



## PSYCHOPHARMACOLOGICAL TARGETS IN PERSONALIZED PSYCHIATRY

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### Abstract

The advances made on genetic influence on response and side effects of psychiatric pharmacotherapy improved the concept of personalized psychiatry. The current evidence suggests that testing can be useful in patients who did not respond or tolerate at least one previous pharmacotherapy. Approximately 90% of all drugs are metabolized by only few different cytochrome enzymes. Pharmacogenetic research has provided important evidence of CYP functional polymorphisms in psychiatric treatment, with numerous studies associating their presence with the variability observed in response to treatment. The study of candidate genes involved in the pharmacokinetics of antidepressants has provided sufficiently strong scientific evidence for clinical applications. These genes encode the cytochrome P450 enzymes and are responsible for the metabolism of antidepressants. Pharmacogenetic testing is thus becoming a useful and increasingly useful tool for antidepressant pharmacotherapy. The efficacy of antidepressant action has been associated with several polymorphisms, located on the gene encoding proteins considered to be involved in the various mechanisms of action of antidepressant treatments.

**Keywords:** pharmacogenetics, candidate genes, polymorphisms, personalized psychiatry

### Introduction

Personalized medicine has become a major field of research and clinical innovation in the post-genomic era, with advances in deciphering the human genome. The development of specific treatments for schizophrenia, depression and bipolar disorder in the middle of the last century has revolutionized the way these disorders are managed. Serious mental illness is still a huge burden on society and health in particular today, reflecting the still limited effectiveness of current treatment. Personalized or precision medicine is of interest in the treatment of human diseases and management based on the genetic model of each individual and the response to drugs. They are thus classified into two areas: pharmacogenetics and pharmacogenomics. *Pharmacogenetics* interests the structural variations of DNA and the impact on the metabolism, efficacy and tolerability of drugs. DNA remains stable and does not change over time or age. Pharmacogenetics is most often based on the cytochrome P450 enzyme system, located mainly in the liver. The response to pharmacotherapy depends on the ability of each individual to metabolize drugs, most of which are transformed by this enzyme system, depending on the genetic structure of each person. *Pharmacogenomics* looks at the characteristics of DNA and RNA that influence the functioning of genes, but these may change or be influenced by factors (eg. environment). Therefore, pharmacogenetics deals with unique genes and their structure, while pharmacogenomics refers to the function of environmentally influenced genes, both of which play an important role in human diseases, including drug metabolism (Butler M., 2018).

Although there may be small differences between psychiatric drug treatments in terms of their effectiveness, there are major interindividual differences in response to them. Although psychiatric medication has larger differences in the profile of side effects compared to their effectiveness, the side effects still differ greatly between individuals. It is believed that these unexplained differences in response and side effects reflect, at least in part, the genetic differences between patients. Thus, pharmacogenetics in psychiatry has much to offer in identifying risk factors for drug treatment limitations (Reynolds P.G., 2013).

The optimization and personalization of treatments is based on the extensive study of the genetic influence on a number of complex human traits, such as drug response and side effects. Current psychiatric evaluation, clinical decision making, and choice of treatment depend primarily on the physician's clinical experience. No known biological marker is currently available to perform either a diagnostic test or a prognostic test. The response to treatment of patients with mood disorders treated by current approaches to psycho-pharmacotherapy shows great interindividual variability and is often unsatisfactory (Amare A.T., 2017).

Despite advances in psychopharmacological treatment, there is still a significant proportion of patients who do not respond to single drug therapy satisfactorily. Thus, an attempt was made to identify a variety of biological factors to explain the inter-individuality of the response between patients. It has been hypothesized that the initial conditions of receptor site kinetics and the sensitivity of receptor-related responses may determine drug response (Rausch, 1998).

Disorders have a major impact on social health, with considerable direct and indirect costs. Major depressive disorder (MDD) contributes significantly to the global burden of the disease and affects people in all communities around the world (Grunze H., 2002).

The treatment with selective serotonin reuptake inhibitors (SSRIs) reduced morbidity and had a favorable side effect profile. Unfortunately, not all individuals receive adequate treatment and 30–40% of patients do not have a complete response to treatment (Fava M. 2003). The action of SSRIs is based on the inhibition of serotonin transporter (5-HTT), thus modulating serotonergic activity (Serretti A., 2007). In this regard, interesting evidence was provided due to interaction between the environment and SERT (serotonin transporter) or 5-HTTLPR (serotonin-transporter-linked promoter region). Regarding the effects of environmental stress on SERT (serotonin transporter), SERT density can be lowered in the brain by a single social defeat (Berton et al., 1999).

### Candidate genes for personalized treatment

Approximately 90% of all drugs are metabolized by only few different cytochrome enzymes, including CYP1A2, CYP3A4, CYP3A5, CYP2C19, CYP2D6, CYP2C9 and CYP2B6. For example, CYP2D6 contributes to the breakdown or oxidative metabolism of 25% of the most commonly prescribed drugs. These include tricyclic antidepressants, opioids, antipsychotics, tamoxifen, cough suppressants and antiarrhythmics. Side effects occur in a large percentage of the general population if the individual is prone to specific variants of the *CYP2D6* gene. These are now detectable by pharmacogenetic tests (Butler M., 2018).

Pharmacogenetic research has provided important evidence of CYP functional polymorphisms in psychiatric treatment, with numerous studies associating their presence with the variability observed in response to treatment. Pharmacogenetic testing is thus becoming a useful and increasingly useful tool for antidepressant pharmacotherapy.

More than ten antidepressants (including tricyclics, selective serotonin reuptake inhibitors, and venlafaxine) already have genetic biomarkers for response or side effects in clinical guidelines and on drug labels. These are represented by functional genetic variants of genes encoding cytochrome enzymes (*CYP2D6* and *CYP2C19*). Depending on the anticipated metabolic activity, the guidelines provide recommendations on drug selection and dosing (Fabbri C., 2020). The study of candidate genes involved in the pharmacokinetics of antidepressants has provided sufficiently strong scientific evidence for clinical applications. These genes encode the cytochrome P450 enzymes and are responsible for the metabolism of antidepressants. Functional genetic variants within these genes (*CYP2D6* and *CYP2C19*) are common in the population and lead to significant variations in enzymatic activity. They can be classified into four main groups (weak metabolizers - PM, intermediate metabolizers - IM, extensive metabolizers - EM and ultra-fast metabolizers - UM). These metabolic groups have been associated with pharmacokinetic parameters (eg. plasma concentrations of drugs and metabolites) for several antidepressants, demonstrating an impact on drug metabolism (Porcelli S., 2011, Florio V., 2017).

However, there is little evidence for the association between metabolic groups and clinical outcomes (response / side effects) and a clear relationship between plasma drug concentration and clinical outcomes, excluding tricyclic antidepressants (TCAs), *es* (citalopram) and venlafaxine (Perry PJ., 1994). Selective serotonin reuptake inhibitors (SSRIs) probably have a largely flat plasma concentration-response curve, with relevant changes only for very low and very high plasma concentrations (Florio V., 2017). This means that significant differences in clinical outcomes can be seen in patients with severely compromised or increased enzyme activity (PM and UM, respectively). However, there is no conclusive evidence in the literature due to the relative rarity of these groups in the population. Recent data from a larger sample of patients show that PM with *CYP2C19* has an increased risk of side effects (gastrointestinal, neurological and sexual) during treatment with (*es*) citalopram, but also a greater improvement in symptoms and a higher chance of remission of symptoms (Fabri C., 2018).

### Polymorphism of genes involved in pharmacokinetic processes

Pharmacokinetics involve processes such as absorption, metabolism, distribution and elimination of the drug, which have a major impact on the release of the drug to the target. Studies of the genes involved in the pharmacokinetics of antidepressants have focused primarily on those encoding enzymes that metabolize drugs, especially on the genes of certain members of cytochrome P450. To a lesser extent, those that encode the molecules involved in drug transport, especially certain members of the ATP binding box family (ABC) of transporter genes. The ABC transporter  $\beta$ -glycoprotein, encoded by the *ABCB1* gene (also known as *MDR1*), is a member of a superfamily of ABC transporter enzymes that regulate the transport of certain antidepressants across the blood-brain barrier (O'Brien, 2012).

Cytochrome P450 (CYP) are enzymes involved in the metabolism of drugs and may affect the concentration of the drug in the blood, depending on their genotype and therefore the availability of the drug. These biomarkers thus indicate both the efficacy of the drug and its safety (Levchenko A., 2020).

*CYP* genes encode a family of proteins involved in drug metabolism. Most of them (eg. *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP3A4* and *CYP1A2*) play a particularly important role in the metabolism of various antidepressants. Several functional

variants have been identified for these genes which can reduce or increase the level or activity of enzymes (Gaedigk A., 2018). Some of these variants have been extensively studied in connection with the pharmacokinetics of antidepressants. The doses initially set for a drug in the general population depend on the specific genetic model of cytochrome P450. If an individual had a loss of allele at the same time as the normal or wild-type allele (eg. the heterozygous state), then the enzyme encoded by that gene would have reduced activity. If an individual wears two variants of allele with loss of function (i.e., homozygous or heterozygous condition), such as two alleles with deletion (e.g., *CYP2D6*\*5) or a non-functional model (e.g., *CYP2D6*\*4), then a non-functional enzyme or a reduced-function enzyme would be labeled as a weak metabolizer for certain drugs degraded by that enzyme. If the individual wears doubles / multiplications of wild-type functional alleles, then the activity would be significantly increased and labeled as a fast or ultra-fast metabolizer. For example, homozygous and heterozygous carriers of allele variants of the *CYP2C9* gene with little or no enzyme activity, such as deletions, would require lower doses to maintain therapeutic levels and to avoid an increased risk of high-dose toxicity (Butler M., 2018). Also, weak metabolites of *CYP2C9* with the involvement of several antidepressants lead to an increased risk of side effects and lower doses are recommended for both fluoxetine and sertraline. Individuals who inherit multiple copies (duplicates) of the wild-type allele are labeled as fast or ultra-fast metabolizers and degrade certain drugs that are more rapidly targeted by a particular enzyme and less effective in treating the disease. Increased toxicity is observed in weak metabolizers with *CYP2D6* variants for several psychotropic drugs, such as desipramine, haloperidol, amitriptyline, and venlafaxine (Samer C.F., 2013).

### **Polymorphism of genes involved in pharmacodynamic processes**

The current knowledge of the pharmacodynamics of antidepressants (eg. the direct effect of the drug on the target) is much lower than that of the pharmacokinetics of antidepressants. Although the target and carrier binding targets are at least partially known for most antidepressants, the full mechanisms of action of these drugs and how they ultimately influence clinical symptoms are largely unknown. Selecting candidate genes for appropriate pharmacodynamic action is a challenge. Thus, a number of strong candidates have been studied, especially because of their role in the monoaminergic system, which has been hypothesized to play an important role in depressive and antidepressant mechanisms of action (Fabbri C., 2013).

*CYP2D6* is involved in the metabolism of 40% of antipsychotics, ADHD (attention deficit hyperactivity disorder) drugs and various antidepressants, such as tricyclics or tetracyclics, which are serotonin and/or norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors (Levchenko A., 2020). The gene responsible for enzyme synthesis is characterized by a number of functional genetic variants that determine its catalytic activity. The enzyme *CYP2D6* has a major influence on the efficacy and side effects of antipsychotics. Recent studies have shown a higher incidence of these when switching from risperidone to another antipsychotic when administered to weak or ultra-fast metabolizers of *CYP2D6* (Jukic M.M. 2019). Children who are weak or intermediate metabolizers of *CYP2D6* have a higher risk of side effects when using risperidone (Oshikoya K.A., 2019). Another adverse reaction, hyperprolactinemia, has been observed in patients with *CYP2D6* functional variants treated for schizophrenia (Fedorenko O.Y., 2017). The metabolic activity of *CYP2D6* is correlated with the duration of hospitalization, the weak and ultra-fast metabolizers being hospitalized for longer periods (Kurylev A.A., 2018).

*CYP1A1* and *CYP2C9* gene variants have been associated with a higher incidence of drowsiness and neurological effects when evaluating the use of quetiapine in healthy volunteers (Cabaleiro T., 2015). In addition, *CYP1A2* genetic variants are associated with higher serum concentrations and a better response to olanzapine. Side effects of antipsychotics, such as tardive dyskinesia (TD), have also been linked to the presence of functional variants of the *CYP1A2* and *CYP2D6* genes (Arranz J.M., 2021).

### **Receptor and transporter polymorphisms**

#### **The serotonergic system**

Most antidepressants used today act on SERT (serotonin transporter). SERT determines the duration and intensity of 5-HT responses. The most widely used antidepressants (AD), selective serotonin reuptake inhibitors (SSRIs) target SERT. SSRIs increase extracellular serotonin (5-HT) concentrations by inhibiting 5-HT transport (Rausch J.L., 2005). Serotonin transporter promoter polymorphism (SERTPR) has been independently associated with efficacy for a number of treatments. Another polymorphism located on the tryptophan hydroxylase gene, the 5-HT<sub>2a</sub> receptor and the G beta 3 protein showed some association, while for other candidates the genes were not associated with treatment efficacy. The most intensely studied polymorphism is that of the gene for the human serotonin transporter, being useful in predicting the antidepressant response. The transporter is important in the transfer of serotonin back to presynaptic neurons so it is the major pharmacological target for SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) (Lam Y.W.F., 2018). *SLC6A4* gene encode SERT and have the several functional polymorphisms that have been extensively investigated and identified to provide a variable therapeutic response in patients with different *SLC6A4* genotypes (Lam Y.W.F., 2018).

The serotonin transporter gene, *SLC6A4*, has been the most studied gene in the context of the antidepressant response (Licinio J., 2011). The most studied polymorphism of *SLC6A4* is a variant insertion / deletion of 44 base pairs in the promoter region (5-HTTLPR), which results in short (s) and long (l) alleles. Allele s reduces the transcriptional efficiency of the serotonin transporter gene promoter, resulting in reduced transporter expression and, consequently, lower serotonin uptake. However, given the ability of SSRIs to down-regulate SERT function, it has been hypothesized that SSRI efficacy may be affected by 5HTTLPR polymorphism. Many studies have shown an association between homozygosity for the s allele and the lower

response to SSRIs, as opposed to homo- or heterozygotes for the allele *l* gene, which predict a beneficial outcome with SSRI treatment (Lam Y.W.F., 2018). These facts are important because opposite but comparable associations (alleles that provide a good therapeutic response) have been reported in Korean and Japanese populations. It is possible, at least in part, that ethnic differences in the frequency of the *5HTTLPR* S allele may be greater in Asians (80%) than in Caucasians (40%) but also by the interaction with other functional gene variants or the interaction between gene and environment. Another study showed that *5HTTLPR* is not a simple insertion / deletion of a repeat of 44 base pairs, but a complex and highly polymorphic structure consisting of 14 types of alleles in different populations, including Japanese and Caucasian, with a frequency of variable distribution. (Nakamura M., 2005). Because 5-HTT is the main site of action of SSRIs, its gene has been extensively studied in association with depression and antidepressant action. The pharmacogenetics of *HTTLPR* polymorphism (*l* / *s*) has been investigated as a potential marker for the response of symptoms to SSRIs. It has been shown that in patients with major depression, carriers of the *l* allele have a better response to fluvoxamine than homozygotes for the short variant (*s* / *s*) (Smeraldi E., 1998).

### The catecholaminergic system

The neurotransmitter dopamine controls a variety of central nervous system functions, including cognition, emotion, endocrine regulation, food intake, and locomotor activity. The five dopamine receptors are grouped into D1-type receptors (DRD1 and DRD5) generally associated with stimulatory functions and D2-type receptors (DRD2, DRD3 and DRD4), which are more associated with inhibitory functions. All antipsychotic agents, especially first-generation antipsychotics, are D2 (DRD2) dopamine receptor blockers (Lam Y.W.F., 2018).

For more than five decades, dopamine has been essential for understanding the pathology of schizophrenia, and it is known that the main mechanism of antipsychotic drugs involves the antagonistic action of dopamine on D2 receptors in the brain. Dopamine receptor and transporter genes are strong candidates for studying the association between genetic polymorphisms, the outcome of antipsychotic treatment, and the magnitude of side effects. However, associations between polymorphisms of these genes and susceptibility to major depression, attention deficit hyperactivity disorder (ADHD), and anxiety disorders have also been observed (Reynolds G.P., 2013).

The neuronal dopamine transporter (DAT) helps control synaptic dopamine. There is conflicting evidence for differences in DAT binding associated with the number of repeats, some studies report increased binding associated with the 10-repeat allele, and others associated increased binding with the nine-repeat allele. Methylphenidate, the most commonly prescribed drug for ADHD, binds to DAT1 and reduces dopamine reuptake, increasing synaptic dopamine. A number of studies have shown the association of the 10-repeat allele with a poorer treatment outcome. Other studies have investigated the effect of repeated *DAT 9/10* on response to treatment for schizophrenia and depression. Thus, in schizophrenics, is reported an association with the response to clozapine, but no association with the response to risperidone (Xu M., 2010).

Polymorphisms have been reported for all five dopamine receptor genes (*DRD1* – *DRD5*) and for the *SLC6A3* / *DAT1* dopamine transporter gene. This provided a set of potential variants for investigating genetic associations with drug efficacy and side effects. Hyperprolactinemia following pituitary dopamine receptor antagonism is a serious side effect of antipsychotics that increases the risk of amenorrhea, galactorrhea, sexual dysfunction, breast cancer, and osteoporosis (Cookson J., 2012).

### GABA and glutamate system

In the past, psychiatric pharmacogenetics has focused primarily on genes encoding proteins involved in monoaminergic neurotransmission. This is due to the fact that many of the psychoactive drugs have their effects on the synapses of dopamine, norepinephrine, and serotonin. Today, research is focusing on neurotransmitter genes, which have reflected a growing interest in the roles that GABA and glutamate neurotransmission disorders may play in mental illness (Reynolds G.P., 2013). Glutamate receptors bind selectively to glutamate to modulate excitatory neurotransmission, and elevated glutamate levels have been observed in patients with depression. Chronic use of SSRIs, such as citalopram, has been shown to attenuate glutaminergic transmission and reduce glutamate excitatory activity (Lam Y.W.F., 2018).

Glutamate and GABA are fast neurotransmitters, with faster and more transient effects than the typical synaptic activity of monoamine transmitters. Essential to this is a quick-release mechanism, as provided by reuptake transporters are excitatory amino acid transporters (EAAT). EAAT3 is found primarily in neurons, while EAAT2 is a glial transporter responsible for most of the clearance of glutamate from the synapse. Single nucleotide polymorphisms in *EAAT* genes have been studied mainly in the context of neurological disorders. Genetic variation of the *EAAT3* gene (*SLC1A1*) has been associated with obsessive-compulsive disorder in several studies, so it is not surprising that it is also associated with symptoms of obsessive-compulsive disorder that occur as a side effect of antipsychotic treatment (Kwon J.S., 2009). The definition of a genetic profile for specific antidepressant treatment will be available soon, providing considerable help in the early detection of effective therapy in affective disorders. Another common problem is side effects, which are often associated with poor adherence to treatment and early discontinuation of treatment (Ho S.C., 2017).

The study of genetic factors that predispose to drug response or side effects in affective disorders has intensified in recent years. The efficacy of antidepressant action has been associated with several polymorphisms, located on the gene encoding proteins considered to be involved in the various mechanisms of action of antidepressant treatments. Among them, gene variants in serotonin protein sequences have been candidates for both the well-known evidence of its involvement in the development of depressive symptoms and the widespread use of selective serotonin reuptake inhibitors as the primary treatment of depression.



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