline, there was increasing evidence that the intermediate metabolizer status increased the area under the curve (AUC), but there was no guideline recommendation.[25] The potential number of actionable genotypes would be much higher in our cohort if this received the guideline annotation level since 20 patients were receiving sertraline in our naturalistic cohort. This was also of economic interest, as the length of hospitalization depended on the genotype: non-normal metabolizers had a 5.7-day longer stay ($p = 0.002$).[26]

Whether the genotype might be the reason for admission to the hospital could also be assumed due to the fact that the number of patients with divergent genotypes was higher than that in other

Table 3. Antipsychotics that were prescribed before the PGx testing and the guideline annotation for the different genotypes with recommendations other than "initiate or treat with standard dose" as of October 2021

Antipsychotic	CYP2D6 guideline annotation	CYP2C19 guideline annotation
Aripiprazole (n = 4)	DPWG (PM)	–
Olanzapine (n = 2)	DPWG (no genotype required dose adaption.)	–
Quetiapine (n = 9)	–	–

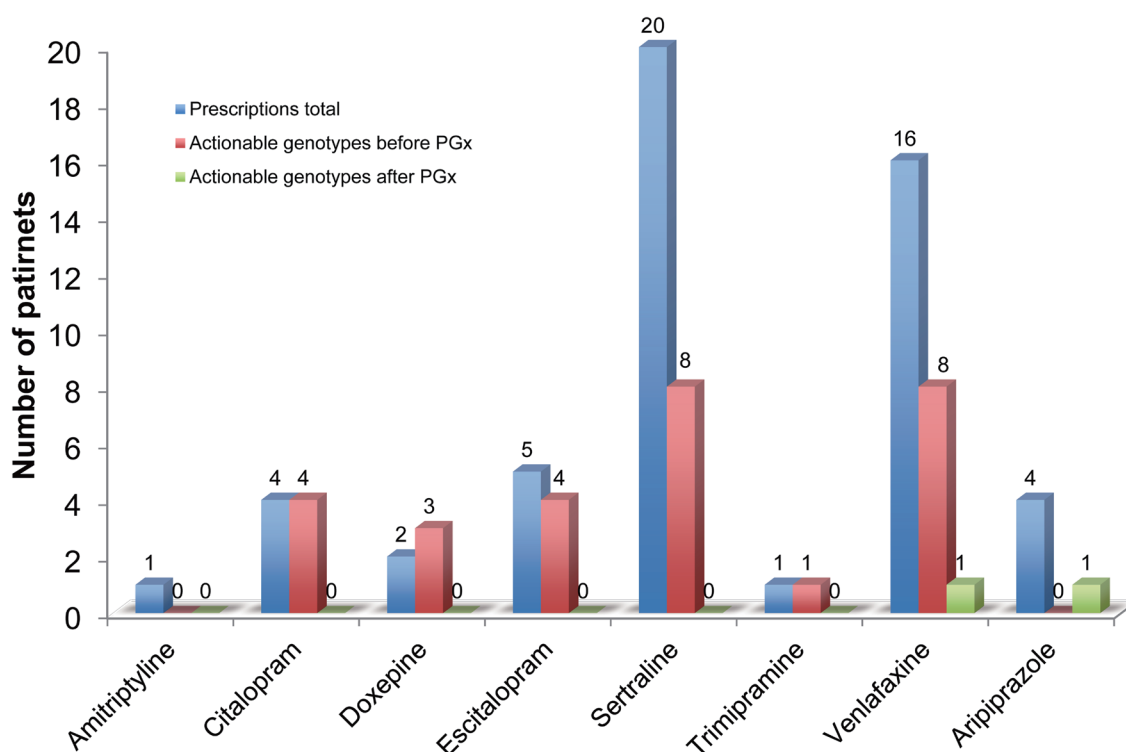DPWG, Dutch Pharmacogenetic Working Group.

Fig. 2. The number of the total prescriptions of a drug in comparison to the number of actionable genotypes. For doxepin, the patients had actionable genotypes for both CYP2D6 and CYP2C19, so the number exceeded the number of prescriptions.

European cohorts.[27–34] To enhance the response rate of 49.6%, as seen in the StarD trial, the PGx testing of CYP2C19 and CYP2D6 could therefore be beneficial.[35] This could also have implications on the mortality of MDD patients, as a systematic review showed that non-responders to one or more antidepressants had a 15% likelihood of suicide ideation compared to 6% of patients with treatment-responsive depression and 1% in the general population.[36] As shown by a recent meta-analysis, patients with PGx-guided therapy (n = 887) were 1.71 times more likely to achieve symptom remission when compared to patients receiving usual treatment ($p = 0.005$).[37] Thus, the chronicity of the disease could be prevented.[38]

Notably, only 14 patients (13%) had a normal metabolizer status for both CYP2D6 and CYP2C19 in our cohort, which was even lower than 27.3% of the patients in a large Danish cohort with 77,684 psychiatric patients.[39] If used in daily practice, PGx testing could help to prevent adverse drug reactions in psychiatric patients and decrease the utilization of health professionals.[40–42]

The interprofessional collaboration between psychiatrists and clinical pharmacists facilitated an individualized therapy approach with the interpretation and incorporation of the PGx data into the antidepressant selection process. This resulted in a reduction rate of 93 % in our study. With this collaboration, uncertainties of the physician about the interpretation of the genotyping results could be overcome as a barrier of implementation.[43] Other studies also found the pharmacist to be the most appropriate person to deliver PGx counseling services in a multiprofessional healthcare team.[44,45]

However, there would still be a need for more clinical guidelines and guidelines harmonization, as well as harmonization of the technical issues and star alleles that were included in the testing panel to facilitate the use of the PGx results for the clinician.[46]

Furthermore, there were many different tests available, but they and their results were not comparable due to the different panels that were tested. Regulations also differed, so that testing panels in the US became broader and also included genes that were a risk for the development of the disease, which was prohibited in Germany and other countries. Accordingly, the comparability of the study outcomes based on those testing panels could not be applied to other countries,[45] which made small studies like ours valuable for other German hospitals that want to implement PGx testing, as they could use the same panel.

Nevertheless, implementing PGx testing still faces barriers, especially missing knowledge and misconceptions on the prescriber's side.[47] The challenge in the coming years would be to overcome the identified barriers. New RCTs, like the "PRIME Care" trial, would be implemented to increase the scientific evidence on the cost-effectiveness of pre-emptive testing in mental health.[48] As a consequence, pre-emptive PGx testing would likely increase drug therapy safety for the patients. Additionally, the barrier of the reimbursement of the PGx testing needs to be overcome; it is still not regulated and health insurance companies do not yet provide reimbursement. The cost of commercial tests also varies, but might be as high as 485 Euros in Germany, which would limit the use of PGx testing in daily practice.

Future directions

As we could show that divergent genotypes are very common among psychiatric inpatients, pre-emptive testing should become a requirement before starting and antidepressant to avoid adverse drug events, prevent disease progression due to inefficacy of the

drug therapy and increase the response and remission rate, which improves the quality of life of the patients in a very direct way as depression leads to a tremendous decline in quality of life. Reimbursement of PGx in mental health is essential for a global implementation for this group as mental health disease often comes along with social decline. Further prospective RCTs would be needed to confirm the clinical effects of PGx testing in psychiatric patients.

Conclusions

Actionable genotypes for CYP2D6 and CYP2C19 are fairly common among psychiatric inpatients. Ignoring the scientific evidence on the influence of genetic polymorphism on the pharmacokinetics of antidepressants and antipsychotics would put patients at risk for adverse drug reactions or inefficacy of the drugs that could lead to the chronicity of the disease and/or admission to a psychiatric hospital. Our recommendation to advocate for pre-emptive genotyping for clinically actionable gene-drug pairs was also consistent with our previous analyses of the same data set published elsewhere, where we reported that genotyped patients responded earlier and better to antidepressant drugs and therefore had a shorter duration of stay in the hospital and lower rehospitalization rates.[16] As the number of patients with depressive disorders is increasing, the implementation of PGx testing is not only of benefit for the patient, but also for the healthcare system and the economy. Hence, PGx testing should be routinely conducted in patients that need antidepressants or antipsychotics, as many clinical annotations exist, especially for the starting doses of the drug. Pre-emptive testing might therefore be especially valuable. Interprofessional collaboration between the psychiatrist and a clinical pharmacist would also be helpful, especially during the implementation phase of PGx testing in the hospital setting.

Conflict of interest

Both authors declare no conflicts of interest.

Author contributions

Study design (SCR and MH), performance of experiments (SCR and MH), analysis and interpretation of the data (MH and SCR), manuscript writing (SCR and MH), critical revision (SCR and MH), and statistical analysis (MH and SCR).

Ethical statement

The retrospective analyses received approval by the Hesse Ethics Committee (approval number FF88/2018) on September 27, 2018.

Data sharing statement

The data set is available from the corresponding author at martina.hahn@kgu.de.

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