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Case Report

Generalized Anxiety Disorder Therapy, Associated with Pronounced Side Effects, and Prospects for the Use of Pharmacogenetic Testing: Case report

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Abstract: New generation antidepressants (AD) are widely used as first-line treatment for generalized anxiety disorder (GAD) and considered safely than tricyclics. Some side effects of AD are transient and may disappear after few weeks of treatment, but potentially severe may persist for a long time or occur later. Cardiovascular disorders (abnormal heart rhythm, QT prolongation, arterial hypertension, orthostatic hypotension) are especially dangerous side effects. Genetic polymorphisms of the enzymes involved in the metabolism of antidepressants may be one of the causes of side effects development. The objective of this case report is to demonstrate that timely assessment of the risk of side effects using pharmacogenetic testing (PGx) could have influenced choice of an antidepressant, timely dose adjustment, avoiding ineffective appointments. Use of the PGx can help to optimize GAD pharmacotherapy, its introduction into clinical practice requires further research.

Keywords: *pharmacogenetic testing; genetic polymorphisms; antidepressants; side effects; cardiac arrhythmia; arterial hypertension; generalized anxiety disorder.*

Introduction

Generalized anxiety disorder (GAD) is a common and disabling disease. Patients with GAD have a higher risk of suicide, cardiovascular complications and death [1]. Symptoms include chronic severe anxiety and worry accompanied by nonspecific physical and psychological symptoms (fatigue, concentration difficulties, irritability, muscle tension or sleep disorders). Effective methods of GAD treatment are psychotherapy and pharmacotherapy. Pharmacotherapy of GAD primarily includes selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors [2].

Consistent efforts to develop effective AD with better safety and tolerability profile were made over the years. However currently there is no clear evidence in support of clinically important differences for acceptability between various new AD, and there remains disagreements in the literature [3]. Some side effects of AD are transient and may disappear after few weeks of treatment, but potentially severe may persist for a long time or occur later. Cardiovascular disorders (abnormal heart rhythm, QT prolongation, arterial hypertension, orthostatic hypotension) are especially dangerous side effects [4]. Genetic polymorphisms of the enzymes involved in the metabolism of antidepressants may be one of the causes of side effects development. It is known that cytochrome P450 (CYP) isoenzymes contribute significantly to the process of psychiatric drugs metabolism,

including AD. Pharmacogenetic testing (PGx) serves as a powerful tool for selection of effective and safe treatment in the personalized healthcare approach [5].

Objective

The objective of this case report is to demonstrate that timely assessment of the risk of side effects using PGx could have influenced choice of an antidepressant, timely dose adjustment, avoiding ineffective appointments.

Materials and Methods

Procedure

The screening PGx with detection of the most frequent low-functioning and non-functional single nucleotide polymorphisms (SNPs) of *CYP2C9*, *CYP2C19*, *CYP1A2*, *CYP3A4* и *CYP2D6* genes, encoding activity of the 2C9, 2C19, 1A2, 3A4 и 2D6 isoenzymes of liver cytochrome P450, and *MDR1* gene, encoding transport protein P-gp (P-glycoprotein). Type of material – venous blood. The cumulative risk of adverse reactions due to medication with hepatic and primarily hepatic metabolism, risk of pseudoresistance to antidepressants was evaluated.

Ethical Aspects

The study was conducted in accordance to the standards of proper clinical practice and the principles of the Declaration of Helsinki. The participant signed voluntary informed consent. The patient didn't receive any remuneration for participation in the clinical study. Researchers didn't receive any remuneration for conducting clinical trials.

Results

Case Description

72 years old woman of Caucasian race diagnosed with generalized anxiety disorder (*DSM-5:* 300.02, *ICD-10: F41.1*) was referred by outpatient psychiatrist to PGx due to the development of adverse reactions of pharmacotherapy in the form of rise in blood pressure, abnormal heart rhythm, weight gain, increase of blood prolactin levels. For ten years the patient received different treatment regimens, including mirtazapine, fluvoxamine, sulpiride, vortioxetine, agomelatine, hydroxyzine. Coffee intake was 1-2 cups per day, the patient is non-smoking.

Conducted Therapy and Side Effects

- Mirtazapine was taken in 2013 for a long time with occasional breaks, however, during therapy episodes of increased blood pressure occurred, and, according to the patient, they were "quite high" (antihypertensive drugs had no effect); weight gain during treatment was 5 kg; mirtazapine was prescribed repeatedly after 2015 – after a while blood pressure increased again, resulting in the drug withdrawal in February 2021 (levels of blood pressure are not specified, blood pressure diary is not provided, ABPM wasn't conducted);
- Fluvoxamine (the end of 2014 – the beginning of 2015): poor tolerance, drug withdrawal; repeated prescription in 2021 – high blood pressure spikes (levels of blood pressure are not specified, blood pressure diary is not provided, ABPM wasn't conducted) accompanied by abnormal heart rhythm (nature of the abnormalities isn't specified, results of ECG HM are not provided);
- Sulpiride (2021): the drug was well tolerated, however, prolactin levels reached 10-fold excess of the upper limit; repeated prescription in 2022 – in a month another increase of blood prolactin levels resulted in the drug withdrawal; from May to mid-June 2022 there were "attacks of severe arrhythmia" (nature of the heart rhythm abnormalities

isn't specified, results of ECG HM are not provided); resumed taking sulpiride in February 28, 2023 (the patient noted a feeling of "faintness" during blood pressure spikes and a feeling of abnormal heart rhythm, levels of blood pressure are not specified, blood pressure diary is not provided, ABPM wasn't conducted; nature of the heart rhythm abnormalities isn't specified, results of ECG HM are not provided);

- Vortioxetine (in 2022) combined with sulpiride: increase of blood pressure, abnormal heart rhythm, vortioxetine withdrawal in 3 weeks (levels of blood pressure are not specified, blood pressure diary is not provided, ABPM wasn't conducted; nature of the heart rhythm abnormalities isn't specified, results of ECG HM are not provided);
- Agomelatine (from June 23, 2022): was administered in a dose of 25 at night; 5 months after blood pressure started to increase in the evening, remaining above 140/90 mmHg during night and in morning; in the middle of the day blood pressure returned to normal or even lower; but increased again in the evening; in February 2023 stopped taking agomelatine, tachycardia remained (levels of blood pressure are not specified, blood pressure diary is not provided, ABPM wasn't conducted; nature of the heart rhythm abnormalities isn't specified, results of ECG HM are not provided);
- Hydroxyzine (June 2022): took for a week, but also noticed a feeling of abnormal heart rhythm (nature of the heart rhythm abnormalities isn't specified, results of ECG HM are not provided).

Pharmacogenetic Testing

Results of the conducted PGx showed heterozygous carriage of the nonfunctional allelic variant G rs2740574 of the *CYP3A4* gene, homozygous carriage of the nonfunctional allelic variant T rs2069522 of the *CYP1A2* gene, and heterozygous carriage of the nonfunctional allelic variant T rs1045642 of the *MDR1* gene, which belongs to the most common non-functional single-nucleotide variant of this gene in the European population (Table 1). Patient's pharmacogenetic profile identified as poor metabolizer.

Table 1. Result of pharmacogenetic testing.

Name/indicator	NCBI SNP, allelic variant	Genotype	Estimation
Analysis of the frequent genetic variants in the *CYP2C9* gene (2 polymorphisms). PCR method, sequencing	rs1799853(C430T, Cys144Arg) rs1057910 (Ile359Leu, A1075C)	C/C A/A	Normal, pharmacogenetic profile EM (extensive metabolizer)
Analysis of the frequent genetic variants in the *CYP2C19* gene (3 polymorphisms). PCR method, sequencing	rs4244285 (CYP2C19*2) rs4986893 (CYP2C19*3) rs28399504 (CYP2C19*4)	G/G G/G A/A	Normal, pharmacogenetic profile EM (extensive metabolizer)
Analysis of the frequent genetic variants in the *CYP2D6* gene (3 polymorphisms). PCR method, sequencing	rs4986774 (CYP2D6*3A) rs1065852 (CYP2D6*10) rs3892097 (CYP2D6*4)	A/A C/C G/G	Normal, pharmacogenetic profile EM (extensive metabolizer)
Analysis of the frequent genetic variants in the *CYP3A4* gene (3 polymorphisms). PCR method, sequencing	rs4987161 (CYP3A4*17) rs28371759 (CYP3A4*18) rs2740574 (CYP3A4*1B)	T/T T/T **A/G!**	Heterozygous carrier of the non-functional allelic variant G, pharmacogenetic profile IM (intermediate metabolizer)
Analysis of the frequent genetic variants in the *CYP1A2* gene (1 polymorphism). PCR method, sequencing	rs2069522	**T/T!**	Homozygous carrier of the non-functional allelic variant

			T, pharmacogenetic profile PM (poor metabolizer)
Analysis of the frequent genetic variants in the *MDR1* gene (1 polymorphism). PCR method, sequencing	rs1045642 (C3435T)	**T/C!**	Heterozygous carrier of the non-functional allelic variant T, pharmacogenetic profile IM (intermediate metabolizer)

Identified genetic markers are associated with moderate decrease in functional activity of the 3A4 isoenzyme, pronounced decrease in functional activity of 1A2 isoenzyme of liver cytochrome P450, resulting in a slowdown in utilization of the medications metabolized by liver and increased risk of adverse reactions, including cardiovascular. Furthermore, there was identified genetic marker associated with moderate decrease in functional activity of transport protein P-gp, leading to disruption of transport (delivery) and excretion (efflux) of psychiatric drugs through the blood-brain barrier. Cumulative risk of adverse reactions during admission of drugs with hepatic and primarily hepatic metabolism, involving 3A4 and 1A2 isoenzymes of liver cytochrome P450, and transported through the blood-brain barrier, involving transport protein P-gp (P-glycoprotein), was estimated as high, as well as the risk of pseudoresistance to antidepressants.

Pharmacokinetics of mirtazapine varies depending on gender and age of patients. Women and elderly people have higher drug concentration in the blood than men and young people, which may require 25-30% lower daily dosage when treating woman and elderly people, compared to average therapeutic dose used when treating men. Mirtazapine is extensively metabolized in the body. Demethylation and hydroxylation with subsequent conjugation of glucuronides are the main ways of the metabolism of mirtazapine. 2D6 and 1A2 liver isoenzymes lead to the formation of mirtazapine 8-hydroxymetabolit. 3A4 isoenzyme metabolizes this drug into its N-desmethyl and N-oxide metabolites. There are other unconjugated metabolites of this drug that pharmacologically active, but their blood concentration is in limited quantities. The patient is identified as homozygous carrier of non-functional allelic variant of the *CYP1A2* gene and heterozygous carrier of non-functional allelic variant of the *CYP3A4* gene. Common low-functioning single-nucleotide variants of the *CYP2D6* gene haven't been identified. Genes, encoding mirtazapine glucuronidation enzymes, are not included in the present screening dashboard. Overall, considering age, gender and also patient's cumulative pharmacogenetic profile identified as "poor metabolizer" with pronounced decrease in functional activity of 1A2 isoenzyme and moderate decrease in functional activity of the 3A4 isoenzyme, use of mirtazapine is significantly limited when appointed as monotherapy (single and average drug doses shouldn't exceed 50% of average therapeutic doses) and contraindicated when appointed as polytherapy. Mirtazapine can cause blood pressure spike, including significant and requiring emergency care, even with a single admission of a low dose in patients with unfavorable pharmacological profile "poor metabolizer".

Fluvoxamine is extensively metabolized in the liver primarily by 2C19 and 2D6 isoenzymes and, to a lesser extent, by 1A2 isoenzyme. Common low-functioning allelic variants of the *CYP2C19* and *CYP2D6* genes weren't identified in patient, but homozygous carriage of non-functional allelic variant of the *CYP1A2* gene was, which may require lower single and daily dose of fluvoxamine compared to average therapeutic (25% when appointed as monotherapy and 50% when appointed as polytherapy in case of using drugs that inhibit 2C19 and 2D6 isoenzymes). Fluvoxamine can cause significant blood pressure spike and an increase in heart rate, especially in poor metabolizers, and therefore it's advisable to conduct an extended PGx with search for genetic biomarkers of the *CYP2C19* and *CYP2D6* genes, that aren't included in the present screening PGx dashboard.

Vortioxetine is extensively metabolized in the liver primarily through oxidation by 2D6, 3A4/5, 2C19, 2C9, 2A6, 2C8 and 2B6 isoenzymes and subsequent conjugation with glucuronic acid. 2D6 isoenzyme is the key enzyme, catalyzing metabolism of vortioxetine to its main, pharmacologically inactive carboxylic acid metabolite, and in poor metabolizers of CYP2D6 vortioxetine concentration in the blood plasma approximately twice as high as in normal metabolizers. Common low-functioning allelic variants of the *CYP2D6* gene weren't identified in patient, but heterozygous carriage of non-functional allelic variant of the *CYP3A4* gene was, which may require lower single and daily dose of vortioxetine compared to average therapeutic (25% when appointed as monotherapy and 50% when appointed as polytherapy in case of using drugs that inhibit 2D6 isoenzyme). Vortioxetine can cause blood pressure spike, especially in poor metabolizers in CYP2D6, therefore it's advisable (considering the patient's pharmacotherapy anamnesis) to conduct an extended PGx with search for other genetic of the *CYP2D6* gene that aren't included in the present screening PGx dashboard.

Agomelatine is metabolized in the liver primarily by 1A2 and 2C9 isoenzymes. Agomelatine is transported by transport protein P-gp (MDR1). The patient identified as homozygous carrier of non-functional allelic variant of the *CYP1A2* gene, which require lower single and daily dose of agomelatine compared to average therapeutic (50% when appointed as monotherapy and appointment of agomelatine with other drugs metabolized by 1A2 isoenzyme should be excluded). Furthermore, drugs that inhibit or induce 1A2 and/or 2C9 can significantly disrupt pharmacokinetics of agomelatine. Admission of drugs that inhibit these enzymes is contraindicated to the patient, because their admission can significantly (to toxic levels) increase exposure of agomelatine in the patient's body and cause agomelatine-induced side effects. The patient identified as heterozygous carrier of non-functional allelic variant of the *MDR1* gene, which leads to moderate decrease in functional activity of transport protein P-gp and slowdown in efflux of agomelatine from brain to blood, which may require lower single and daily dose of agomelatine on average by 25% of average therapeutic when appointed as monotherapy and by 50% when appointed as polytherapy, if agomelatine is combined with drugs-inhibitors of this transport protein, in case of appointing them due to primary or concomitant diseases. Risk or severity of side effects of agomelatine may increase when agomelatine is combined with benzodiazepines, including diazepam, therefore such polytherapy should be excluded.

Hydroxyzine is metabolized in the liver by 3A4 and 3A5 isoenzymes. Though the exact metabolic fate of hydroxyzine isn't clear, its main and active metabolite (~ 45-60% of the orally administered dose) that forms as the result of oxidation of its alcohol part to carboxylic acid is cetirizine. Hydroxyzine is probably broken down into several other metabolites, though exact structures and ways in people aren't clear. Half-life of hydroxyzine is long and is 14-25 hours in adults. Half-life increases in elderly people, on average it's approximately 29 hours and, perhaps, will likewise increase in poor CYP3A4/CYP3A5 metabolizers, which leads to significant increase in the level of drug in the blood and risk of side effects. The patient was identified as heterozygous carrier of non-functional allelic variant of the *CYP3A4* gene, which may require lower single and daily dose of hydroxyzine compared to average therapeutic (25% when appointed as monotherapy and 50% when appointed as polytherapy if additional drugs metabolized by 3A4 isoenzyme). Furthermore, drugs that inhibit or induce 3A4 and/or 3A5 can significantly disrupt pharmacokinetics of hydroxyzine. Admission of drugs that inhibit these enzymes is contraindicated to the patient, because their admission can significantly increase exposure of hydroxyzine in the patient's body and cause hydroxyzine-induced side effects. Hydroxyzine is transported through blood-brain barrier by transport protein P-gp. The patient identified as heterozygous carrier of non-functional allelic variant of the *MDR1* gene, which leads to moderate decrease in functional activity of transport protein P-gp and slowdown in efflux of hydroxyzine from brain to blood, which may require lower single and daily dose of hydroxyzine on average by 25% of average therapeutic when appointed as

monotherapy and by 50% when appointed as polytherapy, if hydroxyzine is combined with drugs-inhibitors of this transport protein, in case of appointing them due to primary or concomitant diseases. Hydroxyzine and hydroxyzine-containing drugs may prolong the QT interval, induce abnormal heart rhythm and increase the risk of sudden cardiac death syndrome in predisposed patients; therefore appointment of hydroxyzine requires dynamic ECG control (according to indications – ECG-Holter monitoring). Admission of hydroxyzine is not recommended to patients with unfavorable metabolic profile and to elderly patients because of decreased excretion of hydroxyzine in these patients and greater vulnerability to anticholinergic effects and other adverse reactions. Taking into account the data of patient's burdened pharmacotherapy anamnesis about hydroxyzine-induced abnormal heart rhythm, re-administration of this drug and other hydroxyzine-containing drugs requires great care and observation of a cardiologist-arrhythmologist, ECG (according to indications – ECG-Holter monitoring), but overall should be considered undesirable, even as monotherapy.

About 95% of sulpiride dose isn't metabolized in the liver. Sulpiride is transported by P-gp (MDR1). Patient identified as heterozygous carrier of non-functional allelic variant of the *MDR1* gene, which leads to moderate decrease in functional activity of transport protein P-gp and slowdown in efflux of sulpiride from brain to blood, which may require lower single and daily dose of sulpiride on average by 25% of average therapeutic when appointed as monotherapy and by 50% when appointed as polytherapy, if sulpiride is combined with drugs-inhibitors of this transport protein, in case of appointing them due to primary or concomitant diseases.

Discussion

Pronounced side effects of antidepressant therapy may be due to genetic factors. When appointing drugs that metabolize involving cytochrome P450 or use transport protein such as MDR1, the results of pharmacogenetic testing should be taken into account. In this case report in the result of screening PGx with detection of the most common low-functioning and non-functional single-nucleotide variants of the *CYP2C9*, *CYP2C19*, *CYP1A2*, *CYP3A4* and *CYP2D6* genes, encoding activity of the 2C9, 2C19, 1A2, 3A4 and 2D6 isoenzymes of liver cytochrome P450, and the *MDR1* gene, encoding transport protein P-gp (P-glycoprotein), showed heterozygous carriage of the non-functional allelic variant G rs2740574 of the *CYP3A4* gene, homozygous carriage of the non-functional allelic variant T rs2069522 of the *CYP1A2* gene, and heterozygous carriage of the non-functional allelic variant T rs1045642 of the *MDR1* gene, which are one of the most common non-functional single-nucleotide variants of these genes in the European population. Identified genetic markers are associated with moderate decrease in functional activity of the 3A4 isoenzyme, pronounced decrease in functional activity of 1A2 isoenzyme of liver cytochrome P450, resulting in a slowdown in utilization of the medications metabolized by liver and increased risk of adverse reactions, including neurotoxic. Furthermore, there was identified genetic marker associated with moderate decrease in functional activity of transport protein P-gp, leading to disruption of transport (delivery) and excretion (efflux) of psychiatric drugs through the blood-brain barrier. The data obtained by PGx allowed to explain pronounced side effects during therapy that the patient had and to give recommendations on the selection of further pharmacotherapy.

This case report highlights the important contribution of PGx into predicting response to psychiatric drugs and understanding of individual differences in such clinical reaction to these drugs. Timely conduct of PGx can have a significant impact on lower costs of psychiatric care [6].

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