DOI 10.4149/BLL_2024_106

Bratisl Med J 2024; 125 (11):
701–705

CLINICAL STUDY

Perspective on the role of pharmacogenetic testing in mental health care in Slovakia

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ABSTRACT
BACKGROUND: The pathophysiology of mental illnesses is not fully understood, leading to insufficient remission, frequent adverse drug reactions, and treatment resistance. Pharmacogenetic (PGx) testing, a personalized approach recently adopted also in psychiatry, can guide effective drug therapy and minimize side effects. The objective of this study was to determine the perspective of Slovak clinicians regarding the integration of PGx testing in psychiatric clinical practice.
METHODS: Questionnaires covering various aspects such as prior experience with PGx testing, self-perceived competence, perceived utility, potential risks and challenges were distributed directly to attendees at two psychiatric conferences held in Slovakia in 2023 and their responses were statistically analysed.
RESULTS: Out of 54 respondents, only 7.4% had previous experience with PGx in clinical practice. The most clinicians felt that they should possess the skills to apply PGx testing in psychiatric clinical practice and were enthusiastic about increasing their expertise. They found PGx useful in medication selection, adverse effect management, and treatment-resistant depression. The primary concerns centered around the lack of well-defined guidelines and the financial considerations linked to the testing.
CONCLUSIONS: Considering the participants' interest in PGx and its integration into clinical practice, educational programmes based on recommendations, guidelines, and convincing evidence could be organized *(Tab. 4, Ref. 30)*. Text in PDF www.elis.sk
KEY WORDS: pharmacogenetics, pharmacogenomics, psychiatry, personalized treatment, Slovakia, perspective.

Introduction

In the shadow of global pandemics of COVID-19, a new silent one concerning mental health is emerging. Globally, 970 million people were living with a mental disorder in 2019, with anxiety and depression being the most common (1). Although the evidence is varying, recently published studies describe a highly probable increase in the burden of mental health issues in the postpandemic era (2). The complete understanding of the pathophysiology of mental diseases remains elusive, resulting in insufficient remission, frequent incidence of adverse drug reactions as well as resistance to treatment. While a vast number of affected individuals worldwide do not have access to effective mental disorder care, treatment resistance affects 20–60% patients (3).

Very few new psychiatric drugs have entered the market in recent period. Therefore, improvements in the mental health care using antidepressants and antipsychotics need to focus mainly on the rational and more personalised treatment with currently available drugs (4). The pharmacological response is multifactorial and depends on several variables such as gender, age, weight, polypharmacy, comorbidities, and genetic predisposition. Different patients may respond differently to the same drug (interindividual variability), while also the same individual may respond differently to a drug at different time points referred as intraindividual variability (5).

Thanks to the complete sequencing of the human genome achieved through the Human Genome Project, scientists have uncovered significant insights into the potential of pharmacogenetics (PGx). This ground-breaking achievement has enabled researchers to understand how individual genetic variations affect drug responses, paving the way for personalized medicine. By

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Acknowledgements: The study was supported by the Ministry of Education, Science, Research and Sport of the Slovak Republic (grant VEGA-1/0145/22).

identifying specific genetic markers, scientists can now predict which medications will be most effective and which may cause adverse reactions in different individuals, ultimately leading to more tailored and effective treatments (6, 7).

PGx testing has become over time a routine practice in various medicine fields including oncology and infectious diseases, and recently has been incorporated to the therapy also in psychiatry (8). PGx studies the effect of single genes while pharmacogenomics refers to the genome-wide approaches to elucidate individual differences in the drug therapy outcome. Genetic variations can affect the pharmacokinetics of the drug (absorption, distribution, metabolism, elimination) as well as mechanism of its action (pharmacodynamic changes) via altered receptor or transporter function.

Currently, the application of PGx testing in psychiatry is scarce considering a lack of standardization of gene panels and sufficient clinical evidence supporting their role (5).

The aim of the present study was to evaluate the viewpoints of Slovak psychiatrists and related professionals on the implementation of PGx testing in psychiatric clinical practice.

Materials and methods

Survey

The survey on the clinicians' perspective on PGx testing in psychiatry was adopted by Chan et al (9) and was administered to a cohort of Slovak psychiatrists and other related professionals. Informed consent was obtained from all participants in the study. There were 10 questions in total: 1 was dropdown question, 2 were dichotomous, 2 were multiple choice, 4 were matrix questions, and the last one was open-ended for free comments. In the first section, the demographic data were collected (gender, age group, profession/background). Next, there was a question regarding previous experience with PGx testing and then, we asked questions on self-perceived competency, usefulness of PGx, related risks and challenges, and willingness to learn about this topic and its application in psychiatric clinical setting.

Tab. 1. Demographic data of the survey participants.

Characteristics	Frequency (n)	Frequency (%)
Gender		
Male	18	33.3
Female	36	66.7
Age group		
20–30	8	14.8
31–40	13	24.1
41–50	17	31.5
51–60	9	16.7
61–70	2	3.7
>70	5	9.2
Profession/Background		
pedopsychiatrist	8	14.8
psychiatrist for adults	25	46.3
both psychiatrist for adults and pedopsychiatrist	2	3.7
currently in psychiatry residency program	11	20.4
other related (pharmacists, researchers)	8	14.8

Participants

The survey was administered in-person during two psychiatric conferences (one for pedopsychiatrists) held in Slovakia in 2023 and subsequently was shared also online and distributed within the Slovak psychiatric community. Inclusion criteria for participants were: psychiatrists or related professionals settled in Slovakia. Exclusion criteria were reluctance to participate and different professions.

Statistical analyses

Descriptive analyses were performed in GraphPad Prism, version 8.0.1 (GraphPad, San Diego, USA). Comparison according to the groups (age, gender, position) were performed using Chi square test. $p<0.05$ was considered significant.

Results

Out of 70 directly approached conference participants we received 54 responses as 5 individuals declined to participate because of the questionnaire topic, 7 reported time constraints, and 4 did not meet inclusion criteria. Thus, the response rate was 75.7%. The basic demographic data can be found in Table 1.

Out of 54 respondents, only 4 (7.4%) had previous experience with PGx testing. All of them confirmed that the test was useful, 3 clinicians (75%) had adjusted the therapy accordingly and claimed clinical benefit (higher efficacy, higher tolerance and fewer adverse effects). 88.8% of respondents agree that it is a psychiatrist' role to offer PGx testing in appropriate clinical conditions while there were no significant differences according to the gender, age group, nor professional position. 59.3% of respondents do not feel competent to order a PGx test, however, 50% feel competent to identify a clinical situation, in which a PGx test is indicated, 42.6% feel competent to inform about the risks and benefits of the testing, and 44.4% could make recommendations according to the test results. There are no differences in self-perceived competency between males and females. These results can be found in Table 2.

More than a half of respondents find PGx as very or extremely useful in medication selection (64.8%), managing adverse effects (63%), as well as in appropriate dosing regimen (55.6%). Majority of asked finds PGx useful in management of treatment-resistant depression (64.8%), in treatment-resistant schizophrenia (61.1%), and in treatment-resistant OCD (59.2%). All answers can be found in Table 3.

The most frequent challenge with PGx testing in psychiatry according to the respondents is a lack of guidelines (77.8%), the financial aspects (64.8%), and test accuracy (46.3%). Besides, 72.2% believed there are no risks apart from those related to blood withdrawal. The perceived risks and challenges can be found in Table 4.

46 participants (85.2%) agreed that would like to learn more about PGx and its application in clinical psychiatry. 64.8% would

Tab. 2. Self-perceived competency in PGx testing.

Do you agree with the following statements?	Strongly disagree	Disagree	Agree	Strongly agree	No answer
It is a psychiatrist's role to offer pharmacogenomic testing in appropriate clinical circumstances	3 (5.6%)	2 (3.7%)	22 (40.7%)	26 (48.1%)	1 (1.9%)
I feel competent to order/suggest pharmacogenomic tests	17 (31.5%)	15 (27.8%)	13 (24.1%)	6 (11.1%)	3 (5.5%)
I feel competent to identify clinical situations in which testing is indicated	13 (24.1%)	12 (22.2%)	21 (38.9%)	6 (11.1%)	2 (3.7%)
I feel competent to inform patients of the risk and benefits of testing	12 (22.2%)	17 (31.5%)	15 (27.8%)	8 (14.8%)	2 (3.7%)
I feel competent to make treatment recommendations based on results	13 (24.1%)	14 (25.9%)	18 (33.3%)	6 (11.1%)	3 (5.6%)

Tab. 3. Perceived usefulness according to the clinical situation.

Can PGx be useful in this clinical situation?	not useful	slightly useful	very useful	extremely useful	I do not know
Medication intolerance, adverse effects	5 (9.2%)	4 (7.4%)	19 (35.2%)	15 (27.8%)	11 (20.4%)
Medication selection	1 (1.9%)	3 (5.5%)	20 (37.0%)	15 (27.8%)	15 (27.8%)
Dosing	4 (7.4%)	8 (14.8%)	11 (20.4%)	19 (35.2%)	12 (22.2%)
Treatment-resistant depression	1 (1.9%)	4 (7.4%)	19 (35.2%)	16 (29.6%)	14 (25.9%)
Treatment-resistant schizophrenia	2 (3.7%)	4 (7.4%)	18 (33.3%)	15 (27.8%)	15 (27.8%)
Treatment-resistant OCD	2 (3.7%)	6 (11.1%)	16 (29.6%)	16 (29.6%)	14 (25.9%)

OCD – obsessive compulsive disorder

Tab. 4. Perceived risks and challenges in PGx testing.

Do you agree with the following statements?	Strongly disagree	Disagree	Agree	Strongly agree	I do not know
There are no clear guidelines to order pharmacogenomic tests	0 (0%)	8 (14.8%)	28 (51.9%)	14 (25.9%)	4 (7.4%)
The tests may not be accurate	3 (5.6%)	19 (35.2%)	21 (38.9%)	4 (7.4%)	7 (12.9%)
Testing could cause a patient psychological distress	8 (14.8%)	24 (44.4%)	12 (22.2%)	4 (7.4%)	6 (11.1%)
The costs of testing are a significant concern	1 (1.9%)	11 (20.4%)	20 (37.0%)	15 (27.8%)	7 (12.9%)
There are no risks apart from those related to blood withdrawal	3 (5.6%)	7 (12.9%)	25 (46.3%)	14 (25.9%)	5 (9.2%)

prefer to have a lecture, 50% would prefer e-learning, 16.7% team meetings and discussion on this topic and 1 respondent (1.9%) mentioned looking in medical databases such as PubMed.

Discussion

The major findings in our study are that PGx in psychiatry has been used only rarely in Slovakia so far (7.4%) but majority of participants believe it is a psychiatrist' role to offer such test to their patients (88.8%). Currently, more than a half of the participants do not feel competent to order a PGx test (59.3%). The participants find the major benefit in medication selection, adverse effect guidance, and management of treatment-resistant depression. The most perceived drawback is a lack of standardized guidelines. Importantly, 85.2% of asked find PGx testing relevant in psychiatric clinical practice and would like to learn more about its application.

Perspectives on PGx testing has been previously analysed also in other countries including the United States (10, 11), New Zealand (12), or Singapore (9). In concordance with our study, the majority of respondents in the previous studies recognized the potential of this test in clinical practice. The most perceived challenges were cost-effectiveness, lack of guidelines and recommendations, and there was expressed a need for genetic counselors in psychiatric patient care. In comparison with our study, there was a considerably higher number of clinicians with prior PGx testing experience. Similar results of the survey were obtained in Chile, which was only limited experience with the tests so far but high willingness and likelihood to incorporate them in the clinical practice (13).

Regarding the European countries, there have been already published studies on PGx psychiatric use, for instance, in Spain (14), Denmark (15), and Italy (16, 17). Similar survey-based study as ours was conducted in France and observed French psychiatrists' attitude towards PGx implementation. The outcomes were rather favourable and costs and delays of tests were the biggest concerns of practitioners (18).

One of the leading European countries in implementation of PGx into the clinical psychiatric practice is the Netherlands. Recently, they have published a first guideline on this issue (19). Introducing such initial guideline could play a crucial role in removing the obstacle posed by a lack of sufficient recommendations. This guideline could address the current gap and ensure that healthcare professionals have the necessary information to make informed decisions.

In Slovakia, there were previously published association studies of various genetic polymorphisms and potential risk of affective disorders (20, 21), schizophrenia spectrum disorders (22), and completed suicide (23). Authors from Czech Republic have wider experience with the use of PGx in psychiatry. Already in 2012, they published a study demonstrating the relevance for CYP2D6 genotyping in patients receiving risperidone (24).

Considering the potential benefits, there has been recently published a multicentre, large-scale prospective study PREPARE analysing positive outcomes of genome-guided treatment in a large cohort (n=1076) of psychiatric patients suffering from bipolar disorder, major depressive disorder (MDD), and schizophrenia. Out of these, 262 patients were so called actionable patients based on genotyping results, as Dutch Pharmacogenetics Working Group (DPWG) recommendations were available for them. Specifically, 136 patients were in the PGx-guided arm while 126 in the control arm. The major findings are that the patients in the PGx-guided arm presented with 34.1% fewer adverse drug reactions, 41.2% fewer hospitalisations, 40.5% fewer re-admissions, and shorter duration of hospitalisations. Moreover, the authors observed less drug dose administrated per drug, less polypharmacy, smaller average number of co-administered psychiatric drugs and fewer deaths in the PGx-guided arm. Finally, PGx-guided treatment led to the significant reduction of treatment costs in MDD patients with reciprocal slight increase of their quality of life (25).

Another study assessed the effect of PGx testing in paediatric population suffering from anxiety, MDD, and attention-deficit/hyperactivity disorder (ADHD). At a 6-month follow-up, only ADHD treatment was substantially improved in PGx group. There were not any significant improvements in MDD nor anxiety, potentially caused by small sample size, selection bias, but also limited treatment choices in this population (26).

To address other barriers perceived by the respondents, there were already published studies of the cost-effectiveness of PGx in psychiatry (27–29). Supportive evidence exists mainly in case of CYP2D6 and CYP2C19 drug-gene associations and for combinatorial PGx panels while there is lack of evidence for many other drug-gene combinations (28). PGx-guided care led to a 37% reduction in patients experiencing refractory depression over a span of 20 years. Sensitivity analyses suggest that the costs associated with PGx testing could be offset within approximately 2 years of implementation.

Another seen barrier was test accuracy. It is generally accepted that the more genetic variants are evaluated, the more precise outcome and stronger prediction can be reached. It is substantial that every laboratory report exactly which SNPs were investigated. The clinical application of PGx could benefit from an agreement on the minimum set of genetic variants that should be examined (30).

Ultimately, profound knowledge and experience limit the application of PGx in routine psychiatric practice. Therefore, it is necessary to establish educational programmes based on the current recommendations and guidelines to provide clinicians with relevant education.

In conclusion, the application of PGx testing in psychiatry remains a discussed topic, however, there is an increasing number of studies determining the benefits on clinical improvements and cost-effectiveness. Our study showed that although the clinicians from Slovakia had only limited experience in the field of pharmacogenetics, they expressed their willingness to learn more about its application and implementation in clinical psychiatric practice.

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Received May 27, 2024.
Accepted June 11, 2024.