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STRUCTURAL POLYMORPHISM OF CYP2D6 AND CYP2C19 GENES MODIFIES THE EFFICACY AND TOXICITY OF PHARMACOTHERAPY FOR DEPRESSIVE STATES

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Nature has created protective systems on against the entry of drugs, for metabolism in the human body. Structure of biotransformation systems is formed through the expression of genetic regulators – cytochrome P450 (CYP) enzymes, which have individual allele variability. CYP2D6 and CYP2C19 are active for the antidepressants' metabolism (substrates). Against the background of different alleles (there are more than 140 for CYP2D6), different enzyme activity occurs, it varies from maximally slow to ultrarapid, destroying the drug. Enzyme speed options are different in countries and regions of the Earth. The history of differences began in the late 1970s, the frequency of adverse drug reactions (ADRs) from antidepressants analyzed. The CYP2D6 activity covers more than 300 substrates, so the results of pharmacotherapy differ significantly, depending on the cytochromes' genetic polymorphism. Discrepancies increase with the drugs' interaction (cytochromes' inhibitors or inducers) in conditions of polypharmacy and comorbidity. Such variants of interaction are given, and the list of NLRs varies significantly for both cytochromes, because they are represented in different organs of the body. The frequency of depressive states in the world and in Ukraine should emphasize attention to the competent use of antidepressants: a promising tactic of genetic testing is proposed for the drug's selection and prescription, with the aim of timely forecasting the effectiveness and prevention of the dangers of therapy.

Key words: *cytochromes CYP2D6 and CYP2C19, genetic polymorphism, antidepressant therapy, liver, biotransformation, pharmacogenomics.*

Connection of the publication with planned research works.
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Introduction.

Current situation in Ukraine due to the state of war undeniably has a negative impact on the psychological well-being of the population, rendering the definition of health in terms of happiness and prosperity, as per the WHO, unattainable in conditions of such social upheaval. Furthermore, the WHO forecast is becoming a reality: by 2020, mental disorders will become the leading cause of disability worldwide, ranking second in frequency after ischemic heart disease.

According to data from the Ministry of Health of Ukraine and projections regarding the consequences of the war, over 15 million Ukrainians will require psychological assistance, with an estimated 3-4 million among them needing pharmacological treatment [1]. Consequently, given this situation, the understanding and significance of pharmacotherapy for depressive states should be more practically emphasized in terms of its optimal effectiveness and safety. Thus, it is necessary to consider the pathways of antidepressant metabolism adequately and in line with modern concepts across various aspects of their application. The issue of the real impact of antidepressants encompasses a wide spectrum within clinical pharmacology: mechanisms of depression development due to neurotransmitter imbalances, correction of these deviations using medications targeting various neural system components based on the classification of antidepressants, the role of biotransformation (detoxification) systems in these drugs' effects on the human body, and above all, their dependence on genetic predispositions and genetic laws [2, 3]. Thus, research into the consequences of pharmacotherapy branches out into a wide spectrum of five genetic categories involved in disease development and its dynamics: 1) genes of pathology; 2) genes responsible for drug mechanisms of action; 3) drug metabolism genes; 4) drug transport genes; 5) pleiotropic genes of cascading metabolic reactions [4, 5].

The aim of the study.

To conduct an analysis of international scientific data in modern databases regarding the genetic variability of CYP450 during pharmacotherapy with antidepressants, to make the forecast of the effectiveness and safety of treatment on the background of genetic polymorphism of enzymes' biotransformation.

Main part.

Among the listed genetic categories, particular attention is drawn to metabolic genetic dependency – the body's ability to respond to the administration of these medications. This concerns the importance of enzymatic systems that interact with drugs, reducing their concentrations in the body to safe levels. Thus, these systems protect the body from excessive, toxic therapy effects, eliminate drugs from tissues, organs, and systems [5, 6, 7]. Conversely, without considering patients' pharmacogenetic profiles (typical trial-and-error therapy), the frequency of failures and negative responses can exceed 60% [8].

Nature has devised systems that primarily encompass the monooxygenase enzyme systems of the cytochrome P450, which will be discussed further [9]. The scope of information regarding the role of cytochromes has significantly expanded in recent years, particularly branching out through the understanding of their genetic individual variability, known as genetic polymorphism. Reflecting this diversity is the classification of cytochromes (CYP), which comprises three variable components: family (designated by numbers), subfam-

ily (letters), and gene (numbers) encoding that particular cytochrome, for example, 2D6. It's essential to understand which drugs are targeted by a specific cytochrome, identified as substrates of the CYP. The CYP450 enzymes comprise 57 proteins, each encoded by individual genes. Moreover, each gene can alter its structure based on substitutions in these proteins, even by 1-2 amino acids. These substitutions are considered as allelic variants [3, 5].

In terms of pharmacotherapy for depression and other psychological disorders, the focus often revolves around CYP2D6, as this system actively participates in the metabolism of antidepressants. CYP2D6 is a highly polymorphic gene with 75 allelic variants, designated as CYP2D6*1 through *75, along with more than 30 additional subvariants [10, 11]. Over the past years, the spectrum of variants has further expanded, and today, this enzyme – debrisoquine hydroxylase – a gene with 9 exons, mapped to chromosome 22q13.2, is known to have up to 141 allelic variants. Compared to other cytochromes, it is considered to be the most influential in metabolizing the majority of substrates used in antidepressant therapy: for instance, the role of CYP2D6 accounts for 85%, CYP1A2 – 24%, CYP2B6 – 5%, CYP2C19 – 38%, and CYP3A4 – 38% of substrate metabolism.

CYP2D6 is widely expressed in most tissues, with a preference in the liver. Although it constitutes no more than 2% of the total liver enzyme count, its potency effectively manages the metabolism of 25-30% of medications [12]. Simultaneously, within the central nervous system (CNS), the CYP2D6 gene primarily expresses itself in the hippocampus and Purkinje cells of the brain. This may define its role in regulating neurotransmitter levels, including serotonin and dopamine, both of which decrease in concentration during depressive episodes.

Bariability in the structure of different alleles results in various reaction phenotypes: extensive metabolizers (EM), intermediate metabolizers (IM), poor metabolizers (PM), and ultra-rapid metabolizers (UM) of enzyme substrates. CYP2D6 plays a crucial role in detoxifying a wide range of drugs, although it constitutes a small percentage among other cytochromes [13, 11]. However, it is projected to be highly significant for future genetic control, particularly in psychiatry and addiction clinics [14, 15, 16, 17].

According to the "World Guide for Drug Use and Pharmacogenomics" (2012), among 982 medications, this cytochrome interacts as follows: 371 are substrates, over 300 are inhibitors, and 18 are inducers [11, 18].

The history of further understanding the peculiarities of genetic polymorphism of CYP2D6 emerged unexpectedly in the late 1970s. During investigations involving debrisoquine and sparteine, it was discovered that 5-10% of patients experienced severe adverse reactions, which were later linked to CYP2D6 [13, 19].

Later, it was clarified that enzyme activity levels significantly differ among specific patient groups. Variability in polymorphism became evident among healthy individuals. For instance, it can be as follows: extensive metabolizers (EM) up to 55.7%, intermediate metabolizers (IM) at 34.7%, poor metabolizers (PM) at 2.28%, and ultra-rapid metabolizers (UM) up to 7.3%. However, among patients with depression, these activities are respectively altered and constitute 64.76%, 27.31%, 4.85%, and 3.08%. Furthermore, these variations can differ among ethnic groups and along a north-to-south gradient in different countries. For instance, the prevalence of ultrarapid variants is over 2 times higher in southern European countries (such as Portugal and Spain – 8.4% and 7-10%, respectively) compared to northern European nations, where the prevalence is significantly lower (1-2% for Sweden and 3.6% for Germany). Thus, ultrarapid variants are less common in northern regions. This trend persists in Africa as well, with fewer occurrences of these variants in its northern countries [19]. Other researchers also note discrepancies in allele variants. For instance, among Europeans and Africans, the prevalence of poor metabolism (7.8-6.7%) shows a north-to-south gradient, significantly exceeding the low type observed in the Middle East (0.94%) [20, 21].

For practical pharmacotherapy in patients genetically metabolizing medications, extreme variants of cytochrome 2D6 activity entail corresponding risks: for ultrarapid metabolizers (UM), the breakdown of the drug diminishes its levels to inefficacy, yielding unexpected results. Conversely, for poor and poor metabolizers (PM), there's an increased risk of toxic effects due to elevated concentrations of medications without proper elimination. For ultrarapid metabolizers, there's a need for increased doses. However, this might decrease patient compliance due to the delayed effects of antidepressants (over 2-3 weeks) and potentially lead to discontinuation of therapy. In worse scenarios, there's a risk of increased suicidal tendencies [19, 5].

It is important to emphasize that drugs, substrates of the enzyme CYP2D6, are widely used in practice, which raises concerns regarding their adequate application and efficacy control. Therefore, this list includes: amphetamines (dexfenfluramine, methoxyamphetamine, phenformin); anesthetics (lidocaine); among antiarrhythmic drugs – mexiletine, propafenone, flecainide, encainide, sparteine; among antihypertensives – carvedilol, nebivolol, S-metoprolol, propranolol (CYP2C19), timolol, alprenolol, bufuralol, debrisoquine; antihistamines – chlorpheniramine. There is also a significant spectrum for the metabolism of CYP2D antidepressants: atomoxetine, amitriptyline (CYP1A2, CYP2C19), nortriptyline, duloxetine, clomipramine, desipramine, imipramine, paroxetine, fluoxetine, fluvoxamine, venlafaxine. Similarly, the metabolism of antipsychotic agents includes aripiprazole, haloperidol (CYP1A2), perphenazine, risperidone, thioridazine, zuclopenthixol, chlorpromazine, promethazine. Among opioid analgesics are codeine, oxycodone, tramadol; among cough suppressants – dextromethorphan; for antitumor agents – tamoxifen (CYP2C9); for antiemetics – metoclopramide, ondansetron (CYP1A2). The alternative metabolism pathways by other variants of cytochromes P450 are indicated in brackets [22].

These examples highlight significant differences in the impact of cytochromes on various groups of medications. This demands careful consideration from physicians when choosing each drug based on its individual pharmacokinetic characteristics. For instance, in the review by Cacabelos Torrellas (2015), information is provided on the role of CYP in the pharmacogenomics of selective serotonin reuptake inhibitors (SSRIs) and SNRIs, tricyclic antidepressants – listing over 20 drugs with their properties as substrates or possessing inhibitor and inducer properties [20].

The problem becomes even more complex in the context of polypharmacy, which is quite common in medical practice, especially in the treatment of comorbid conditions [23]. This includes the impact of concurrent therapy on the activity of cytochrome enzymes. Additional medications can yield conflicting outcomes: the stimulation of enzymes leads to a several-fold increase in their activity and quantity, a process termed "enzyme induction." The consequences of such biotransformation include rapid drug metabolism and a decrease in its effectiveness.

On the contrary, when the activity of enzymes is suppressed by "inhibitors" of cytochromes, the metabolism of drugs slows down. This leads to an increase in their concentration in the blood and organs, understandably causing toxic reactions [22].

Accordingly, as previously mentioned, concerning interaction with varying activity of the enzyme CYP2D6, SSRIs medications demonstrate the following impact, for instance, on the metabolism of sparteine or dextromethorphan towards diminishing their effects: paroxetine, fluoxetine=norfluoxetine, sertraline, fluvoxamine, venlafaxine. Fluoxetine and paroxetine are stronger inhibitors of CYP2D6 than sertraline. When combined with desipramine (50 mg/day), sertraline had less pharmacokinetic interaction than paroxetine with desipramine [24]. Fluvoxamine can also inhibit CYP1A2 and CYP2C19, which dictates the control of expected reactions when co-administered with substrates of these respective enzymes, especially given the narrow therapeutic index of such drugs. Duloxetine and bupropion are slow inhibitors of CYP2D6, while sertraline causes significant inhibition only at high doses. Poor inhibitors of cytochromes with lower risks of concurrent interactions include citalopram, escitalopram, venlafaxine, mirtazapine, reboxetine (which does not affect the CYP2D6 genotype). Therefore, it's essential to assess and forecast the use of antidepressants with more favorable drug interaction profiles and ensure mandatory monitoring of consequences upon discontinuation over time since the sustained effects of antidepressants persist for several weeks, especially for fluoxetine [25]. Official recommendations for dosing psychotropic medications do not consider the significance of differences in metabolic phenotypes [26], although genotyping for CYP2C19 and CYP2D6 is already available in commercial tests.

From the perspective of personalized medicine and dose selection of a medication, a meta-analysis was conducted using international databases (January 1990 – June 2020) [26] concerning identified genotypes of CYP2D6 and CYP2C19 and their three phenotypes in assessing 16 psychiatric medications. For instance, among 94 unique outcomes (among 8379 patients), the most significant deviations were observed in the context of prescribing aripiprazole (CYP2D6 slow metabolism vs. normal phenotype). The majority of comparative studies in the review suggest that the poor metabolizer (PM) or intermediate metabolizer (IM) phenotypes of CYP2D6 and CYP2C19 show an increase in the effectiveness of medications compared to the normal phenotype. It's crucial to differentiate the metabolic categories through CYP2D6 concerning reactions to aripiprazole, haloperidol, and risperidone, and for CYP2C19 – escitalopram and sertraline. Moreover, the intermediate variant (IM) less frequently affects dosage, particularly as it is observed in more than half of East Asian populations for both CYP2D6 and CYP2C19.

The more practical significance could lie in the direct assessment of drug concentration levels in the blood, even though this level is achieved later during their steady state, typically after a few weeks or months. In an ideal clinical scenario, a doctor would have knowledge of the patient's known genotype before initiating dosage, along with specific gene-drug associations [26].

Undoubtedly, the activity of cytochromes in drug transformation pathways will serve as the basis for the risks of adverse drug reactions (ADRs), depending on the achieved drug concentrations in the blood as a result of metabolism. The aim of the study by Andy R. Eugene (Lublin, Poland, 2019), conducted between 2016 and 2017, was to observe the variants of adverse drug reactions (ADRs) related to selective serotonin reuptake inhibitors (SSRIs) based on two biomarkers in their pharmacogenomic pathway: specifically, for CYP2D6 involving 2876 cases (chromosome 22q13.2, metabolizes fluvoxamine, fluoxetine, paroxetine), and CYP2C19 involving 2403 cases (chromosome 10q23.33, as per FDA data, metabolizes citalopram, escitalopram, sertraline). The authors [27] examined 40 statistical ADRs, with the most common among all being anxiety (p=3332), followed by suicidal thoughts (2841). Meanwhile, for the CYP2D6 group, night terrors (p=938), panic attacks (p=1243), hyperhidrosis (1476), withdrawal syndrome, and cognitive derealization were observed. However, among the CYP2C19 metabolizers, QT interval prolongation (p=351) and hyponatremia prevailed, with reactions involving autonomic nervous system modulation, seizures, pain, rectal dysfunction, and absorption. Such differences are justified by the distinct localization of these cytochromes in organs: high levels among 53 registered anatomical structures in the liver and the terminal part of the ileum. Additionally, for CYP2C19, it's also found in the mucous membranes of the esophagus, stomach, vagina, and the epidermis. For CYP2D6, apart from the initial two, sufficient expression is observed in the thyroid gland, cerebellum, brain, pituitary gland, and testicles. Thus, the adverse reactions associated with CYP2C19 may be more related to the gastrointestinal tract, diarrhea, alimentary responses, the enteric nervous system, pain reactions, besides influencing pregnancy, reproductive functions (with the uterus among 53 structures having the second highest frequency of CYP2C19 gene expression). Additionally, observations included shortness of breath, sleep apnea (further influenced by the high expression of the presynaptic serotonin transporter in the lungs), hyper – or hypotension.

However, for CYP2D6, the effects on the pituitary gland, thyroid (which ranks third in CYP2D6 gene expression among organs), and impacts on cognitive brain processes, sleep disturbances, consciousness alterations, hallucinations, paranoia, suicidal thoughts, and mood swings are more prominent [27]. These observations illustrate the significance of subtle differences between individual cytochromes and can inform the strategy of selecting prescribed medications in psychopharmacology.

The genetic variability of drug-metabolizing enzymes, such as CYP2D6 and CYP2C19, may underlie the toxicity when using antidepressants (pharmacokinetic effect). Simultaneously, the modification of genes en-

coding serotonin receptor structure also contributes to adverse drug reactions (pharmacodynamic effects). Variations between patients in the 5-HT2B receptor structure may be more significant, even against pharmacokinetic modifications of medications. Such diverse targets (cytochrome genes or receptor genes) may require a separate identification of genetic markers to forecast the outcomes of SSRI therapy [28]. Moreover, the impact of the CYP2D6 genotype holds more significance (especially in slow metabolizers leading to adverse reactions) concerning the plasma concentrations of antidepressants, as opposed to the minor influences of CYP2C19 genotypes and their absence in CYP2C9 [29].

However, in a study conducted by a group of authors in New Zealand [30], there was no confirmation of selecting antidepressants based on pharmacogenetics. The comparison was carried out using a 'case-control' observation method (n=194: comprising 70% Europeans, 11% Maori, and 4% Asians) against the backdrop of taking SSRIs and SSNRIs for 2 years, while considering variations in the genes CYP2D6, CYP2C19, and CYP2C9. The authors described few correspondences between these phenotypes and the levels of psychological distress, anxiety about one's health, and neuroticism. The authors emphasize the significance of such comparisons because, in their opinion, the achievement of antidepressant therapy 'over the past 50 years has been associated with tolerability rather than effectiveness' [30], especially considering the significant variability in the relative contribution of each cytochrome. Clinicians, even with known test results, are yet to fully appreciate the value of this approach. The authors hope that the increased accessibility of these testing methods 'will become clearer and more understandable in managing antidepressant therapy' [30].

The information provided indicates the current lack of clear regulations regarding the choice of antidepressant use in psychiatry and psychology. It underscores the debated directions as potential avenues for future research and directs healthcare professionals to comprehend these issues in practical medicine, aiming to increase the accessibility of this complex information.

Conclusions.

The achievements of modern pharmacogenetics help expand the understanding of individual variability in the interaction between medications and the human body, particularly in drugs used for treating depressive conditions. These variabilities are determined by the diverse structural features of genes.

To ensure adequate effectiveness and safety in antidepressant therapy, there's a need for broader implementation of genetic testing methods for the metabolism enzymes of antidepressants, specifically the cytochrome P450 system.

Technological advancements and the control of pharmacogenetic foundations in therapy pose challenges in the effectiveness of clinical assistance for depression. These challenges may also stem from economic disparities among countries, especially in Ukraine amidst the conditions of armed conflict and increasing levels of depression.

Familiarizing oneself with new approaches in selecting antidepressants based on individual genetic prognosis needs broader implementation through relevant publications and scientific forums.

Prospects for further research.

Referral of the patient to the diagnosis of genetic polymorphism of cytochromes should be more critical in the real practice of pharmacotherapy in current conditions. Implementation of a pharmacogenomics strategy for personalized medicine will serve as a helpful asset for monitoring optimal therapy.

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СТРУКТУРНИЙ ПОЛІМОРФІЗМ ГЕНІВ ЦИТОХРОМУ CYP2D6 ТА CYP2C19 МОДИФІКУЄ ЕФЕКТИВНІСТЬ ТА ТОКСИЧНІСТЬ ФАРМАКОТЕРАПІЇ ДЕПРЕСИВНИХ СТАНІВ

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Резюме. Сучасна ситуація в світі супроводжується зростанням депресивних станів серед популяцій, що засвідчують висновки та прогнози ВООЗ. Для України, в умовах воєнного стану ця проблема ще більше актуальна, що підтверджують спостереження Міністерства Охорони Здоров'я – кількість хворих, яким може бути потрібна психологічна допомога, досягає понад 15 млн. Це привертає увагу до оптимальної фармакотерапії антидепресантами, яка охоплює спектр їх різних варіантів. Метою огляду є проведення аналізу клінічної фармакології антидепресантів, залежність ефективності та безпеки їх застосування від особливостей їх метаболізму, на шляхах детоксикації ферментативними системами цитохромів Р450, з акцентами на генетичний контроль цих реакцій. Інформаційні матеріали були отримані при аналізі міжнародних англомовних баз даних. Наслідки терапії антидепресантами залежить від індивідуальної варіабельності структурних компонентів генів цитохрому Р450, в найбільший мірі від змін алельного їх складу. Лікарські засоби, що за механізмами дії відносяться до антидепресантів (тобто вони є субстратами, на які діють цитохроми Р450), найчастіше метаболізуються CYP2D6 та CYP2C19. Приведено структуру цих обох цитохромів, особливості їх експресії в ЦНС, в печінці та інших органах. Варіабельність структури різних алелей в їх генах забезпечує різні фенотипи активності ферментів для метаболізму субстратів: екстенсивні (EM), проміжні (IM), слабкі (PM) або ультрашвидкі (UM). Дослідження генетичного поліморфізму структури CYP2D6 та CYP2c19 віддзеркалюють значну їх варіабельність: вона засвідчена як у здорових осіб, так і тим більше при відповіді пацієнтів на терапію антидепресантами. Такі відмінності спостерігаються в окремих популяціях в різних країнах Європи, Азії та Африки. Варіабельність фенотипів ферментів для практичної фармакотерапії обертається ризиками неадекватного дозування ліків: для ультрашвидких потребує збільшення дози, а для повільних фенотипів, навпаки, її зменшення (захист від токсичних впливів). В умовах поліпрагмазії при коморбідних станах необхідно враховувати взаємодію між базисними препаратами та антидепресантами. Нехтування такою тактикою стає підґрунтям для небажаних лікарських реакцій. Відмінності частоти таких реакцій окремо для CYP2D6 та CYP2C19 обумовлені різною локалізацією цих генів в органах. Наведена інформація націлює на ширше впровадження методів генетичного тестування до початку фармакотерапії, заради наступного прогнозу тактики оптимального вибору антидепресантів.

Ключові слова: цитохроми CYP2D6 та CYP2C19, генетичних поліморфізм, терапія антидепресантами, печінка, біотрансформація, фармакогенетика.

STRUCTURAL POLYMORPHISM OF CYP2D6 AND CYP2C19 GENES MODIFIES THE EFFICACY AND TOXICITY OF PHARMACOTHERAPY FOR DEPRESSIVE STATES

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Abstract. Current global circumstances are accompanied by an increase in depressive states among populations, as evidenced by the conclusions and forecasts of the WHO. For Ukraine, in the conditions of a state of war, this issue becomes even more pressing, as confirmed by observations from the Ministry of Health – the number of individuals who may need psychological assistance exceeds 15 million. This draws attention to the optimal pharmacotherapy of antidepressants, encompassing a spectrum of their various options. The aim of the review is to conduct an analysis of the clinical pharmacology of antidepressants, the dependency of their effectiveness and safety on the peculiarities of their metabolism through detoxification pathways involving the cytochrome P450 enzymatic systems, emphasizing the genetic control of these reactions. Informational materials were obtained from the analysis of international English-language databases. The consequences of antidepressant therapy depend on the individual variability of structural components of the cytochrome P450 genes, primarily from changes in their allele composition. Medications that fall within the mechanisms of action of antidepressants (meaning they are substrates acted upon by cytochrome P450) are most frequently metabolized by CYP2D6 and CYP2C19. Details regarding the structure of both these cytochromes, their expression specifics in the CNS, liver, and other organs, are provided. The structural variability of different alleles within their genes yields various phenotypes of enzyme activity for substrate metabolism: extensive metabolizers (EM), intermediate metabolizers (IM), poor metabolizers (PM), or ultra-rapid metabolizers (UM). Studies on the genetic polymorphism of the CYP2D6 and CYP2C19 structures reflect their significant variability, observed not only in healthy individuals but more notably in patients' responses to antidepressant therapy. Such differences are observed within specific populations across different countries in Europe, Asia, and Africa. The variability in enzyme phenotypes for practical pharmacotherapy entails risks of inadequate drug dosing: ultra-rapid metabolizers require increased doses, while slow phenotypes, on the contrary, necessitate dose reduction (protective measure against toxic effects). In conditions of polypharmacy in comorbid states, it's crucial to consider the interaction between baseline medications and antidepressants. Neglecting such tactics becomes the basis for adverse drug reactions. Differences in the frequency of these reactions specifically for CYP2D6 and CYP2C19 are due to the distinct localization of these genes in organs. This information directs toward broader implementation of genetic testing prior to commencing pharmacotherapy, aiming for subsequent prognosis for optimal selection of antidepressants.

Key words: cytochromes CYP2D6 and CYP2C19, genetic polymorphism, antidepressant therapy, liver, biotransformation, pharmacogenomics.

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