FARMAKOGENETIKA ANTIDEPRESIVA – KORAK KA INDIVIDUALIZACIJI TERAPIJE

AKTUELNA TEMA

CURRENT TOPIC

PHARMACOGENETICS OF ANTIDEPRESSANTS – A STEP TO INDIVIDUALIZED THERAPY

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SAŽETAK

Farmakogenetika analizira interindividualne razlike koje dovode do varijabilnog odgovora pacijenata na primenjenu terapiju, sa ciljem da ukaže na koji način pojedini geni i interindividualne genetičke varijacije mogu da utiču na farmakokinetiku i farmakodinamiku lekova. Ona je kritična komponenta personalizovane medicine u psihofarmakologiji. Najveći broj dosadašnjih ispitivanja ukazuje na veliki potencijal farmakogenetičkih ispitivanja prilikom individualizacije terapije antidepresivima. Klinički značaj je, do sada, pokazalo utvrđivanje genetičkog profila i metaboličkog fenotipa za CYP2C19 kod pacijenata na escitalopramu i sertralinu, odnosno CYP2C19 i CYP2D6 kod pacijenata na amitriptilinu. Iako manje ispitana, farmakodinamička varijabilnost nije ništa manje značajna od farmakokinetičke. Polimorfizmi serotoninskog transportera u značajnoj meri utiču na terapijski odgovor na selektivne inhibitore preuzimanja serotonina. Farmakogenetički pristup predstavlja inovativni model u razumevanju heterogenosti terapijskog odgovora na antidepresive. Prednost ovakvog pristupa je nepromenljivost genotipa u vremenu. S druge strane, postoje brojni izazovi i ograničenja za rutinsko izvođenje ovih analiza, poput dostupnosti ovih testova i složenosti interpretacije rezultata. Učinak leka je kompleksan fenomen i pojedinačne mutacije u pojedinačnim genima ne mogu objasniti svu varijabilnost psihofarmakoterapije. Iako farmakogenetika nedvosmisleno ima veliki potencijal u razvoju lekova i individualizaciji terapije, neophodna su dalja istraživanja da bi se ovaj potencijal u potpunosti primenio u kliničkoj praksi.

Ključne reči: farmakogenetika, polimorfizmi, antidepresivi, individualizacija terapije

ABSTRACT

Pharmacogenetics analyzes interindividual differences that lead to variable patient responses to therapy, with the aim of indicating how individual genes and interindividual genetic variations can affect the pharmacokinetics and pharmacodynamics of drugs. It is a critical component of personalized medicine in psychopharmacology. Most studies to date indicate the great potential of pharmacogenetic studies in the individualization of antidepressant therapy. So far, the determination of the genetic profile and metabolic phenotype for CYP2C19 in patients on escitalopram and sertraline, and CYP2C19 and CYP2D6 in patients on amitriptyline, has shown clinical significance. Although less studied, pharmacodynamic variability is no less significant than pharmacokinetic variability. Serotonin transporter polymorphisms significantly influence the therapeutic response to selective serotonin reuptake inhibitors. The pharmacogenetic approach is an innovative model in understanding the heterogeneity of the therapeutic response to antidepressants. The advantage of this approach is the permanence of the genotype over time. On the other hand, there are numerous challenges and limitations to performing these analyses routinely, such as the availability of these tests and the complexity of interpreting the results. The effect of the drug is a complex phenomenon and single mutations in individual genes cannot explain all the variability of psychopharmacotherapy. Although pharmacogenetics clearly has great potential in drug development and individualization of therapy, further research is needed to fully implement this potential in clinical practice.

Keywords: pharmacogenetics, polymorphisms, antidepressants, individualized therapy

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UVOD

Depresivni poremećaji su među najčešćim oboljenjima današnjice, sa preko 350 miliona obolelih i godišnjom prevalencijom od 4,7% na globalnom nivou [1,2]. To je najčešći mentalni poremećaj u opštoj populaciji, sa dva puta češćim javljanjem kod žena u odnosu na mušku populaciju. Depresivne poremećaje mogu da prate ozbiljne posledice, poput visokog rizika za suicid, komorbiditeta sa drugim mentalnim i somatskim bolestima, značajno narušavanje kvaliteta života i radne sposobnosti pojedinaca [3]. U savremenoj psihofarmakologiji dostupan je veliki broj lekova iz grupe antidepresiva čija je bezbednost i efikasnost pokazana u kontrolisanim, randomizovanim kliničkim ispitivanjima. Ipak, ostaje činjenica da 30–50% pacijenata nema adekvatan odgovor na prvi primenjeni lek [4].

Značajne interindividualne varijacije u odgovoru na terapiju pokazane su kod svih dostupnih antidepresiva, kao i za većinu drugih psihofarmaka [5]. Jasno je da je farmakoterapijski pristup *one-size-fits-all* nedovoljan i da se moderna klinička praksa, u skladu sa principima medicine zasnovane na dokazima, usmerava ka preciznoj medicini i individualizaciji terapije. Jedan od brojnih, ako ne i presudnih faktora, koji utiču na odgovor na farmakoterapiju je genetički profil pacijenta. Naime, savremena metodologija omogućila je sekvenciranje gena, uključujući one koji kodiraju proteine koji utiču na farmakokinetiku (FK) i farmakodinamiku (FD) lekova [6]. Rasvetljavanje kompleksne veze između genetičke osnove i odgovora na terapiju postaje sve značajnije u razvoju novih strategija u lečenju i prevenciji bolesti. U tom smislu, rutinska farmakogenetička testiranja imaju za cilj da omoguće lekaru u kliničkoj praksi individualizaciju doznog režima i bolju predikciju terapijskog odgovora, kako u smislu efikasnosti, tako i u smislu bezbednosti primenjenog leka [6,7].

FARMAKOGENETIKA KAO KRITIČNA KOMPONENTA PERSONALIZOVANE MEDICINE

Uprava za hranu i lekove SAD *(*engl. *Food and Drug Administration – FDA)* definiše koncept personalizovane medicine kao individualni pristup prevenciji i lečenju bolesti, koji uzima u obzir interindividualne razlike u sredinskim faktorima, stilovima života i, sve više, genetičkom profilu pacijenata. U tom smislu, farmakogenetika se nameće kao kritična komponenta personalizovane medicine. *FDA* je do sada preporučila farmakogenetičko testiranje za preko 50 lekova u kliničkoj praksi [8]. Farmakogenetika analizira interindividualne razlike koje dovode do varijabilnog odgovora pacijenata na primenjenu terapiju, sa ciljem da

INTRODUCTION

Depressive disorders are among the most common diseases today, with more than 350 million patients and an annual prevalence of 4.7% globally [1,2]. They are the most common mental disorders in the general population, with an incidence twice as high among women as among men. Depressive disorders can be accompanied by serious effects, such as high risk of suicide, comorbidities with other mental and somatic diseases, considerable impairment of the individual's quality of life and ability to work [3]. There is a large number of drugs from the group of antidepressants in modern psychopharmacology, whose safety and efficacy has been shown in controlled, randomized clinical trials. Nevertheless, the fact remains that 30–50% of patients do not have an adequate response to the first administered drug [4].

Significant interindividual variations in response to therapy have been shown for all available antidepressants, as well as for most other psychopharmaceuticals [5]. It is clear that the "one-size-fits-all" pharmacotherapeutic approach is insufficient and that modern clinical practice, in line with the principles of evidence-based medicine, points to precision medicine and drug therapy individualization. One of the many, if not the crucial factor that influences the response to pharmacotherapy is a patient's genetic profile. Modern methodology has enabled the sequencing of genes, including protein-coding genes that influence the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs [6]. Shedding light on the complex connection between a genetic basis and response to therapy is becoming increasingly important in developing new strategies in the treatment and prevention of diseases. In this sense, routine pharmacogenetic testing is aimed at enabling physicians to individualize dosage regimens in clinical practice and better predict therapeutic responses, both in terms of efficacy and in terms of the safety of the administered drug [6,7].

PHARMACOGENETICS AS A CRITICAL COMPONENT OF PERSONALIZED MEDICINE

The U.S. Food and Drug Administration defines the concept of personalized medicine as an individual approach to disease prevention and treatment that takes into account interindividual differences in people's environments, lifestyles and, increasingly, patients' genetic profiles. In this sense, pharmacogenetics imposes itself as a crucial component of personalized medicine. The FDA has so far recommended pharmacogenetic testing for over 50 drugs in clinical practice [8]. Pharmacogenetics analyzes interindividual differences that lead to patients' variable response to administered therapy, aiming to show how certain genes and interindividual genetic variations can affect the PK and PD of drugs.

ukaže na koji način pojedini geni i interindividualne genetičke varijacije mogu da utiču na FK i FD lekova. Naime, pojedini genetički polimorfizmi kodiraju različite proteine koji određuju FK, poput enzima za metabolisanje lekova, ili FD, poput receptora, enzima, intraćelijskih glasnika i drugih ciljnih molekula za dejstvo lekova [6]. Bolje poznavanje interakcije genoma i etiopatogeneze i terapije bolesti, dovelo je do razvoja farmakogenomike, koja opisuje višestruke varijacije i uticaj genoma u celini na svojstva lekova, kao i farmakoepigenetike, kao nove discipline koja proučava kako epigenetički mehanizmi dovode do varijacija u odgovoru na terapiju [9,10].

FARMAKOGENETIKA ANTIDEPRESIVA

Farmakogenetički pristup predstavlja inovativni model u razumevanju heterogenosti terapijskog odgovora na antidepresive. Prednost ovakvog pristupa je nepromenljivost genotipa u vremenu, kao i sve veća dostupnost pouzdanih, genetičkih testiranja [11]. Kod antidepresiva pretežno su opisane individualne genetičke varijacije, nastale usled jednonukleotidnih polimorfizama u genima: 1) koji kodiraju enzime koji učestvuju u metabolizmu ovih lekova (farmakokinetička varijabilnost) i 2) koji kodiraju ciljne molekule za dejstvo lekova (farmakodinamička varijabilnost).

Genetička osnova farmakokinetičke varijabilnosti

Najveći broj studija do sada analizira genetičku varijabilnost mikrozomalnih citohrom P450 enzima uključenih u metabolizam antidepresiva (Tabela 1) [12]. Rezultati ovih studija ukazuju da polimorfizam gena koji kodiraju ove enzime predstavlja važan faktor koji određuje koncentraciju leka u krvi, a time i njegovu efikasnost i bezbednost. Genotipizacija podrazumeva identifikaciju

Certain genetic polymorphisms encode different proteins that determine the PK, such as enzymes for drug metabolism, or the PD, such as receptors, enzymes, intracellular messengers, and other target molecules for drug effects [6]. The better understanding of the interaction between the genome and etiopathogenesis and the disease therapy has led to the development of pharmacogenomics, which describes multiple variations and the influence of the genome, as a whole, on drug properties, as well as of pharmacoepigenetics as a new discipline that studies ways in which epigenetic mechanisms lead to variations in response to therapy [9,10].

PHARMACOGENETICS OF ANTIDEPRESSANTS

The pharmacogenetic approach is an innovative model in understanding the heterogeneity of the therapeutic response to antidepressants. The advantage of this approach is the invariance of genotypes over time, as well as the increasing availability of reliable genetic testing [11]. In the case of antidepressants, the description predominantly covers individual genetic variations , resulting from single nucleotide polymorphisms in genes: 1) that code enzymes involved in the metabolism of these drugs (pharmacokinetic variability), and 2) that code target molecules for drug action (pharmacodynamic variability).

Genetic basis of pharmacokinetic variability

Most studies to date analyzed the genetic variability of microsomal cytochrome P450 enzymes involved in the metabolism of antidepressants (Table 1) [12]. The results of these studies indicate that the polymorphism of genes that code these enzymes is an important factor that determines the concentration of a drug in the blood and, therefore, its efficacy and safety. Genotyping involves the identification of mutations in CYP genes by molecular diagnostic methods and PCR, and the

Tabela 1. Mikrozomalni citohrom P450 enzimi uključeni u metabolizam antidepresiva

Table 1. Microsomal cytochrome P450 enzymes involved in metabolism of antidepressants

Izoforme citohroma P450 / ***Cytochrome P450 isoforms***	**Antidepresivi /** ***Antidepressants***
CYP2D6	*TCAs,* fluoksetin, paroksetin, sertralin, escitalopram, duloksetin, venlafaksin, mirtazapin / *TCAs, fluoxetine, paroxetine, sertraline, escitalopram, duloxetine, venlafaxine, mirtazapine*
CYP2C9	fluoksetin, sertralin / *fluoxetine, sertraline*
CYP2C19	*TCAs*, fluoksetin, sertralin, escitalopram / *TCAs, fluoxetine, sertraline, escitalopram*
CYP1A2	*TCAs,* duloksetin, mirtazapin, agomelatin / *TCAs, duloxetine, mirtazapine, agomelatine*
CYP3A4	*TCAs,* fluoksetin, paroksetin sertralin, escitalopram, venlafaksin, mirtazapin, trazodon / *TCAs, fluoxetine, paroxetine sertraline, escitalopram, venlafaxine, mirtazapine, trazodone*

mutacija gena CYP metodama molekularne dijagnostike i PCR-a, i prepoznavanje heterozigotnih ili homozigotnih nosilaca mutiranih alela koji rezultiraju odgovarajućim fenotipom (metabolički fenotip). Prema Vodiču dobre kliničke prakse za dijagnostikovanje i lečenje depresije, jedan od koraka racionalnog postupka kod izostanka povoljnog odgovora na terapiju je genotipizacija i farmakogenetičko testiranje [3]. Ilustrativan primer za to je farmakogenetičko testiranje u cilju optimizacije terapije amitriptilinom, na osnovu čega je *Konzorcijum za implementaciju kliničke farmakogenetike* (engl. *Clinical Pharmacogenetics Implementation Consortium – CPIC)* dao preporuke za doziranje tricikličnih antidepresiva *(*engl. *tryciclic antidepressants - TCAs)* u odnosu na genotip pacijenta [13,14]. Amitriptilin, kao tipični predstavnik *TCAs*, metaboliše se putem izoenzima CYP2C19 i CYP2D6. Studije su utvrdile postojanje nekoliko genetičkih varijanti ovih izoenzima, što može imati za posledicu veliku varijabilnost u efikasnosti i bezbednosti amitriptilina. Naime, da bi se utvrdio konkretan fenotipski profil metabolisanja amitriptilina, u odnosu na gene za CYP2C19 i CYP2D6, testira se genotip pacijenta za najčešće polimorfizme CYP2C19 (*2, *3, *17) i CYP2D6 (*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41). Testiranje se optimalno izvodi pre početka terapije, da bi se prilagodio izbor leka i njegovo doziranje.

Na osnovu odgovarajućeg genetičkog profila za CYP2C19 i brzine metabolisanja leka, izdvajaju se osobe sa ultrabrzim metabolizmom, kojih ima oko 30% u evropskoj populaciji i kod kojih se ne preporučuje terapija amitriptilinom. Kod osoba sa brzim i intermedijarnim metabolizmom preporučuje se terapija u skladu sa sažetkom o karakteristikama leka *(*engl. *Summary of Product Characteristics - SmPCs),* dok je kod osoba sa sporim metabolizmom, kojih ima oko 3% u evropskoj populaciji, preporučeno smanjiti početne doze za 50% (Tabela 2).

Na osnovu odgovarajućeg genetičkog profila i metaboličkog fenotipa za CYP2D6, izdvajaju se osobe sa ultrabrzim metabolizmom i sporim metabolizmom,

identification of heterozygous or homozygous carriers of mutated alleles that result in a corresponding phenotype (metabolic phenotype). According to the National guide for good clinical practice for diagnosing and treating depression, one of the steps in rational procedure, in the absence of a favorable response to therapy, is genotyping and pharmacogenetic testing [3]. An illustrative example of this is pharmacogenetic testing, aimed at optimizing treatment with amitriptyline, based on which the Clinical Pharmacogenetics Implementation Consortium (CPIC) issued recommendations for the dosing of tricyclic antidepressants (TCA) depending on the patient's genotype [13,14]. Amitriptyline, as a typical TCA representative, is metabolized by isoenzymes CYP2C19 and CYP2D6. Studies have determined the existence of several genetic variants of these isoenzymes, which may result in high variability in the efficacy and safety of amitriptyline. In order to determine the specific phenotypic profile of amitriptyline metabolism, relative to the genes for CYP2C19 and CYP2D6, the patient genotype is tested for the most common polymorphisms CYP2C19 (*2, *3, *17) and CYP2D6 (*1XN, *2, *2XN, *3, *4, *5, *6, *9, *10, *41). Testing is optimally performed prior to starting therapy, in order to adjust the choice of drug and its dosage.

Individuals with ultra-rapid metabolism represent a special case, based on the corresponding genetic profile for CYP2C19 and the rate of drug metabolism; they account for around 30% of the European population and amitriptyline therapy is not recommended for them. The recommended therapy for persons with rapid and intermediate metabolism is provided in the Summary of Product Characteristics (SmPC), while for persons with slow metabolism (roughly 3% in the European population) it is recommended that the initial dosage be reduced by 50% (Table 2).

Individuals with ultra-rapid metabolism and slow metabolism represent a special case, based on the corresponding genetic profile and metabolic phenotype for CYP2D6; they account for around 10% in the

Tabela 2. Preporuke za terapiju amitriptilinom u zavisnosti od CYP2C19 genotipa

Table 2. Recommendations for amitriptyline therapy, subject to CYP2C19 genotype

CYP2C19 metabolički fenotip / *CYP2C19 metabolic phenotype*	**Terapijske implikacije / *Therapeutic implications***
Osobe sa ultra-brzim metabolizmom / *Ultra-rapid metabolizers*	Ne preporučuje se terapija amitriptilinom / *Therapy with amitriptyline is not recommended*
Osobe sa uobičajenim, brzim metabolizmom / *Extensive, normal metabolizers*	Terapija u skladu sa *SmPCs-em* / *Use in accordance with SmPCs*
Osobe sa intermedijernim metabolizmom / *Intermediate metabolizers*	Terapija u skladu sa *SmPCs-em* / *Use in accordance with SmPCs*
Osobe sa sporim metabolizmom / *Poor metabolizers*	Preporučuje se smanjenje početne doze za 50% / *Reduction of the initial dose by 50% is recommended*

Tabela 3. Preporuke za terapiju amitriptilinom u zavisnosti od CYP2D6 genotipa

Table 3. Recommendations for amitriptyline therapy, subject to CYP2D6 genotype

CYP2D6 metabolički fenotip / ***CYP2D6 metabolic phenotype***	**Terapijske implikacije /** ***Therapeutic implications***
Osobe sa ultra-brzim metabolizmom / *Ultra-rapid metabolizers*	Ne preporučuje se terapija amitriptilinom / *Therapy with amitriptyline is not recommended*
Osobe sa uobičajenim, brzim metabolizmom / *Extensive, normal metabolizers*	Terapija u skladu sa *SmPCs-em* / *Use in accordance with SmPCs*
Osobe sa intermedijernim metabolizmom / *Intermediate metabolizers*	Preporučuje se smanjenje početne doze za 25% / *Reduction of the initial dose by 25% is recommended*
Osobe sa sporim metabolizmom / *Poor metabolizers*	Ne preporučuje se terapija amitriptilinom / *Therapy with amitriptyline is not recommended*

kojih ima oko 10% u evropskoj populaciji i kojima se ne preporučuje terapija amitriptilinom. Osobama sa brzim metabolizmom preporučuje se uobičajeno doziranje u skladu sa *SmPCs-em*, dok je osobama sa intermedijarnim metabolizmom preporučeno smanjenje početne doze za 25% (Tabela 3).

Selektivni inhibitori preuzimanja serotonina *(*engl. *Selective serotonin reuptake inhibitors - SSRIs)*, escitalopram i sertralin, kao najčešće propisivani antidepresivi, bili su posebno analizirani sa farmakogenetičkog aspekta. Iako je najselektivniji i jedan od najefikasnijih *SSRIs*, escitalopram pokazuje terapijski neuspeh kod određenog broja pacijenta, bilo usled izostanka adekvatnog odgovora na terapiju ili zbog izraženih neželjenih efekata. Fokus farmakognetičkih studija je CYP2C19 genotipizacija kod pacijenata na terapiji escitalopramom [15] (Tabela 4). U studiji sa preko 2.000 pacijenata, pokazano je da su osobe sa ultrabrzim i sporim metabolizmom imale značajno povećan rizik od terapijskog neuspeha, pri čemu su ove dve podgrupe činile čak 33% svih pacijenta na escitalopramu [16]. Osim escitaloprama, sertralin je takođe supstrat za CYP2C19 čiji polimorfizmi značajno utiču na individualne varijacije u njegovom metabolizmu (Tabela 4). U meta-analizi koja je procenjivala kliničku efikasnost i bezbednost 21 antidepresiva kod odraslih pacijenata sa dijagnostikovanom depresijom, sertralin se pokazao kao jedan od optimalnih antidepresiva, u pogledu efikasnosti i bezbednosti, pri čemu su zabeležene značajne interindividualne varijacije u terapijskom odgovoru [17,18]. Studija iz 2019. godine, sa 1.200 pacijenata, potvrdila je relevantnost CYP2C19 genotipizacije kod terapije sertralinom. Naime, pacijenti sa intermedijernim i sporim metabolizmom imali su značajno povišene serumske koncentracije leka i rizik za razvoj neželjenih efekta prilikom uobičajenog doziranja, što ukazuje na potrebu smanjenja doze i povećanog opreza kod ovih pacijenata [19].

Pored ekstenzivno proučavane genetičke varijabilnosti pojedinih enzima uključenih u metabolizam

European population and amitriptyline therapy is not recommended for them. The usual dosage, in accordance with the SmPC, is recommended for persons with fast metabolism, while the reduction of the initial dosage by 25% is recommended for persons with intermediate metabolism (Table 3).

Selective serotonin reuptake inhibitors (SSRI), escitalopram and sertraline, as the most commonly prescribed antidepressants, have been specifically analyzed from a pharmacogenetic aspect. Even though it is the most selective and one of the most effective SSRIs, escitalopram exhibits therapeutic failure in a certain number of patients, either due to the lack of an adequate response to therapy or due to pronounced side effects. The focus of pharmacogenetic studies is CYP2C19 genotyping in patients treated with escitalopram [15] (Table 4). A study that included more than 2,000 patients showed that persons with ultra-rapid and slow metabolism had a significantly increased risk of therapeutic failure, with these two subgroups accounting for as many as 33% of all patients on escitalopram [16]. In addition to escitalopram, sertraline is also a substrate for CYP2C19 whose polymorphisms significantly affect individual variations in its metabolism (Table 4). The meta-analysis that assessed the clinical efficacy and safety of 21 antidepressants in adult patients diagnosed with depression, sertraline proved to be one of the optimal antidepressants in terms of efficacy and safety, with significant interindividual variations in therapeutic response being recorded [17,18]. A 2019 study with 1,200 patients confirmed the relevance of CYP2C19 genotyping in sertraline therapy. Patients with intermediate and slow metabolism had significantly elevated serum drug concentrations and a risk of developing side effects at the usual dosage, which indicated the need to reduce the dosage and increase caution in the case of such patients [19].

In addition to the extensively studied genetic variability of certain enzymes involved in antidepressant metabolism, other genes of importance for the PK of

Tabela 4. Preporuke za terapiju escitalopramom i sertralinom u zavisnosti od CYP2C19 genotipa

Table 4. Recommendations for escitalopram and sertraline therapy, subject to CYP2C19 genotype

CYP2C19 metabolički fenotip / *CYP2C19 metabolic phenotype*	**Terapijske implikacije za escitalopram / *Therapeutic implications for escitalopram***	**Terapijske implikacije za sertralin / *Therapeutic implications for sertraline***
Osobe sa ultra-brzim metabolizmom / *Ultra-rapid metabolizers*	Razmotriti povećanje doze za 50% ili primenu drugog leka / *Consider increasing the dose by 50% or administering alternative drug*	Terapija u skladu sa *SmPCs-em* / *Use in accordance with SmPCs*
Osobe sa uobičajenim, brzim metabolizmom / *Extensive, normal metabolizers*	Terapija u skladu sa *SmPCs-em* / *Use in accordance with SmPCs*	Terapija u skladu sa *SmPCs-em* / *Use in accordance with SmPCs*
Osobe sa intermedijernim metabolizmom / *Intermediate metabolizers*	Terapija u skladu sa *SmPCs-em* / *Use in accordance with SmPCs*	Oprez zbog povećanog rizika za pojavu neželjenih efekata / *Caution for increased risk of side effects*
Osobe sa sporim metabolizmom / *Poor metabolizers*	Oprez zbog povećanog rizika za pojavu neželjenih efekata / *Caution for increased risk of side effects*	Preporučuje se smanjenje početne doze za 50%; oprez zbog povećanog rizika za pojavu neželjenih efekata / *The initial dose should be reduced by 50%; caution for increased risk of side effects*

antidepresiva, identifikovani su i drugi geni od značaja za FK antidepresiva, čiji polimorfizmi mogu uticati na njihov farmakološki profil, njihovo doziranje i pojavu neželjenih efekata. Porodica ABC transportnih proteina predstavlja važan faktor farmakokinetičke varijabilnosti. Jedan od najbolje proučenih je P-glikoprotein, koji je kodiran genom ABCB1 ili MDR1 [11]. P-glikoprotein je integralni membranski protein koji utiče na transport i distribuciju lekova, međusobne interakcije i efikasnost. Pretklinička istraživanja su pokazala višestruko povećane koncentracije pojedinih antidepresiva, poput amitriptilina, paroksetina i venlafaksina, u nedostatku P-glikoproteina, što može izazvati kumulaciju leka i povećan rizik za razvoj neželjenih efekata [20]. Osim toga, pokazane su i klinički značajne interakcije gotovo svih AD i njihovih metabolita sa P-glikoproteinom. Do sada je opisano više mutacija u genu MDR1/ABCB1 koje rezultiraju izmenjenom ekspresijom i funkcijom P-glikoproteina. Uticaj polimorfizama na farmakokinetičke paramatre i potencijalne mogućnosti farmakogenetičke analize P-glikoproteina se i dalje ispituju.

Genetička osnova farmakodinamičke varijabilnosti

Iako manje ispitana, farmakodinamička varijabilnost nije ništa manje značajna od farmakokinetičke. Polimorfizmi u genima koji kodiraju ciljne molekule za dejstvo lekova mogu značajno uticati na efikasnost i bezbednost lekova. S obzirom da antidepresivi imaju brojna mesta svog delovanja u centralnom nervnom

antidepressants have also been identified, whose polymorphisms may affect their pharmacological profile, dosage and side effects. The ABC transport protein family is an important factor in pharmacokinetic variability. One of the best studied is the P-glycoprotein, which is encoded by the ABCB1 or MDR1 gene [11]. P-glycoprotein is an integral membrane protein that affects the transport and distribution of drugs, their mutual interactions and efficacy. Preclinical studies have shown multiple increases in the concentration of certain antidepressants, such as amitriptyline, paroxetine and venlafaxine, in the absence of P-glycoproteins, which may result in drug accumulation and increased risk of side effects [20]. In addition, clinically significant interactions of nearly all ADs and their metabolites with P-glycoprotein have been shown. So far, several mutations in the MDR1/ABCB1 gene have been described, which result in altered P-glycoprotein expression and function. The influence of polymorphisms on pharmacokinetic parameters and potential possibilities of pharmacogenetic analysis of P-glycoproteins are still being investigated.

Genetic basis of pharmacodynamic variability

Although less studied, pharmacodynamic variability is no less important than pharmacokinetic variability. Polymorphisms in genes encoding target molecules for drug action can significantly affect drug efficacy and safety. Given that antidepressants have a number of sites of action in the central nervous system, including in neurotransmitter synthesis, and the transporter

sistemu, uključujući sintezu neurotransmitera, funkciju transportera i receptora, mogu se očekivati značajne kliničke implikacije genetičke varijabilnosti.

Ilustrativni primer je polimorfizam serotoninskog transportnog sistema (SERT) koji je do sada bio u fokusu farmakogenetičkih testiranja. SERT je protein odgovoran za aktivni transport serotonina iz sinapse u presinaptički neuron i predstavlja ciljno mesto delovanja serotonergičnih antidepresiva. Osim serotonina, SERT ima sposobnost transporta i drugih endogenih amina, poput dopamina. Funkcionalni polimorfizmi gena SERT identifikovani su u različitim oboljenjima, uključujući psihijatrijske bolesti i depresiju [21], a najviše je ispitivan SERTPR polimorfizam koji se odlikuje varijabilnim brojem ponovaka u promotorskoj regiji, usled čega se ispoljava duža (*L*) i kraća (*S*) varijanta. *L* alel se karakteriše povećanom transkripcijom i većom biološkom aktivnošću SERT proteina. Pokazano je da osobe homozigotne za *S* alel mogu biti podložnije razvoju depresije i suicidalnom ponašanju. Pretpostavlja se da ovi pacijenti imaju lošiji odgovarajući terapijski odgovor i slabije podnose SSRIs antidepresive. Nasuprot tome, osobe sa *L* alelom bolje reaguju na akutni stres i primenu antidepresiva [22]. Međutim, pojedine studije pokazuju kontradiktorne rezultate o povezanost između SERTPR polimorfizama i efektivnosti antidepresiva [23]. Neophodna su dodatna, psihofarmakološka ispitivanja u cilju utvrđivanja značaja, kako polimorfizama serotoninskog transportera, tako i farmakodinamičke varijabilnosti uopšte.

ZAKLJUČAK

Farmakogenetika je jedan od temelja personalizovane medicine i individualizacije farmakoterapije u psihijatriji. Najveći broj dosadašnjih ispitivanja ukazuje na veliki potencijal farmakogenetičkih ispitivanja prilikom individualizacije terapije antipsihoticima i antidepresivima. To potvrđuju i najnovije preporuke *FDA* za farmakogenetičko testiranje i utvrđivanje genetičkog profila i metaboličkog fenotipa za CYP2D6 kod pacijenta na aripiprazolu. U grupi anksioznih i depresivnih poremećaja, farmakogenetičko testiranje se preporučuje kod pacijenata koji nisu pokazali zadovoljavajući terapijski odgovor na više primenjenih antidepresiva. Do sada je najviše kliničkih implikacija pokazalo utvrđivanje genetičkog profila i metaboličkog fenotipa za CYP2C19 kod pacijenata na escitalopramu i sertralinu, odnosno CYP2C19 i CYP2D6 kod pacijenata na amitriptilinu. I pored dokazanog kliničkog benefita, još uvek nema dovoljno farmakoekonomskih podataka koji bi podržali rutinsko sprovođenje farmakogenetičkih testiranja u ovoj oblasti.

Farmakogenetički pristup predstavlja inovativni model u razumevanju heterogenosti terapijskog

and receptor function, significant clinical implications of genetic variability can be expected.

An illustrative example is the polymorphism of the serotonin transporter (SERT) which has so far been the focus of pharmacogenetic testing. SERT is a protein responsible for the active transport of serotonin from the synapse to the presynaptic neuron and is the target site of action for serotonergic antidepressants. In addition to serotonin, SERT also has the ability to transport other endogenous amines, such as dopamine. Functional polymorphisms of the SERT gene have been identified in a variety of diseases, including psychiatric illnesses and depression [21], and the most studied among them is the SERTPR polymorphism, which is characterized by a variable number of repeats in the promoter region, resulting in a longer (L) and a shorter (S) variant. The L allele is characterized by increased transcription and higher biological activity of SERT proteins. It has been shown that individuals homozygous for the S allele may be more susceptible to the development of depression and suicidal behavior. These patients are thought to have a poorer appropriate therapeutic response and a poorer tolerance to SSRI antidepressants. As opposed to this, people with the L allele respond better to acute stress and the use of antidepressants [22]. Some studies, however, show contradictory results regarding the connection between SERTPR polymorphisms and the effectiveness of antidepressants [23]. Additional psychopharmacological studies are needed to determine the significance of both serotonin transporter polymorphisms and pharmacodynamic variability in general.

CONCLUSION

Pharmacogenetics is one of the foundations of personalized medicine and of individualized pharmacotherapy in psychiatry. Most of the studies carried out to date point to the great potential of pharmacogenetic studies in the individualization of therapy using antipsychotics and antidepressants. This is also confirmed by the latest FDA recommendations on pharmacogenetic testing and determination of the genetic profile and metabolic phenotype for CYP2D6 in patients on aripiprazole. In the case of anxiety and depressive disorders, pharmacogenetic testing is recommended for patients who have not shown a satisfactory therapeutic response to multiple antidepressants. To date, the determination of the genetic profile and metabolic phenotype for CYP2C19 in patients on escitalopram and sertraline, and CYP2C19 and CYP2D6 in patients on amitriptyline, respectively, has shown the greatest clinical implications. Despite the proven clinical benefit, there is still insufficient pharmacoeconomic data to support the routine use of pharmacogenetic testing in this field.

odgovora na antidepresive i psihofarmake uopšte. Prednost ovakvog pristupa je što se pojedinačni genotip ne menja, odnosno potrebno je da se odredi samo jednom i u bilo kom trenutku tokom trajanja lečenja. S druge strane, postoje brojni izazovi i ograničenja za rutinsko izvođenje ovih analiza, poput dostupnosti ovih testova i složenosti interpretacije rezultata. Učinak leka je kompleksan fenomen i pojedinačne mutacije u pojedinačnim genima ne mogu objasniti svu varijabilnost psihofarmakoterapije. Iako farmakogenetika nedvosmisleno ima veliki potencijal u razvoju lekova i individualizaciji terapije, neophodna su dalja istraživanja da bi se ovaj potencijal u potpunosti primenio u kliničkoj praksi.

Sukob interesa: Nije prijavljen.

The pharmacogenetic approach is an innovative model in understanding the heterogeneity of the therapeutic response to antidepressants and psychopharmaceuticals in general. The advantage of this approach is that the individual genotype does not change, in other words, it is necessary to determine it only once at any time during treatment. On the other hand, there are many challenges and limitations to routinely performing these analyses, such as the availability of the tests and the complexity of interpreting the results. The effect of a drug is a complex phenomenon and individual mutations in individual genes cannot explain all the variability of psychopharmacotherapy. Although pharmacogenetics unequivocally has great potential in drug development and individualization of therapy, further research is needed to fully apply this potential in clinical practice.

Conflict of interest: None declared.

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