



Review

The Role of Pharmacogenetics in Personalizing the Antidepressant and Anxiolytic Therapy

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Abstract: Pharmacotherapy for neuropsychiatric disorders, such as anxiety and depression, has been characterized by significant inter-individual variability in drug response and the development of side effects. Pharmacogenetics, as a key part of personalized medicine, aims to optimize therapy according to a patient's individual genetic signature by targeting genetic variations involved in pharmacokinetic or pharmacodynamic processes. Pharmacokinetic variability refers to variations in a drug's absorption, distribution, metabolism, and elimination, whereas pharmacodynamic variability results from variable interactions of an active drug with its target molecules. Pharmacogenetic research on depression and anxiety has focused on genetic polymorphisms affecting metabolizing cytochrome P450 (CYP) and uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes, P-glycoprotein ATP-binding cassette (ABC) transporters, and monoamine and γ -aminobutyric acid (GABA) metabolic enzymes, transporters, and receptors. Recent pharmacogenetic studies have revealed that more efficient and safer treatments with antidepressants and anxiolytics could be achieved through genotype-guided decisions. However, because pharmacogenetics cannot explain all observed heritable variations in drug response, an emerging field of pharmacoeugenetics investigates how epigenetic mechanisms, which modify gene expression without altering the genetic code, might influence individual responses to drugs. By understanding the epi(genetic) variability of a patient's response to pharmacotherapy, clinicians could select more effective drugs while minimizing the likelihood of adverse reactions and therefore improve the quality of treatment.

Keywords: pharmacogenetics; pharmacogenomics; anxiety; depression; genetic variations; stress



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1. Introduction

The pharmacotherapy of neuropsychiatric disorders, such as anxiety and depression, has been characterized by significant inter-individual variability in drug response and the development of severe adverse effects, which has been recognized as a major clinical problem [1,2]. In addition to various environmental, physiological, and psychological factors, these individual differences might be largely due to genetic factors [3,4]. Therefore, various pharmacogenetic studies have been conducted to identify genetic variants that can predict patients who may optimally benefit from specific, individually tailored treatments [5–9] (Figure 1).

Pharmacogenetic studies have focused primarily on candidate genes involved in drug metabolism and transport (pharmacokinetics) as well as drug action (pharmacodynamics), which can influence both treatment efficacy and the development of adverse drug effects [9–11]. Pharmacokinetics addresses the variability in the drug's absorption, distri-

bution, metabolism, and elimination (ADME), which modulates the delivery of drugs and their active metabolites or their removal from action targets.

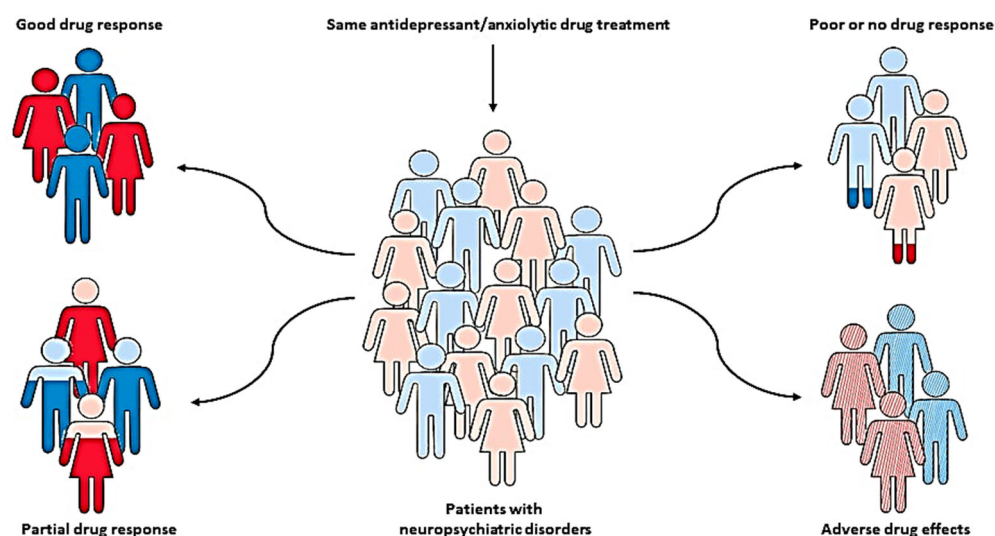


Figure 1. Pharmacogenetics, as a key part of personalized medicine, can help clinicians predict the therapeutic response and adverse drug reactions in patients with the same diagnosis and treatment, but different genotypes, and therefore identify patients who may optimally benefit from specific, individually tailored treatment.

The molecules involved in ADME processes include enzymes responsible for drug metabolism and drug transport molecules that mediate drug uptake and efflux [4]. In this context, the cytochrome P450 (CYP) and multidrug resistance (MDR) gene families have been extensively studied [6,12]. The CYP450 enzyme family in the liver is responsible for the metabolism of many psychotropic drugs [13]. For certain CYPs, the genotype affects the serum/plasma drug levels, and consequently, its efficacy and development of adverse effects [14,15]. There are four major CYP phenotypes produced by combinations of various alleles with different degrees of enzymatic activity: poor (PM), intermediate (IM), extensive (normal) (EM), and ultrarapid metabolizer (UM). PMs tend to accumulate higher drug levels in the blood and may require lower drug doses to achieve therapeutic effects, whereas UMs may require higher doses due to faster drug elimination [16,17].

In addition, the therapeutic action of psychotropic drugs depends on their effective delivery to the brain. Although some substances may diffuse passively through the brain-blood barrier (BBB), the influx and efflux of most substances are actively regulated by a complex system of transporters, influencing both pharmacokinetics and pharmacodynamics. In the case of a genetically determined decrease in functional activity or expression of transport proteins in the BBB, drug efflux from the brain into the blood is disturbed. This could lead to increased drug exposure time in the brain, its accumulation during long-term therapy, and an increased risk of developing severe adverse effects [18].

In contrast to pharmacokinetics, pharmacodynamics describes variability in drug action not dependent on variable drug concentrations but rather on the interaction of the active drug with its target molecules, including receptors, ion channels, and enzymes, and it can also influence both therapeutic responses and drug side effects.

Single nucleotide polymorphisms (SNPs) are the most commonly investigated genetic variants in both pharmacokinetic and pharmacodynamic studies [11]. Genetic polymorphism refers to the occurrence of two or more common variants (alleles) of a specific DNA sequence in a population with a frequency of more than 1% [19]. Identifying SNPs associated with variability in drug response and toxicity has been the primary focus of a significant number of pharmacogenetic and pharmacogenomic studies [7,20,21]. In these studies, two major research approaches have been used: the traditional candidate gene approach, which is hypothesis-driven and based on accumulated knowledge, and

new methodologies such as genome-wide association studies (GWAS) or whole exome sequencing, which are data-driven and generate new hypotheses and knowledge [22,23].

However, pharmacogenetics is not able to explain all observed heritable variations in drug responses, and there is growing evidence that responses to drugs could be influenced by individual epigenetic states [24,25]. An emerging field of pharmacoepigenetics investigates how epigenetic mechanisms that modify gene expression without altering the genetic code might influence individual responses to drugs [24,26]. Some of the most frequently studied epigenetic modifications include DNA methylation, histone modifications, and noncoding RNA actions [25]. Various environmental factors, including drugs, nutrition, and stress, may induce epigenetic changes [27] that can be transmitted over generations [28]. Acute or chronic exposure to stressors can contribute to the development and progression of various neuropsychiatric disorders [29–32], including anxiety and depression, but it is also associated with alterations in the epigenome that may affect the expression of genes involved in drug metabolism, transport, and target molecules, and therefore impact the variability in antidepressant and anxiolytic drug responses [33,34]. The most significant findings, obtained by both pharmacogenetic and pharmacoepigenetic research on antidepressants and anxiolytics, drugs commonly used for the therapy of various neuropsychiatric disorders, have been summarized and discussed in this review.

2. Pharmacogenetics of Antidepressants

Antidepressants are drugs commonly used to treat depression and anxiety disorders, although only half of patients respond to treatment, and only a third of patients experience symptom remission [35]. Genetic factors seem to account for more than 60% of the variability in drug response and side effects for various types of antidepressant drugs, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic (TCAs) and tetracyclic compounds, monoamine oxidase inhibitors (MAOIs), and noradrenergic and serotonergic modulators [36]. Therefore, an individual's genetic profile should be considered when choosing an antidepressant and determining the appropriate drug dosage. However, despite ongoing research, the effects of genetic variants on the pharmacokinetics and pharmacodynamics of antidepressant drugs remain unclear. Discovering the genetic factors that contribute to the variability of antidepressant responses can help clinicians select the most appropriate medication, dosage, and treatment duration for each individual patient. Therefore, the application of precision medicine may improve the treatment response rates to antidepressants and minimize the risk of adverse drug reactions.

2.1. Pharmacokinetic Variability

2.1.1. Cytochrome P450 Family

The CYP450 family is a large group of enzymes responsible for the metabolism of various drugs and xenobiotics, including antidepressant drugs. Among the many identified CYP450 enzymes, the most important ones involved in the metabolism of a variety of psychotropic drugs are CYP2D6, CYP2C19, CYP3A4, CYP1A2, CYP2B6, CYP2C8, and CYP2C9 [9,37]. Various CYP450 enzymes are capable of metabolizing more than one drug, and a single drug can be metabolized by multiple CYP enzymes [15]. The activity of these enzymes could be influenced by genetic variations, which may result in individual differences in antidepressant drug metabolism and responses [15,16]. Most genes encoding CYPs are highly polymorphic [19]. The impact of CYP polymorphisms on drug metabolism is an important area of research in personalized medicine [19]. While more than 2000 mutations have been found in CYP genes, only specific SNPs are known to affect CYP enzymatic activity [14,15]. Depending on the genetic variants that influence enzyme activity, individuals can be classified into four main CYP phenotypes: from poor, via intermediate and extensive (normal), to ultrarapid metabolizers [17,38,39]. Due to genetic variations, PMs have little to no CYP enzyme activity, whereas IMs have reduced enzyme activity. As a result of slower antidepressant drug metabolism, both PMs and IMs may be at an increased

risk for adverse drug reactions and require lower dosages or less frequent dosing regimens for antidepressant medications. On the other hand, NMs possess typical enzyme activity and a normal drug metabolism rate. However, UMs exhibit increased enzymatic activity, resulting in faster drug metabolism. Therefore, they may require higher antidepressant doses or more frequent drug administration to achieve the desired therapeutic effect in patients with depression [17,18,38,39]. The pharmacogenetics of the most important CYPs involved in the metabolism of antidepressant drugs are summarized below.

CYP2D6

The *CYP2D6* gene is highly polymorphic, meaning that it harbors genetic variations that can affect enzyme function [15,16,40]. CYP2D6 enzyme is involved in the metabolism of SSRIs (paroxetine, fluvoxamine, and fluoxetine), amitriptyline (TCA), and venlafaxine (SNRI) [16]. Different allele variants result in normal, decreased, and no enzyme function, characterized by extensive, intermediate, and poor metabolizer phenotypes, respectively [16,41]. *CYP2D6**1, *2, *33, and *35 allele variants are associated with normal function, whereas *9, *10, *14B, *17, *29, and *41 variants reduce CYP2D6 enzymatic capacity. Furthermore, *CYP2D6**3, *4, *5, *6, *7, *11, *12, *14A, *36, and *68 variants are responsible for the loss of enzyme function [16,41]. Apart from genetic variations, paroxetine and fluoxetine are potent inhibitors of CYP2D6, which may result in an “iatrogenic poor phenotype” or “phenocopy” when taken with drugs that are also metabolized by CYP2D6, such as venlafaxine. Patients with an “iatrogenic poor phenotype” may be at high risk of developing toxicity due to elevated plasma drug levels [42]. Specifically, individuals with poor CYP2D6 function may have reduced metabolism of fluoxetine and paroxetine, resulting in higher plasma drug levels and an increased risk of side effects, such as the development of suicidal ideation or antidepressant-induced mania during the initiation of treatment. As a result, the U.S. Food and Drug Administration (FDA) has issued a black box warning for SSRIs cautioning that these side effects can occur, especially in the first few weeks of treatment. Therefore, close monitoring is required for all patients starting antidepressant therapy [42,43].

Furthermore, studies have shown that poor metabolizers of fluoxetine may be at a risk of QT interval prolongation. [42]. Similar to fluoxetine, poor metabolizers of venlafaxine (genotype *CYP2D6* *6/*4, *5/*4, or *6/*6) are also at risk for developing adverse effects, such as arrhythmias, gastrointestinal problems, and hyponatremia [44,45]. Ahmed et al. showed that CYP2D6 UM status contributes to venlafaxine treatment remission in patients with major depressive disorder [46]. Therefore, when prescribing SSRIs and other antidepressants, clinicians must consider a patient’s *CYP2D6* genotype and adjust the dose or choose an alternative medication, if necessary, to minimize the risk of adverse effects while maximizing therapeutic benefit [6,7,20]. Despite the growing literature on the clinical implications of the *CYP2D6* genotype and phenoconversion on patient-related outcomes, implementation of pharmacogenetics to guide antidepressant prescribing is rare.

CYP2C19

In addition to clinically significant variants of the *CYP2D6* gene, a high number of polymorphisms in the *CYP2C19* gene have also been discovered [47], resulting in different metabolizer phenotypes [16,41]. Drugs that are mainly metabolized by CYP2C19 include SSRIs such as escitalopram, citalopram, and sertraline [15]. Variations in the *CYP2C19* gene can result in individuals having different levels of CYP2C19 enzyme activity, affecting how drugs such as escitalopram and sertraline are metabolized [48,49]. According to previous research, the *CYP2C19**1 allele variant is associated with normal function, whereas the *CYP2C19**17 variant increases CYP2C19 enzymatic capacity. Furthermore, *CYP2C19**2 and *3 variants are responsible for the loss of enzyme function [16,41].

For example, PMs of escitalopram are more likely to have adverse effects and psychotherapy discontinuation. However, they respond better to escitalopram, provided the therapy is tolerated. A retrospective study involving more than 2000 escitalopram-treated

patients demonstrated that those with *CYP2C19**1/*17 and *CYP2C19**17/*17 variants (IMs) were more likely to experience treatment failure [50], whereas UMs exhibited suicidal thoughts [51]. For sertraline, recent findings demonstrated that *CYP2C19* PMs had higher plasma levels in comparison to normal metabolizers [52]. Ricardo-Silgado et al. [53] suggested that *CYP2C19* genotypes might be associated with an increased risk of weight gain in patients on citalopram therapy. These findings indicate the importance of *CYP2C19* variants and different metabolic phenotypes in antidepressant treatment tolerability and outcome. The American Molecular Pathology published guidelines for testing *CYP2C19**2, *3, and *17 variants and *CYP2C19**4A-*4B, *5, *6, *7, *8, *9, *10, and *35 variants [41]. In addition, the relevance of *CYP2C19* polymorphisms in inter-individual predisposition to mental diseases was also investigated. Sim et al. [54] found that individuals who were poor *CYP2C19* metabolizers displayed lower levels of depressive symptoms compared to individuals who were normal metabolizers. These results raise the possibility that *CYP2C19* variations contribute to susceptibility to depression. Recent studies have also demonstrated a correlation between low *CYP2C19* activity and the severity of depression symptoms [55,56].

Moreover, a cross-sectional observational retrospective study, which included over 700 psychiatric patients with depression and anxiety, analyzed the frequencies of *CYP2C19**2, *4, and *17, as well as *CYP2D6**2, *3, *4, *5, *6, *10, and *41 variants [37]. This study revealed that 77% of patients have at least one allele variant significantly affecting drug metabolism, with roughly half of the individuals with reduced *CYP2D6* enzyme function and the majority of them being *CYP2C19* rapid and ultrarapid metabolizers [37]. Therefore, due to their clinical relevance, both *CYP2D6* and *CYP2C19* are included in pharmacogenetics guidelines and recommendations published by the Clinical Pharmacogenetics Implementation Consortium (CPIC), Dutch Pharmacogenetics Working Group (DPWG), and regulatory agencies such as the FDA [57–59].

CYP2C9

The *CYP2C9* gene encodes an enzyme that is involved in the metabolism of many drugs, including antidepressants, such as MAOIs, TCAs, and SSRIs [17]. The *CYP2C9**1 variant is associated with normal enzyme function, whereas *CYP2C9**2, *5, *8, and *11 variants reduce *CYP2C9* enzymatic capacity. Furthermore, *CYP2D9**3, *6, and *13 variants are responsible for the loss of enzyme function [16,41]. Different *CYP2C9* variants result in normal, decreased, and no enzyme function, characterized by extensive, intermediate, and poor metabolizer phenotypes, respectively [16,41]. Moreover, variants of the *CYP2C9* gene have been linked to mental disorders such as depression and psychosis [60,61].

CYP1A2

The *CYP1A2* enzyme, encoded by the *CYP1A2* gene, is responsible for the metabolism of approximately 24% of antidepressant drugs, including agomelatine, escitalopram, venlafaxine, duloxetine, and mirtazapine [16,36]. Several *CYP1A2* variants, including *1C, *1F, and *1B, have been identified as potential indicators of the *CYP1A2* phenotype and agomelatine pharmacokinetics. Notably, the *CYP1A2**1C variant is associated with reduced enzyme activity, resulting in higher plasma agomelatine concentrations and an increased risk of adverse effects. On the contrary, individuals with the *CYP1A2**1F and *1B variants, who are characterized by increased enzyme activity, may metabolize agomelatine more rapidly, leading to lower plasma concentrations and potentially reduced efficacy [62,63]. Kuo et al. [64] conducted a study to investigate the association between *CYP1A2* polymorphisms and the metabolism of escitalopram in patients with major depressive disorder. The study found that several SNPs in the *CYP1A2* gene, such as rs2069521, rs4646425, and rs4646427 polymorphisms, were associated with altered escitalopram metabolism and an increased risk of adverse effects, such as fatigue and nausea/vomiting, particularly during the initial stages of treatment. In addition, Lin et al. [65] demonstrated that *CYP1A2* SNPs, such as rs4646425, rs2472304, and rs2470890, are associated with a slower response to parox-

etine treatment. Furthermore, the study of the linkage between *CYP1A2* polymorphisms and the response to venlafaxine suggested that the rs2470890 polymorphism might be related to venlafaxine treatment remission [66].

2.1.2. P-glycoprotein

P-glycoprotein, commonly referred to as P-gp, is a membrane transporter within the ATP-binding cassette (ABC) transporter family. It is encoded by the *ABCB1* or *MDR1* gene, located on chromosome 7. P-gp functions as an efflux pump, contributing to drug absorption, distribution, and elimination [12]. P-gp has been found in various tissues throughout the body, including the liver, kidneys, intestines, and the blood-brain barrier. At the blood-brain barrier, P-gp can limit the entry of some drugs into the brain, which can affect their efficacy. The expression and activity of P-gp can vary widely between individuals, contributing to differences in drug responses and drug interactions [18]. Genetic factors play a role in determining the level of P-gp expression in different tissues and individuals. Certain genetic variants of the *ABCB1* gene have been associated with altered P-gp expression and activity, which can affect the pharmacokinetics and efficacy of drugs that are substrates for P-gp [67]. P-gp has broad substrate specificity, including antidepressants such as escitalopram, fluvoxamine, paroxetine, amitriptyline, and imipramine. Therefore, when P-gp is absent or not functioning properly, these drugs can accumulate in the body, resulting in higher concentrations and potentially an increased risk of adverse effects. However, newer antidepressants (levomilnacipran, vortioxetine, and vilazodone) have been proven as poor P-gp substrates [18].

There has been interest in studying the relationship between genetic variations in the *MDR1/ABCB1* gene and antidepressant treatment outcomes [68]. Several genetic variants of the *MDR1/ABCB1* gene have been associated with altered P-gp activity. The three most common *MDR1/ABCB1* variants, C3435T (rs1045642), C1236T (rs1128503), and G2677T (rs2032582), have been the subject of extensive research [68,69]. A recent study on experimental models suggested that the 2677G > T polymorphism in the *ABCB1* gene has been associated with altered P-gp function and increased brain penetration of P-gp substrates without affecting P-gp protein expression in the blood-brain barrier [70]. In addition, genetic variants of the *ABCB1* gene, including the rs2235040 and rs4148739 polymorphisms, may be associated with the onset of response to antidepressant medications rather than the response rate [8]. Furthermore, a significant link has been found between the *ABCB1* rs2235015 GG genotype and better response to antidepressant treatment [8,71]. Overall, while pharmacogenetic research on *MDR1/ABCB1* suggests the potential for improving outcomes of antidepressant treatment, further investigation is necessary to better comprehend the connection between genetic variations and treatment response, as well as to assess its clinical utility.

2.2. Pharmacodynamic Variability

2.2.1. Monoamine Metabolic Enzymes

Tryptophan Hydroxylase

Tryptophan hydroxylase (TPH) is an enzyme that catalyzes the conversion of the amino acid tryptophan to 5-hydroxytryptophan, which is the first step in the synthesis of serotonin, a neurotransmitter involved in the regulation of mood, appetite, sleep, and stress response [72]. There are two isoforms of the TPH enzyme, TPH1 and TPH2, encoded by separate genes. TPH1 is primarily expressed in peripheral tissues, such as the pineal gland, skin, and gut, whereas TPH2 is mainly expressed in neurons in the central nervous system (CNS). The two isoforms have similar enzymatic activities but differ in regulation, tissue distribution, and developmental expression patterns [73]. Overall, while TPH1 may be less expressed in the brain than TPH2, it appears to play an important role in the regulation of mood and stress responses and may contribute to antidepressant effects [74]. Several variants of *TPH* genes associated with differences in serotonin production have been identified. Some of these variants have been linked to an increased risk of developing

psychiatric disorders [75]. The modulation of *TPH* genes has been studied as a potential approach for the treatment of various psychiatric disorders, including depression, anxiety, and addiction [76,77]. However, several studies have demonstrated controversial results regarding *TPH* polymorphisms and response to SSRIs [21,75,78].

Monoamine Oxidases

Monoamine oxidases (MAOs) are a family of enzymes that play critical roles in the metabolism of monoamine neurotransmitters in the CNS [79]. There are two types of MAOs, MAO-A and MAO-B, which are encoded by separate genes. MAO-A and MAO-B are found in the CNS, particularly in neurons and astroglia. MAO-A is primarily responsible for the metabolism of several important monoamine neurotransmitters, including serotonin, norepinephrine, and dopamine. These neurotransmitters play a crucial role in the regulation of mood, behavior, and cognition [80]. Several genetic variants of the *MAOA* gene associated with differences in enzyme activity and monoamine metabolism have been identified. In addition, some of these variants have been linked to an increased risk of developing psychiatric disorders [80]. However, the relationship between the *MAOA* gene variants and psychiatric disorders remains unclear. Polymorphisms in *MAO* genes have also been studied for their potential role in response to antidepressant medications. Some studies have suggested that certain genetic variants in *MAO* genes may affect the metabolism of antidepressants, potentially leading to differences in drug efficacy and side effects [81–83]. For example, individuals with a specific variant of the *MAOA* gene had a better response to fluvoxamine compared to those without this variant [82]. In addition, a recent study reported that the *MAOA* rs979605 polymorphism might modulate the response to antidepressant therapy in a sex-specific manner [84].

Catechol-O-Methyltransferase

Catechol-O-methyltransferase (COMT) is an enzyme that plays a crucial role in the degradation of catecholamines such as dopamine, epinephrine, and norepinephrine. The *COMT* gene has several polymorphisms, and the most extensively studied is the rs4680 polymorphism, also known as Val158Met [85]. This SNP causes the substitution of valine (Val) for methionine (Met) at position 158 in the COMT enzyme. The Val allele is associated with higher COMT activity, whereas the Met allele leads to lower activity. Therefore, individuals with the Val/Val genotype tend to have the highest level of COMT activity, followed by Val/Met individuals with intermediate activity, and Met/Met with the lowest activity [86]. The *COMT* Val158Met polymorphism has been implicated in various psychiatric disorders, including depression, anxiety, and schizophrenia [85]. Furthermore, studies have linked the *COMT* Val158Met polymorphism with response to SSRIs such as fluoxetine and paroxetine [87,88]. For instance, one study discovered that the Val/Met genotype significantly affected the response to fluvoxamine [87]. Additionally, it has been suggested that the effects of the *COMT* genotype on antidepressant responses may depend on other factors, such as the type of medication, severity and duration of depression, and other genetic and environmental factors [89]. However, on the contrary, Brunoni et al. [21] did not observe a significant association between *COMT* variants and responses to escitalopram treatment.

2.2.2. Monoamine Transporters

Serotonin Transporter

The serotonin transporter (SERT) encoded by the *SLC6A4* gene plays a critical role in regulating serotonin neurotransmission in the brain. SERT is responsible for serotonin reuptake from the synaptic cleft, thereby regulating the amount of serotonin available to bind to serotonin receptors in the brain [90]. Several classes of antidepressant drugs, including SSRIs, SNRIs, and TCAs, target SERT and inhibit its activity [91].

The *SLC6A4* gene was the first gene genotyped as part of the Genome-Based Therapeutic Drugs for Depression (GENDEP), and several genetic variants have been identified [92].

The most studied is the variant of the serotonin transporter-linked polymorphic region (5-HTTLPR). The 5-HTTLPR is located in the promoter region of the *SLC6A4* gene and has two alleles: the short (S) and the long (L) allele. The S allele is associated with lower transcriptional efficiency and reduced expression of the SERT protein compared to the L allele. As a result, carriers of the S allele have been found to have lower serotonin reuptake efficiency, leading to higher serotonin levels. Therefore, individuals carrying the S/S genotype have been shown to have a poorer response to SSRI treatment and may experience more side effects compared to those with the L/L or L/S genotypes [21,93]. Numerous studies have investigated the relationship between the 5-HTTLPR polymorphism and response to SSRIs [94–97]. A recent case report suggested that the S/S genotype resulted in ineffective fluoxetine treatment and may have caused exacerbation of depression [98]. Maron et al. [99] investigated the association between 5-HTTLPR polymorphism and clinical response to escitalopram and found no significant association. However, they did observe a linkage between this polymorphism and a higher risk for adverse effects [99]. This finding is consistent with other studies that have reported an association between SSRIs side effects and 5-HTTLPR polymorphism [100–102]. Therefore, the 5-HTTLPR polymorphism may be a valuable marker for predicting antidepressant responses and tolerability in individuals with psychiatric disorders. In particular, genotyping for the 5-HTTLPR variant may help identify patients who are less likely to respond to SSRIs and may benefit from alternative treatment strategies, such as SNRIs or TCAs. Additionally, several studies have reported an association between the 5-HTTLPR S/S genotype and suicidal behavior [102–104], although other risk factors, such as life stressors, psychiatric disorders, and substance use, must be considered.

Norepinephrine Transporter

The norepinephrine transporter (NET) is a protein encoded by the *SLC6A2* gene and plays an important role in the reuptake of norepinephrine (NE) [105]. TCAs, such as desipramine and imipramine, work by inhibiting the reuptake of NE by the NET, which increases the levels of NE in the synapse and enhances its effects on target neurons. Although antidepressants, such as SSRIs, have largely replaced TCAs, they are still used in some cases where other treatments have been ineffective. Several genetic variants have been identified in the human *SLC6A2* gene, which have functional consequences and can affect the efficacy of antidepressant drugs [105]. A recent study found an association between certain *SLC6A2* polymorphisms and antidepressant response variability [106]. Although, the role of *SLC6A2* variants in antidepressant responses is still being studied, current evidence suggests that these associations are complex and not fully understood.

Dopamine Transporter

The dopamine transporter (DAT), encoded by the *SLC6A3* gene, is a protein responsible for dopamine reuptake from the synaptic cleft into the presynaptic neuron. To date, the *SLC6A3* gene has been identified with at least 502 variations [107]. However, the relationship between *SLC6A3* polymorphisms and antidepressant responses is yet to be thoroughly researched. Nevertheless, some studies have suggested that specific *SLC6A3* polymorphisms may influence the response to antidepressant therapy [108,109]. For example, Kirchheiner et al. [110] suggested that the *SLC6A3* polymorphism increased the risk of a poorer and slower response to various antidepressants in individuals with the 9/10 and 9/9 genotypes compared to carriers of the 10/10 genotype.

2.2.3. Monoamine Receptors

5-HT_{1A} Receptor

The serotonin 1A (5-HT_{1A}) receptor is a G protein-coupled receptor found in the CNS and peripheral tissues. It is widely distributed in various brain regions, including the hippocampus, hypothalamus, cortex, and amygdala. It plays a crucial role in regulating the release of neurotransmitters, particularly serotonin, and is a target for many

psychoactive drugs, including antidepressants and anxiolytics [111]. The 5-HT_{1A} receptor is encoded by the *HTR1A* gene, and mutations in this gene have been linked to several neuropsychiatric disorders, including major depression, anxiety disorders, and autism spectrum disorder [112]. The role of *HTR1A* polymorphisms in response to antidepressant therapy has also been investigated; however, a few recent studies found no significant associations [113–115]. For instance, Scutt et al. [116] reported no association between *5HT1A* polymorphism and increased risk of SSRIs adverse effects. On the other hand, other studies have reported different findings [117,118]. Villafuerte et al. [117] suggested that the G allele of *HTR1A* rs1364043 polymorphism might predict citalopram response in depressed patients. This study showed that individuals homozygous for the G allele of the *HTR1A* rs1364043 polymorphism responded better to citalopram therapy. In patients with major depressive disorder, Kato et al. [118] found an association between *HTR1A* rs1364043 polymorphism and a better response to antidepressant treatment.

5-HT_{2A} Receptor

The *HTR2A* gene, coding for the 5-HT_{2A} receptor, contains several polymorphisms, some of which have been linked to altered receptor function or expression. However, the *HTR2A* rs6311 and rs6313 polymorphisms have been researched the most, especially their association with response to antidepressant therapy [119]. Recent studies have shown that carriers of the *HTR2A* rs3803189 and rs7997012 polymorphisms responded better to SSRIs [120,121]. On the other hand, a number of other studies reported no linkage between different *HTR2A* polymorphisms and a patient's response to antidepressant treatment [21,97,113,119,122]. Several studies have also investigated the relationship between different *HTR2A* SNPs and the tolerability of antidepressant therapy. According to their findings, specific *HTR2A* polymorphisms, such as rs7997012 and rs6314, may be associated with a reduced risk of adverse effects of antidepressant drugs [123,124].

Dopamine Receptors

Central dopamine receptors can be classified into two major families based on their structural and functional similarities: D1-like (D₁ and D₅ receptors) and D2-like receptors (D₂, D₃, and D₄ receptors). Dopamine D₂ receptors, encoded by the *DRD2* gene, are among the most intensively researched receptors in depressive disorders. Several studies have pointed out the possibility that *DRD2* polymorphisms play an important role in depressive disorder and response to antidepressant therapy [125,126]; however, other authors found no significant association [127,128]. On the other hand, Wang et al. [125] suggested that *DRD2* rs1076562, rs2440390, and rs2734833 polymorphisms are associated with the onset time of the antidepressant response. In addition, according to Perlis et al. [126], *DRD2* rs4245147 polymorphism has been linked to a better lamotrigine response in a group of patients with bipolar depression.

3. Pharmacogenetics of Anxiolytics

In comparison to antidepressants, pharmacogenetic research on anxiolytics is far less prevalent. This is due in part to the fact that benzodiazepines (BZDs), as a prototype of anxiolytic drugs, are administered for shorter periods. Some genes that have been studied regarding BZDs include those encoding drug-metabolizing enzymes, drug transporters, and drug targets [129]. Certain gene polymorphisms that can alter BZDs pharmacokinetics and pharmacodynamics are reviewed in the following sections.

3.1. Pharmacokinetic Variability

3.1.1. UGT2B15 Enzyme

UGT2B15 is an enzyme essential for the metabolism of many drugs, including anxiolytics. It belongs to the uridine diphosphate glucuronosyltransferase (UGT) family of enzymes, which catalyze the conjugation of lipophilic compounds with glucuronic acid, thereby facilitating their elimination from the body [130]. UGT2B15 is primarily expressed

in the liver and is encoded by the *UGT2B15* gene. Genetic polymorphisms in the *UGT2B15* gene can alter enzyme activity, leading to inter-individual variability in anxiolytic drug metabolism and response. For example, individuals with the *UGT2B15**2 allele may have reduced *UGT2B15* activity, resulting in slower drug metabolism and a potentially increased risk of adverse effects [131].

The *UGT2B15**2 variant is one of the most studied genetic polymorphisms in the *UGT2B15* gene. This is due to a single nucleotide substitution (G > T) in the coding region of the gene, resulting in an amino acid change from aspartic acid (D) to tyrosine (Y) at position 85. This modification could alter the enzyme's activity and therefore affect the metabolism of drugs that are substrates of *UGT2B15* [132]. Chung et al. [133] were the first to demonstrate the effect of the *UGT2B15* genotype on the pharmacokinetics of lorazepam in humans. Their study showed that homozygous carriers of the *UGT2B15**2 variant had lower systemic clearance and metabolic activity of lorazepam in comparison to individuals without this variant. Since then, several other studies have also examined the association between the *UGT2B15* genotype and the pharmacokinetics of lorazepam and other BZDs [132,134]. Mijdevik et al. [132] reported a linkage between the *UGT2B15* genotype and the efficacy of lorazepam in reducing postoperative anxiety. Interestingly, the effects of the *UGT2B15**2 variant on the response to lorazepam premedication appeared to differ between male and female patients. Specifically, whereas homozygous male carriers of the *UGT2B15**2 variant had a lesser reduction in anxiety compared to placebo, female patients with the same genotype experienced greater anxiety reduction due to lorazepam premedication [132]. However, Jackson et al. [134] suggested that the greater clinical effect in females compared to males after a single dose of lorazepam is unlikely to be due to differences in pharmacokinetics. Instead, they proposed that differences in endogenous levels of neurosteroid hormones between males and females may play a role.

Additionally, the *UGT2B15**2 variant has also been shown to affect the metabolism of oxazepam. Several studies have shown that the *UGT2B15**2 variant is associated with reduced oxazepam glucuronidation in human liver microsomes and decreased oxazepam clearance [131,135–137]. A decrease in oxazepam metabolism could potentially affect the metabolism of other BZDs, where oxazepam is an active metabolite, including chlor-diazepoxide, clorazepate, diazepam, and temazepam [138]. This could lead to a potential increase in the adverse effects of these drugs, such as sedation, cognitive impairment, and impaired motor coordination [139]. Therefore, patients carrying the *UGT2B15**2 variant may require lower doses of these BZDs in order to achieve the same therapeutic effect and minimize adverse effects.

3.1.2. Cytochrome P450 Enzymes and P-glycoprotein

As previously discussed, the metabolism of many drugs, including anxiolytics, involves numerous CYP enzymes. Anxiolytic diazepam, for instance, is primarily metabolized by the CYP2C19 enzyme. Other CYP enzymes involved in diazepam metabolism include CYP2C9, CYP2B6, CYP3A4, and CYP3A5 [140]. The association between CYP2C19 and CYP2B6 phenotypes and the safety of diazepam was the subject of a recent study by Zubair et al. [141]. This was the first study that demonstrated a significant association between the CYP2B6 phenotype and the pharmacokinetics of diazepam. Their findings suggested that a dose reduction might be necessary for CYP2C19 and/or CYP2B6 PMs to avoid adverse drug reactions, such as dependence on and tolerance to BZDs. The CYP2C19 gene has various genetic variants, some of which have the potential to influence CYP2C19 enzyme activity. For example, the CYP2C19*17 allele is associated with increased enzyme activity, whereas nonfunctional variants, such as CYP2C19*2 and *3, have little or no enzyme function [140]. As stated before, these CYP2C19 polymorphisms can result in altered rates of diazepam metabolism, leading to reduced drug effectiveness or potentially increased risk of adverse effects. Moreover, several recent studies have examined the effects of CYP2C19 polymorphisms, particularly CYP2C19*17 and CYP2C19*2 variants, on the efficacy and safety of diazepam in individuals with alcohol withdrawal syndrome [142–144]. Accord-

ing to their findings, individuals with reduced CYP2C19 activity, such as carriers of the *CYP2C19*2* allele, may be at an increased risk of adverse effects due to slower metabolism and potential drug accumulation. On the contrary, individuals with increased CYP2C19 activity, such as carriers of the *CYP2C19*17* allele, may experience reduced efficacy with standard doses of diazepam due to faster metabolism and potentially lower plasma drug concentrations [142–144]. These findings are consistent with previous studies that investigated the effects of *CYP2C19* polymorphisms on diazepam metabolism and treatment outcomes in patients with alcohol withdrawal syndrome [145,146].

Similarly, the *CYP2C19*17* allele may also be responsible for the UM phenotype of clobazam [147]. As a result, higher doses of clobazam may be required to achieve the same therapeutic effect. In contrast, *CYP2C19*2* and *CYP2C19*3* variants result in a nonfunctional or partially functional CYP2C19 enzyme. Individuals who are homozygous for *CYP2C19*2* and *CYP2C19*3* variants may have a PM phenotype with an increased risk of adverse effects and toxicity [140,148]. Two case reports have shown an association between the *CYP2C19*2* variant and an increased risk of adverse effects in clobazam-treated patients [149,150]. As previously mentioned, the clearance of benzodiazepines, such as diazepam and clobazam, may be reduced in carriers of *CYP2C19* nonfunctional variants. However, BZDs have a wide therapeutic window, indicating that many individuals with this variant can still tolerate standard doses without experiencing substantial adverse effects [151]. Moreover, a recent study found an association between *CYP3A5* polymorphism and the metabolism of midazolam [152]. Specifically, carriers of the *CYP3A5* rs776746 T allele had decreased plasma concentrations of midazolam in comparison to individuals with the C allele and may require higher doses of midazolam to achieve a sedative effect [152]. The *CYP3A5* polymorphism, particularly the *CYP3A5*3* variant, has also been associated with the altered metabolism of alprazolam [153]. Park et al. [154] have shown that homozygous carriers of the *CYP3A5*3* allele might have a slower metabolism of alprazolam, resulting in higher plasma concentrations.

Regarding the CYP3A4 enzyme, the *CYP3A4*22* gene variant has been frequently described in the literature [155]. Individuals who carry the *CYP3A4*22* allele may have reduced CYP3A4 enzyme activity and slower drug metabolism [156]. Although, several studies have suggested that *CYP3A4* polymorphisms may be associated with differences in response to BZDs, the evidence is not yet conclusive [157,158]. In addition, there are currently no established pharmacogenetic biomarkers for BZDs such as bromazepam and lormetazepam [159]. As in the case of antidepressants, BZDs, such as midazolam, are also substrates for P-gp [160]. Several studies have investigated the potential role of P-gp polymorphisms in the response to midazolam [161,162]. However, these findings are inconsistent and sometimes contradictory. Specifically, whereas Park et al. [161] demonstrated that the polymorphism in the *MDR1/ABCB1* gene was linked to an increased midazolam concentration and higher sedation degree, Byon et al. [162] found no significant association.

3.2. Pharmacodynamic Variability

The pharmacodynamics of anxiolytic drugs are yet another target of pharmacogenetic studies investigating the treatment of various conditions [159]. It is well known that BZDs enhance the inhibitory effects of γ -aminobutyric acid (GABA) through the allosteric modulation of GABA type A (GABA_A) receptors, resulting in anxiolytic, sedative, hypnotic, anticonvulsant, and myorelaxant effects [163]. The majority of GABA_A receptors are pentameric complexes composed of two α subunits, two β subunits, and one γ or δ subunit [164]. Depending on the GABA_A receptor subtype, the benzodiazepine effects can differ. The sedative effects of BZDs are primarily mediated by the α_1 subunit of GABA_A receptors, whereas the α_2 and α_3 subunits are responsible for the anxiolytic effects of BZDs. Moreover, the α_5 subunit mediates the amnesic properties of BDZs [165].

A study by Kelly et al. [166] showed that certain polymorphisms in the GABA_A receptor α_5 subunit might result in a conformational change of the receptor, altering the GABA binding site. Several animal models with genetic mutations affecting specific

subunits of the GABA_A receptor complex have been developed [167,168]. For example, one study found that mice lacking the γ_2 subunit showed greatly reduced BZDs sensitivity, including the loss of sedative, anxiolytic, and anticonvulsant effects [169]. On the other hand, Chandra et al. [170] demonstrated that mice without the expression of γ_2 exhibited increased anxiety-like behaviors but did not show significant differences in the hypnotic response to BZDs. In addition, mice with a knock-in F77I mutation in the *GABRG2* gene, coding for the GABA_A receptor γ_2 subunit, were found to have reduced sensitivity to the hypnotic effects of zolpidem [171].

Polymorphisms in the *GABRA2* gene, encoding the α_2 subunit of the GABA_A receptor, have been associated with substance abuse behaviors [172–175]. Another study investigated the connection between polymorphisms in the *GABRA1* gene and the response to zolpidem in patients with insomnia. The *GABRA1* A15G variant has been identified as a polymorphism associated with complex sleep behaviors and amnesia [176]. Choi et al. [177] found that among five known SNPs in the *GABRA1* gene, the rs4263535 polymorphism was associated with deeper sedation in response to intravenous midazolam. Moreover, Bowser et al. [178] discovered that individuals with epilepsy who carried the R43Q mutation in the *GABRG2* gene had reduced sensitivity to BZDs. Similarly, a recent study reported a possible association between two polymorphisms in *GABRA2* and *GABRA5* genes and drug-resistant epilepsy [179]. Overall, research assessing the pharmacodynamic variability of anxiolytic drugs remains a relatively new field. Additional research is necessary to fully understand how genetic variations affect anxiolytic drug responses.

4. Pharmacogenetics of Antidepressants and Anxiolytics

An increasing number of both preclinical and clinical findings suggest that epigenetic changes might be useful for the prediction of treatment response. DNA methylation, one of the most investigated epigenetic modifications, has been shown to play a role in drug responses, including responses to antidepressants and anxiolytics [180,181]. For instance, Takeuchi et al. [182] found an association between DNA methylation at several CpG sites in specific genes and the therapeutic response to paroxetine in patients with major depressive disorder. Moreover, methylation at several CpG sites within the interleukin-11 (*IL11*) promoter was found to be predictive of escitalopram or nortriptyline treatment response [183].

Several studies have also investigated the potential effects of epigenetic regulation of the brain-derived neurotrophic factor (*BDNF*) gene [184–186] on antidepressant treatment responses. For example, Wang et al. [186] suggested that *BDNF* DNA hypomethylation leads to an impaired response to escitalopram. In addition, lower methylation levels at CpG sites within the *BDNF* promoter were associated with an antidepressant response and decreased *BDNF* plasma levels after one week of treatment [187]. DNA methylation of *BDNF* seems to be epigenetically regulated by FKBP5 Binding Protein 5 (FKBP5), according to the antidepressant response [188]. FKBP5 is a cochaperone protein of the glucocorticoid receptor complex involved in intracellular glucocorticoid signaling and the stress response [189]. These findings are not surprising, since glucocorticoid secretion in response to stress, as well as genes involved in the glucocorticoid signaling pathway, are proposed to play an important role in shaping the epigenetic landscape [190]. Moreover, there is strong evidence that antidepressants exert their effects by modulating the glucocorticoid receptor; therefore, epigenetic modifications of the glucocorticoid receptor could be of considerable importance for therapeutic efficacy [191]. In the context of stress response, in addition to *FKBP5* and *BDNF*, other extensively studied epigenetically altered genes include the *NR3C1* gene coding for glucocorticoid receptor, *CRH* gene coding for corticotropin-releasing hormone, and *MAOA* and *SLC6A4* genes. Specifically, the study of Elliott et al. (2010) demonstrated the demethylation of *CRH* gene, involved in the brain stress response, in mice exposed to chronic social stress and attenuation of *CRH* promoter methylation levels with the antidepressant imipramine [192]. Moreover, hypomethylation in the promoter region of the *SLC6A4* gene has been predictive of impaired response to SSRIs [193–195]. On the other

hand, investigations into the relationship between DNA methylation in the *MAOA* gene and the response to antidepressant drugs have produced conflicting results, with some studies reporting an association between *MAOA* DNA methylation and antidepressant response [196], while others observed no significant associations [197,198].

Various studies have implicated histone modifications in stress and depressive phenotypes as well as in antidepressant treatment. As in the case of DNA methylation, the *BDNF* gene has also been investigated regarding histone modifications. For instance, in mice, chronic social defeat stress induced lasting downregulation of *BDNF* transcripts III and IV and increased repressive histone methylation at their corresponding promoters in the hippocampus [199]. However, chronic imipramine treatment increased histone acetylation at the *BDNF* P3 and P4 promoters by selectively downregulating histone deacetylase (Hdac) [199]. In addition, Chen et al. investigated the effects of antidepressant drugs on the human postmortem prefrontal cortex and reported increased expression of *BDNF* IV, which was associated with a decrease in histone H3 lysine 27 (H3K27) methylation at the promoter region [200]. Moreover, a significant decrease in the peripheral blood H3K27 methylation levels at the promoter IV of the *BDNF* gene and a concomitant increase in *BDNF* mRNA expression were found in citalopram responders in comparison to nonresponders [185]. These findings suggest that *BDNF* promoter H3K27 methylation levels could serve as a potential biomarker for citalopram response in depressive patients.

Noncoding RNAs have also been investigated in relation to antidepressant responses [201,202]. Several miRNAs, such as miR-1202, miR-124, miR-135a, miR-145, and miR-20b, have been strongly associated with antidepressant responses [203]. In addition, miR-146a5p, miR-146b-5p, miR-425-3p, and miR-24-3p expression levels decreased during antidepressant therapy and are therefore suggested as potential mediator biomarkers of antidepressant response [204]. In contrast to antidepressants, pharmacoeconomic studies on anxiolytic drugs are still relatively limited. However, some evidence suggests that epigenetic modifications may also play a role in the drug response and efficacy of anxiolytics [205–207].

5. Conclusions

Pharmacogenetics can potentially optimize the treatment of neuropsychiatric disorders via the prediction of clinical outcomes of antidepressant and anxiolytic drug administration, including therapy response and development of drug side effects, without the need for conventional “trial-and-error” approaches. The PREPARE study, which covered a large number of drugs, demonstrated that genotype-guided treatment using a 12-gene pharmacogenetic panel significantly reduced the incidence of clinically relevant adverse drug reactions [208]. These results show the large-scale feasibility and clinical usefulness of implementing of a panel-based pharmacogenetic testing strategy to make drug therapy increasingly safe [208].

As shown in Figure 2, for antidepressant and anxiolytic therapy, the most promising pharmacogenetic candidates are genetic polymorphisms affecting metabolizing cytochrome CYP450 and UGT enzymes, P-glycoprotein ABC transporter, as well as monoamine and GABA metabolic enzymes, transporters, and receptors. Some of these gene candidates, as well as many others, have been shown to be epigenetically altered in response to stress, suggesting the potential of epigenetic profiles for making clinically relevant decisions regarding antidepressant and anxiolytic therapy.

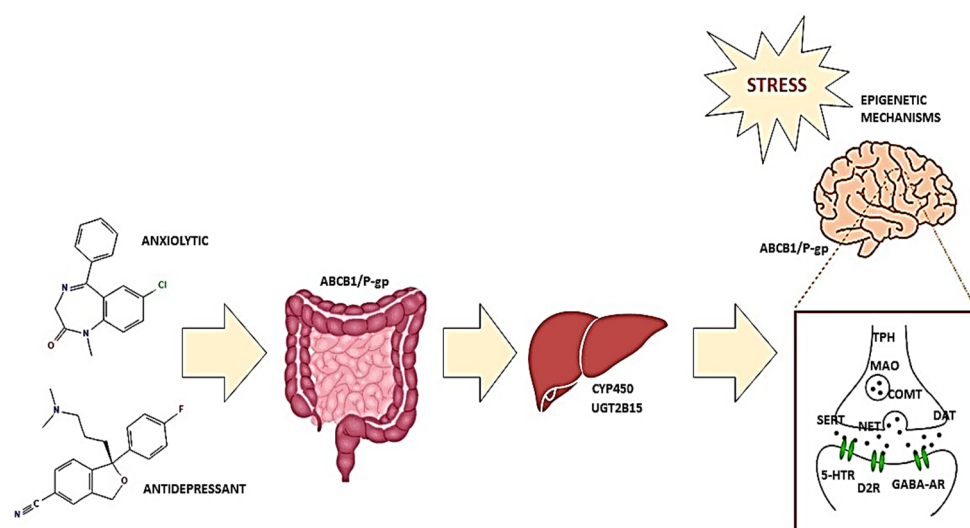


Figure 2. Pharmacogenetics can potentially optimize the treatment of neuropsychiatric disorders via the prediction of clinical outcomes of antidepressant and anxiolytic drug administration based on patients' genetic variations affecting metabolizing cytochrome CYP450 and UGT enzymes, P-glycoprotein ABC transporter, as well as monoamine and GABA metabolic enzymes, transporters, and receptors. Some of these gene candidates, as well as many others, may be epigenetically altered by stress. Pharmacoeugenetics can help make clinically relevant decisions regarding antidepressant and anxiolytic therapy by investigating how epigenetic mechanisms influence drug responses.

Although pharmacogenetic research has revealed that more efficient and safer treatment with antidepressants and anxiolytics can be achieved through genotype-guided decisions, further well-designed trials are needed to overcome various methodological limitations and confirm the current pharmacogenetic findings. The other main constraints of pharmacogenetic studies targeting both pharmacokinetic and pharmacodynamic variability include the high cost of molecular testing, their relative inaccessibility, and the complexity of result interpretation. Nevertheless, with more evidence on the clinical and economic benefits, improved clinical guidelines, lower costs, and shorter delivery times, pharmacogenetics as a key part of personalized medicine may become a routine intervention in neuropsychiatric clinical practice. On the other hand, the pharmacoeugenetic field is still relatively new compared to pharmacogenetic research. Therefore, future research advances on the relationship between epigenetic modifications and drug responses are needed in order to personalize antidepressant and anxiolytic treatment.

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References

1. Willner, P.; Bergman, J.; Vanderschuren, L. The Behavioural Pharmacology of Stress-Related Disorders. *Behav. Pharmacol.* **2019**, *30*, 101–103. [CrossRef] [PubMed]
2. Leichsenring, F.; Steinert, C.; Rabung, S.; Ioannidis, J.P.A. The Efficacy of Psychotherapies and Pharmacotherapies for Mental Disorders in Adults: An Umbrella Review and Meta-Analytic Evaluation of Recent Meta-Analyses. *World Psychiatry* **2022**, *21*, 133–145. [CrossRef] [PubMed]

3. Kam, H.; Jeong, H. Pharmacogenomic Biomarkers and Their Applications in Psychiatry. *Genes* **2020**, *11*, 1445. [[CrossRef](#)] [[PubMed](#)]
4. Jukic, M.; Milosavljević, F.; Molden, E.; Ingelman-Sundberg, M. Pharmacogenomics in Treatment of Depression and Psychosis: An Update. *Trends Pharmacol. Sci.* **2022**, *43*, 1055–1069. [[CrossRef](#)]
5. Lunenburg, C.A.T.C.; Ishtiaq-Ahmed, K.; Werge, T.; Gasse, C. Life-Time Actionable Pharmacogenetic Drug Use: A Population-Based Cohort Study in 86 040 Young People with and without Mental Disorders in Denmark. *Pharmacopsychiatry* **2022**, *55*, 95–107. [[CrossRef](#)]
6. Kee, P.S.; Maggo, S.D.S.; Kennedy, M.A.; Chin, P.K.L. The Pharmacogenetics of CYP2D6 and CYP2C19 in a Case Series of Antidepressant Responses. *Front. Pharmacol.* **2023**, *14*, 1080117. [[CrossRef](#)]
7. Xin, J.; Yuan, M.; Peng, Y.; Wang, J. Analysis of the Deleterious Single-Nucleotide Polymorphisms Associated with Antidepressant Efficacy in Major Depressive Disorder. *Front. Psychiatry* **2020**, *11*, 151. [[CrossRef](#)]
8. Geers, L.M.; Ochi, T.; Vyalova, N.M.; Losenkov, I.S.; Paderina, D.Z.; Pozhidaev, I.V.; Simutkin, G.G.; Bokhan, N.A.; Wilffert, B.; Touw, D.J.; et al. Influence of Eight ABCB1 Polymorphisms on Antidepressant Response in a Prospective Cohort of Treatment-Free Russian Patients with Moderate or Severe Depression: An Explorative Psychopharmacological Study with Naturalistic Design. *Hum. Psychopharmacol.* **2022**, *37*, e2826. [[CrossRef](#)]
9. Del Casale, A.; Pomes, L.M.; Bonanni, L.; Fiaschè, F.; Zocchi, C.; Padovano, A.; De Luca, O.; Angeletti, G.; Brugnoli, R.; Girardi, P.; et al. Pharmacogenomics-Guided Pharmacotherapy in Patients with Major Depressive Disorder or Bipolar Disorder Affected by Treatment-Resistant Depressive Episodes: A Long-Term Follow-up Study. *J. Pers. Med.* **2022**, *12*, 316. [[CrossRef](#)]
10. Shalimova, A.; Babasieva, V.; Chubarev, V.N.; Tarasov, V.V.; Schiöth, H.B.; Mwinyi, J. Therapy Response Prediction in Major Depressive Disorder: Current and Novel Genomic Markers Influencing Pharmacokinetics and Pharmacodynamics. *Pharmacogenomics* **2021**, *22*, 485–503. [[CrossRef](#)]
11. Zięba, A.; Matosiuk, D.; Kaczor, A.A. The Role of Genetics in the Development and Pharmacotherapy of Depression and Its Impact on Drug Discovery. *Int. J. Mol. Sci.* **2023**, *24*, 2946. [[CrossRef](#)]
12. Patel, K.A.; Bhatt, M.H.; Hirani, R.V.; Patel, V.A.; Patel, V.N.; Shah, G.B.; Chorawala, M.R. Assessment of Potential Drug-Drug Interactions among Outpatients in a Tertiary Care Hospital: Focusing on the Role of P-Glycoprotein and CYP3A4 (Retrospective Observational Study). *Heliyon* **2022**, *8*, e11278. [[CrossRef](#)]
13. Daniel, W.A.; Bromek, E.; Danek, P.J.; Haduch, A. The Mechanisms of Interactions of Psychotropic Drugs with Liver and Brain Cytochrome P450 and Their Significance for Drug Effect and Drug-Drug Interactions. *Biochem. Pharmacol.* **2022**, *199*, 115006. [[CrossRef](#)]
14. Mostafa, S.; Polasek, T.M.; Bousman, C.A.; Müller, D.J.; Sheffield, L.J.; Rembach, J.; Kirkpatrick, C.M. Pharmacogenomics in Psychiatry—The Challenge of Cytochrome P450 Enzyme Phenocopy and Solutions to Assist Precision Dosing. *Pharmacogenomics* **2022**, *23*, 857–867. [[CrossRef](#)]
15. van Westrhenen, R.; Aitchison, K.J.; Ingelman-Sundberg, M.; Jukić, M.M. Pharmacogenomics of Antidepressant and Antipsychotic Treatment: How Far Have We Got and Where Are We Going? *Front. Psychiatry* **2020**, *11*, 94. [[CrossRef](#)]
16. Alchakee, A.; Ahmed, M.; Eldohaji, L.; Alhaj, H.; Saber-Ayad, M. Pharmacogenomics in Psychiatry Practice: The Value and the Challenges. *Int. J. Mol. Sci.* **2022**, *23*, 13485. [[CrossRef](#)]
17. Shetty, P. Pharmacogenomics and Its Future Implications in Treatment-Resistant Depression. *Ind. J. Priv. Psychiatry* **2019**, *13*, 71–76. [[CrossRef](#)]
18. Wyska, E. Pharmacokinetic Considerations for Current State-of-the-Art Antidepressants. *Expert Opin. Drug Metab. Toxicol.* **2019**, *15*, 831–847. [[CrossRef](#)]
19. Samardzic, J.; Svob Strac, D.; van den Anker, J.N. The Benefit and Future of Pharmacogenetics. In *Total Intravenous Anesthesia and Target Controlled Infusions*; Absalom, A.R., Mason, K.P., Eds.; Springer: New York, NY, USA, 2017; pp. 697–711.
20. Suzuki, Y.; Sawamura, K.; Someya, T. Polymorphisms in the 5-Hydroxytryptamine 2A Receptor and CytochromeP4502D6 Genes Synergistically Predict Fluvoxamine-Induced Side Effects in Japanese Depressed Patients. *Neuropsychopharmacology* **2006**, *31*, 825–831. [[CrossRef](#)]
21. Brunoni, A.R.; Carracedo, A.; Amigo, O.M.; Pellicer, A.L.; Talib, L.; Carvalho, A.F.; Lotufo, P.A.; Benseñor, I.M.; Gattaz, W.; Cappi, C. Association of BDNF, HTR2A, TPH1, SLC6A4, and COMT Polymorphisms with TDCS and Escitalopram Efficacy: Ancillary Analysis of a Double-Blind, Placebo-Controlled Trial. *Rev. Bras. Psiquiatr.* **2020**, *42*, 128–135. [[CrossRef](#)]
22. Motsinger-Reif, A.A.; Jorgenson, E.; Relling, M.V.; Kroetz, D.L.; Weinshilboum, R.; Cox, N.J.; Roden, D.M. Genome-Wide Association Studies in Pharmacogenomics: Successes and Lessons. *Pharmacogenet. Genomics* **2013**, *23*, 383–394. [[CrossRef](#)] [[PubMed](#)]
23. Li, B.; Ritchie, M.D. From GWAS to Gene: Transcriptome-Wide Association Studies and Other Methods to Functionally Understand GWAS Discoveries. *Front. Genet.* **2021**, *12*, 713230. [[CrossRef](#)] [[PubMed](#)]
24. Smith, D.A.; Sadler, M.C.; Altman, R.B. Promises and Challenges in Pharmacoeugenetics. *Camb. Prism. Precis. Med.* **2023**, *1*, E18. [[CrossRef](#)]
25. Cascorbi, I.; Schwab, M. Epigenetics in Drug Response. *Clin. Pharmacol. Ther.* **2016**, *99*, 468–470. [[CrossRef](#)] [[PubMed](#)]
26. Lauschke, V.M.; Zhou, Y.; Ingelman-Sundberg, M. Novel Genetic and Epigenetic Factors of Importance for Inter-Individual Differences in Drug Disposition, Response and Toxicity. *Pharmacol. Ther.* **2019**, *197*, 122–152. [[CrossRef](#)]

27. Kubota, T.; Miyake, K.; Hirasawa, T. Epigenetic understanding of gene-environment interactions in psychiatric disorders: A new concept of clinical genetics. *Clin. Epigenetics* **2012**, *4*, 1. [\[CrossRef\]](#)
28. Tuscher, J.J.; Day, J.J. Multigenerational epigenetic inheritance: One step forward, two generations back. *Neurobiol. Dis.* **2019**, *132*, 104591. [\[CrossRef\]](#)
29. Halbreich, U. Stress-Related Physical and Mental Disorders: A New Paradigm. *BJPsych Adv.* **2021**, *27*, 145–152. [\[CrossRef\]](#)
30. Abdallah, C.G.; Averill, L.A.; Akiki, T.J.; Raza, M.; Averill, C.L.; Gomaa, H.; Adikey, A.; Krystal, J.H. The Neurobiology and Pharmacotherapy of Posttraumatic Stress Disorder. *Annu. Rev. Pharmacol. Toxicol.* **2019**, *59*, 171–189. [\[CrossRef\]](#)
31. Miniawi, S.E.; Orgeta, V.; Stafford, J. Non-Affective Psychotic Disorders and Risk of Dementia: A Systematic Review and Meta-Analysis. *Psychol. Med.* **2022**, *52*, 1–13. [\[CrossRef\]](#)
32. Vafadari, B. Stress and the Role of the Gut-Brain Axis in the Pathogenesis of Schizophrenia: A Literature Review. *Int. J. Mol. Sci.* **2021**, *22*, 9747. [\[CrossRef\]](#)
33. Park, C.; Rosenblat, J.D.; Brietzke, E.; Pan, Z.; Lee, Y.; Cao, B.; Zuckerman, H.; Kalantarova, A.; McIntyre, R.S. Stress, epigenetics and depression: A systematic review. *Neurosci. Biobehav. Rev.* **2019**, *102*, 139–152. [\[CrossRef\]](#)
34. Hack, L.M.; Fries, G.R.; Eyre, H.A.; Bousman, C.A.; Singh, A.B.; Quevedo, J.; John, V.P.; Baune, B.T.; Dunlop, B.W. Moving pharmacoeigenetics tools for depression toward clinical use. *J. Affect. Disord.* **2019**, *249*, 336–346. [\[CrossRef\]](#)
35. Helton, S.G.; Lohoff, F.W. Serotonin Pathway Polymorphisms and the Treatment of Major Depressive Disorder and Anxiety Disorders. *Pharmacogenomics* **2015**, *16*, 541–553. [\[CrossRef\]](#)
36. Cacabelos, R.; Torrellas, C. Pharmacogenomics of Antidepressants. *HSOA J. Psychiatry Depress. Anxiety* **2015**, *1*, 001. [\[CrossRef\]](#)
37. Ivanov, H.Y.; Grigorova, D.; Lauschke, V.M.; Velinov, B.; Stoychev, K.; Kyosovska, G.; Shopov, P. CYP2C19 and CYP2D6 Genotypes and Metabolizer Status Distribution in a Bulgarian Psychiatric Cohort. *J. Pers. Med.* **2022**, *12*, 1187. [\[CrossRef\]](#)
38. van Westrhenen, R.; van Schaik, R.H.N.; van Gelder, T.; Birkenhager, T.K.; Bakker, P.R.; Houwink, E.J.F.; Bet, P.M.; Hoogendijk, W.J.G.; van Weelden-Hulshof, M.J.M. Policy and Practice Review: A First Guideline on the Use of Pharmacogenetics in Clinical Psychiatric Practice. *Front. Pharmacol.* **2021**, *12*, 640032. [\[CrossRef\]](#)
39. Berrou, I.; Ramsunder, A.; Palmer, R. Making the case for pharmacogenomics in the management of mental health conditions. *Pharm. J.* **2023**, *310*, 7969. [\[CrossRef\]](#)
40. Taylor, C.; Crosby, I.; Yip, V.; Maguire, P.; Pirmohamed, M.; Turner, R.M. A Review of the Important Role of CYP2D6 in Pharmacogenomics. *Genes* **2020**, *11*, 1295. [\[CrossRef\]](#)
41. Pratt, V.M.; Del Tredici, A.L.; Hachad, H.; Ji, Y.; Kalman, L.V.; Scott, S.A.; Weck, K.E. Recommendations for Clinical CYP2C19 Genotyping Allele Selection: A Report of the Association for Molecular Pathology. *J. Mol. Diagn.* **2018**, *20*, 269–276. [\[CrossRef\]](#)
42. Nassan, M.; Nicholson, W.T.; Elliott, M.A.; Rohrer Vitek, C.R.; Black, J.L.; Frye, M.A. Pharmacokinetic Pharmacogenetic Prescribing Guidelines for Antidepressants: A Template for Psychiatric Precision Medicine. *Mayo Clin. Proc.* **2016**, *91*, 897–907. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Fornaro, M.; Anastasia, A.; Valchera, A.; Carano, A.; Orsolini, L.; Vellante, F.; Rapini, G.; Olivieri, L.; Di Natale, S.; Perna, G.; et al. The FDA “Black Box” Warning on Antidepressant Suicide Risk in Young Adults: More Harm than Benefits? *Front. Psychiatry* **2019**, *10*, 294. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Suwała, J.; Machowska, M.; Wiela-Hojeńska, A. Venlafaxine Pharmacogenetics: A Comprehensive Review. *Pharmacogenomics* **2019**, *20*, 829–845. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Chua, E.W.; Foulds, J.; Miller, A.L.; Kennedy, M.A. Novel CYP2D6 and CYP2C19 Variants Identified in a Patient with Adverse Reactions towards Venlafaxine Monotherapy and Dual Therapy with Nortriptyline and Fluoxetine. *Pharmacogenet. Genom.* **2013**, *23*, 494–497. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Ahmed, A.T.; Biernacka, J.M.; Jenkins, G.; Rush, A.J.; Shinozaki, G.; Veldic, M.; Kung, S.; Bobo, W.V.; Hall-Flavin, D.K.; Weinshilboum, R.M.; et al. Pharmacokinetic-Pharmacodynamic Interaction Associated with Venlafaxine-XR Remission in Patients with Major Depressive Disorder with History of Citalopram / Escitalopram Treatment Failure. *J. Affect. Disord.* **2019**, *246*, 62–68. [\[CrossRef\]](#)
47. Bahar, M.A.; Setiawan, D.; Hak, E.; Wilffert, B. Pharmacogenetics of Drug-Drug Interaction and Drug-Drug-Gene Interaction: A Systematic Review on CYP2C9, CYP2C19 and CYP2D6. *Pharmacogenomics* **2017**, *18*, 701–739. [\[CrossRef\]](#)
48. Whirl-Carrillo, M.; Huddart, R.; Gong, L.; Sangkuhl, K.; Thorn, C.F.; Whaley, R.; Klein, T.E. An Evidence-Based Framework for Evaluating Pharmacogenomics Knowledge for Personalized Medicine. *Clin. Pharmacol. Ther.* **2021**, *110*, 563–572. [\[CrossRef\]](#)
49. Brouwer, J.M.J.L.; Nijenhuis, M.; Soree, B.; Guchelaar, H.-J.; Swen, J.J.; van Schaik, R.H.N.; Weide, J.v.d.; Rongen, G.A.P.J.M.; Buunk, A.-M.; de Boer-Veger, N.J.; et al. Dutch Pharmacogenetics Working Group (DPWG) Guideline for the Gene-Drug Interaction between CYP2C19 and CYP2D6 and SSRIs. *Eur. J. Hum. Genet.* **2022**, *30*, 1114–1120. [\[CrossRef\]](#)
50. Jukić, M.M.; Haslemo, T.; Molden, E.; Ingelman-Sundberg, M. Impact of CYP2C19 Genotype on Escitalopram Exposure and Therapeutic Failure: A Retrospective Study Based on 2,087 Patients. *Am. J. Psychiatry* **2018**, *175*, 463–470. [\[CrossRef\]](#)
51. Rahikainen, A.-L.; Vauhkonen, P.; Pett, H.; Palo, J.U.; Haukka, J.; Ojanperä, I.; Niemi, M.; Sajantila, A. Completed Suicides of Citalopram Users-the Role of CYP Genotypes and Adverse Drug Interactions. *Int. J. Leg. Med.* **2019**, *133*, 353–363. [\[CrossRef\]](#)
52. Hicks, J.K.; Bishop, J.R.; Gammal, R.S.; Sangkuhl, K.; Bousman, C.A.; Leeder, J.S.; Llerena, A.; Mueller, D.J.; Ramsey, L.B.; Scott, S.A.; et al. A Call for Clear and Consistent Communications Regarding the Role of Pharmacogenetics in Antidepressant Pharmacotherapy. *Clin. Pharmacol. Ther.* **2020**, *107*, 50–52. [\[CrossRef\]](#)

53. Ricardo-Silgado, M.L.; Singh, S.; Cifuentes, L.; Decker, P.A.; Gonzalez-Izundegui, D.; Moyer, A.M.; Hurtado, M.D.; Camilleri, M.; Bielinski, S.J.; Acosta, A. Association between CYP Metabolizer Phenotypes and Selective Serotonin Reuptake Inhibitors Induced Weight Gain: A Retrospective Cohort Study. *BMC Med.* **2022**, *20*, 261. [\[CrossRef\]](#)
54. Sim, S.C.; Nordin, L.; Andersson, T.M.-L.; Virding, S.; Olsson, M.; Pedersen, N.L.; Ingelman-Sundberg, M. Association between CYP2C19 Polymorphism and Depressive Symptoms. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **2010**, *153B*, 1160–1166. [\[CrossRef\]](#)
55. Milosavljevic, F.; Bukvic, N.; Pavlovic, Z.; Miljevic, C.; Pešic, V.; Molden, E.; Ingelman-Sundberg, M.; Leucht, S.; Jukic, M.M. Association of CYP2C19 and CYP2D6 Poor and Intermediate Metabolizer Status with Antidepressant and Antipsychotic Exposure: A Systematic Review and Meta-Analysis: A Systematic Review and Meta-Analysis. *JAMA Psychiatry* **2021**, *78*, 270–280. [\[CrossRef\]](#)
56. Jukić, M.M.; Opel, N.; Ström, J.; Carrillo-Roa, T.; Miksys, S.; Novalen, M.; Renblom, A.; Sim, S.C.; Peñas-Lledó, E.M.; Courtet, P.; et al. Elevated CYP2C19 Expression Is Associated with Depressive Symptoms and Hippocampal Homeostasis Impairment. *Mol. Psychiatry* **2017**, *22*, 1155–1163. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Hicks, J.K.; Bishop, J.R.; Sangkuhl, K.; Müller, D.J.; Ji, Y.; Leckband, S.G.; Leeder, J.S.; Graham, R.L.; Chiulli, D.L.; Llerena, A.; et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. *Clin. Pharmacol. Ther.* **2015**, *98*, 127–134. [\[CrossRef\]](#)
58. Hicks, J.K.; Sangkuhl, K.; Swen, J.J.; Ellingrod, V.L.; Müller, D.J.; Shimoda, K.; Bishop, J.R.; Kharasch, E.D.; Skaar, T.C.; Gaedigk, A.; et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update. *Clin. Pharmacol. Ther.* **2017**, *102*, 37–44. [\[CrossRef\]](#)
59. Pratt, V.M.; Cavallari, L.H.; Del Tredici, A.L.; Gaedigk, A.; Hachad, H.; Ji, Y.; Kalman, L.V.; Ly, R.C.; Moyer, A.M.; Scott, S.A.; et al. Recommendations for Clinical CYP2D6 Genotyping Allele Selection: A Joint Consensus Recommendation of the Association for Molecular Pathology, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, and the European Society for Pharmacogenomics and Personalized Therapy. *J. Mol. Diagn.* **2021**, *23*, 1047–1064. [\[CrossRef\]](#)
60. Llerena, A.; Berecz, R.; Dorado, P.; González, A.P.; Peñas-Lledó, E.M.; De La Rubia, A. CYP2C9 Gene and Susceptibility to Major Depressive Disorder. *Pharmacogenomics J.* **2003**, *3*, 300–302. [\[CrossRef\]](#)
61. Yenilmez, E.D.; Tamam, L.; Karaytug, O.; Tuli, A. Characterization CYP1A2, CYP2C9, CYP2C19 and CYP2D6 Polymorphisms Using HRMA in Psychiatry Patients with Schizophrenia and Bipolar Disease for Personalized Medicine. *Comb. Chem. High Throughput Screen.* **2018**, *21*, 374–380. [\[CrossRef\]](#) [\[PubMed\]](#)
62. Saiz-Rodríguez, M.; Ochoa, D.; Belmonte, C.; Román, M.; Vieira de Lara, D.; Zubiaur, P.; Koller, D.; Mejía, G.; Abad-Santos, F. Polymorphisms in CYP1A2, CYP2C9 and ABCB1 Affect Agomelatine Pharmacokinetics. *J. Psychopharmacol.* **2019**, *33*, 522–531. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Song, L.; Du, Q.; Jiang, X.; Wang, L. Effect of CYP1A2 Polymorphism on the Pharmacokinetics of Agomelatine in Chinese Healthy Male Volunteers. *J. Clin. Pharm. Ther.* **2014**, *39*, 204–209. [\[CrossRef\]](#)
64. Kuo, H.-W.; Liu, S.C.; Tsou, H.-H.; Liu, S.-W.; Lin, K.-M.; Lu, S.-C.; Hsiao, M.-C.; Hsiao, C.-F.; Liu, C.-Y.; Chen, C.-H.; et al. CYP1A2 Genetic Polymorphisms Are Associated with Early Antidepressant Escitalopram Metabolism and Adverse Reactions. *Pharmacogenomics* **2013**, *14*, 1191–1201. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Lin, K.-M.; Tsou, H.-H.; Tsai, I.-J.; Hsiao, M.-C.; Hsiao, C.-F.; Liu, C.-Y.; Shen, W.W.; Tang, H.-S.; Fang, C.-K.; Wu, C.-S.; et al. CYP1A2 Genetic Polymorphisms Are Associated with Treatment Response to the Antidepressant Paroxetine. *Pharmacogenomics* **2010**, *11*, 1535–1543. [\[CrossRef\]](#)
66. Zhu, Y.; Zhang, N.; Ren, D.; Bi, Y.; Xu, F.; Niu, W.; Sun, Q.; Guo, Z.; Yuan, R.; Yuan, F.; et al. CYP1A2 Genetic Polymorphism Is Associated with Treatment Remission to Antidepressant Venlafaxine in Han Chinese Population. *Clin. Neuropharmacol.* **2019**, *42*, 32–36. [\[CrossRef\]](#) [\[PubMed\]](#)
67. Lazarowski, A.; Czornyj, L. Potential Role of Multidrug Resistant Proteins in Refractory Epilepsy and Antiepileptic Drugs Interactions. *Drug Metabol. Drug Interact.* **2011**, *26*, 21–26. [\[CrossRef\]](#) [\[PubMed\]](#)
68. Magarbeh, L.; Hassel, C.; Choi, M.; Islam, F.; Marshe, V.S.; Zai, C.C.; Zuberi, R.; Gammal, R.S.; Men, X.; Scherf-Clavel, M.; et al. ABCB1 Gene Variants and Antidepressant Treatment Outcomes: A Systematic Review and Meta-Analysis Including Results from the CAN-BIND-1 Study. *Clin. Pharmacol. Ther.* **2023**, *6*, 2854. [\[CrossRef\]](#) [\[PubMed\]](#)
69. Sarginson, J.E.; Lazzeroni, L.C.; Ryan, H.S.; Ershoff, B.D.; Schatzberg, A.F.; Murphy, G.M., Jr. ABCB1 (MDR1) Polymorphisms and Antidepressant Response in Geriatric Depression. *Pharmacogenet. Genom.* **2010**, *20*, 467–475. [\[CrossRef\]](#)
70. Yamasaki, Y.; Moriwaki, T.; Ogata, S.; Ito, S.; Ohtsuki, S.; Minegishi, G.; Abe, S.; Ohta, Y.; Kazuki, K.; Kobayashi, K.; et al. Influence of MDR1 Gene Polymorphism (2677G>T) on Expression and Function of P-Glycoprotein at the Blood-Brain Barrier: Utilizing Novel P-Glycoprotein Humanized Mice with Mutation. *Pharmacogenet. Genom.* **2022**, *32*, 288–292. [\[CrossRef\]](#)
71. Shan, X.-X.; Qiu, Y.; Xie, W.-W.; Wu, R.-R.; Yu, Y.; Wu, H.-S.; Li, L.-H. ABCB1 Gene Is Associated with Clinical Response to SNRIs in a Local Chinese Han Population. *Front. Pharmacol.* **2019**, *10*, 761. [\[CrossRef\]](#)
72. Nakamura, K.; Hasegawa, H. Developmental Role of Tryptophan Hydroxylase in the Nervous System. *Mol. Neurobiol.* **2007**, *35*, 45–54. [\[CrossRef\]](#) [\[PubMed\]](#)
73. Crisafulli, C.; Fabbri, C.; Porcelli, S.; Drago, A.; Spina, E.; De Ronchi, D.; Serretti, A. Pharmacogenetics of Antidepressants. *Front. Pharmacol.* **2011**, *2*, 6. [\[CrossRef\]](#) [\[PubMed\]](#)
74. Kato, M.; Serretti, A. Review and Meta-Analysis of Antidepressant Pharmacogenetic Findings in Major Depressive Disorder. *Mol. Psychiatry* **2010**, *15*, 473–500. [\[CrossRef\]](#)

75. Moskaleva, P.V.; Shnayder, N.A.; Dmitrenko, D.V.; Shilkina, O.S.; Neznanov, N.G.; Nasyrova, R.F. Association of TPH1 and TPH2 Gene Polymorphisms with the Risk of Developing Psychoneurological Disorders. *Neurosci. Behav. Physiol.* **2022**, *52*, 462–469. [\[CrossRef\]](#)
76. Matthes, S.; Mosienko, V.; Bashammakh, S.; Alenina, N.; Bader, M. Tryptophan Hydroxylase as Novel Target for the Treatment of Depressive Disorders. *Pharmacology* **2010**, *85*, 95–109. [\[CrossRef\]](#)
77. Du, J.; Zhang, Z.; Li, W.; He, L.; Xu, J.; Shi, Y. Association Study of the TPH2 Gene with Major Depressive Disorder in the Han Chinese Population. *Eur. J. Psychiatry* **2016**, *30*, 131–140.
78. Secher, A.; Bukh, J.; Bock, C.; Koefoed, P.; Rasmussen, H.B.; Werge, T.; Kessing, L.V.; Mellerup, E. Antidepressive-Drug-Induced Bodyweight Gain Is Associated with Polymorphisms in Genes Coding for COMT and TPH1. *Int. Clin. Psychopharmacol.* **2009**, *24*, 199–203. [\[CrossRef\]](#)
79. Yeung, A.W.K.; Georgieva, M.G.; Atanasov, A.G.; Tzvetkov, N.T. Monoamine Oxidases (MAOs) as Privileged Molecular Targets in Neuroscience: Research Literature Analysis. *Front. Mol. Neurosci.* **2019**, *12*, 143. [\[CrossRef\]](#)
80. Jones, D.N.; Raghanti, M.A. The Role of Monoamine Oxidase Enzymes in the Pathophysiology of Neurological Disorders. *J. Chem. Neuroanat.* **2021**, *114*, 101957. [\[CrossRef\]](#)
81. Bi, Y.; Ren, D.; Guo, Z.; Ma, G.; Xu, F.; Chen, Z.; An, L.; Zhang, N.; Ji, L.; Yuan, F.; et al. Influence and Interaction of Genetic, Cognitive, Neuroendocrine and Personalistic Markers to Antidepressant Response in Chinese Patients with Major Depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2021**, *104*, 110036. [\[CrossRef\]](#)
82. Yoshida, K.; Naito, S.; Takahashi, H.; Sato, K.; Ito, K.; Kamata, M.; Higuchi, H.; Shimizu, T.; Itoh, K.; Inoue, K.; et al. Monoamine Oxidase: A Gene Polymorphism, Tryptophan Hydroxylase Gene Polymorphism and Antidepressant Response to Fluvoxamine in Japanese Patients with Major Depressive Disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2002**, *26*, 1279–1283. [\[CrossRef\]](#) [\[PubMed\]](#)
83. Clark, S.L.; Adkins, D.E.; Aberg, K.; Hettema, J.M.; McClay, J.L.; Souza, R.P.; van den Oord, E.J.C.G. Pharmacogenomic Study of Side-Effects for Antidepressant Treatment Options in STAR*D. *Psychol. Med.* **2012**, *42*, 1151–1162. [\[CrossRef\]](#)
84. Chappell, K.; Colle, R.; Bouligand, J.; Trabado, S.; Fève, B.; Becquemont, L.; Corruble, E.; Verstuyft, C. The MAOA Rs979605 Genetic Polymorphism Is Differentially Associated with Clinical Improvement Following Antidepressant Treatment between Male and Female Depressed Patients. *Int. J. Mol. Sci.* **2022**, *24*, 497. [\[CrossRef\]](#)
85. Srivastava, K.; Ochuba, O.; Sandhu, J.K.; Alkayyali, T.; Ruo, S.W.; Waqar, A.; Jain, A.; Joseph, C.; Poudel, S. Effect of Catechol-O-Methyltransferase Genotype Polymorphism on Neurological and Psychiatric Disorders: Progressing towards Personalized Medicine. *Cureus* **2021**, *13*, e18311. [\[CrossRef\]](#)
86. Hall, K.T.; Loscalzo, J.; Kaptchuk, T.J. Systems Pharmacogenomics—Gene, Disease, Drug and Placebo Interactions: A Case Study in COMT. *Pharmacogenomics* **2019**, *20*, 529–551. [\[CrossRef\]](#)
87. Benedetti, F.; Dallaspesza, S.; Colombo, C.; Lorenzi, C.; Pirovano, A.; Smeraldi, E. Effect of Catechol-O-Methyltransferase Val(108/158)Met Polymorphism on Antidepressant Efficacy of Fluvoxamine. *Eur. Psychiatry* **2010**, *25*, 476–478. [\[CrossRef\]](#)
88. He, Q.; Shen, Z.; Ren, L.; Wang, X.; Qian, M.; Zhu, J.; Shen, X. The Association of Catechol-O-Methyltransferase (COMT) Rs4680 Polymorphisms and Generalized Anxiety Disorder in the Chinese Han Population. *Int. J. Clin. Exp. Pathol.* **2020**, *13*, 1712–1719.
89. Gonda, X.; Petschner, P.; Eszlari, N.; Baksa, D.; Edes, A.; Antal, P.; Juhasz, G.; Bagdy, G. Genetic Variants in Major Depressive Disorder: From Pathophysiology to Therapy. *Pharmacol. Ther.* **2019**, *194*, 22–43. [\[CrossRef\]](#)
90. Yang, D.; Gouaux, E. Illumination of Serotonin Transporter Mechanism and Role of the Allosteric Site. *Sci. Adv.* **2021**, *7*, eabl3857. [\[CrossRef\]](#)
91. Krout, D.; Rodriguez, M.; Brose, S.A.; Golovko, M.Y.; Henry, L.K.; Thompson, B.J. Inhibition of the Serotonin Transporter Is Altered by Metabolites of Selective Serotonin and Norepinephrine Reuptake Inhibitors and Represents a Caution to Acute or Chronic Treatment Paradigms. *ACS Chem. Neurosci.* **2017**, *8*, 1011–1018. [\[CrossRef\]](#)
92. Uher, R.; Perroud, N.; Ng, M.Y.M.; Hauser, J.; Henigsberg, N.; Maier, W.; Mors, O.; Placentino, A.; Rietschel, M.; Souery, D.; et al. Genome-Wide Pharmacogenetics of Antidepressant Response in the GENDEP Project. *Am. J. Psychiatry* **2010**, *167*, 555–564. [\[CrossRef\]](#) [\[PubMed\]](#)
93. Stein, K.; Maruf, A.A.; Müller, D.J.; Bishop, J.R.; Bousman, C.A. Serotonin Transporter Genetic Variation and Antidepressant Response and Tolerability: A Systematic Review and Meta-Analysis. *J. Pers. Med.* **2021**, *11*, 1334. [\[CrossRef\]](#) [\[PubMed\]](#)
94. Mrazek, D.A.; Rush, A.J.; Biernacka, J.M.; O’Kane, D.J.; Cunningham, J.M.; Wieben, E.D.; Schaid, D.J.; Drews, M.S.; Courson, V.L.; Snyder, K.A.; et al. SLC6A4 Variation and Citalopram Response. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **2009**, *150B*, 341–351. [\[CrossRef\]](#) [\[PubMed\]](#)
95. Huezo-Diaz, P.; Uher, R.; Smith, R.; Rietschel, M.; Henigsberg, N.; Marušić, A.; Mors, O.; Maier, W.; Hauser, J.; Souery, D.; et al. Moderation of Antidepressant Response by the Serotonin Transporter Gene. *Br. J. Psychiatry* **2009**, *195*, 30–38. [\[CrossRef\]](#) [\[PubMed\]](#)
96. Porcelli, S.; Fabbri, C.; Serretti, A. Meta-Analysis of Serotonin Transporter Gene Promoter Polymorphism (5-HTTLPR) Association with Antidepressant Efficacy. *Eur. Neuropsychopharmacol.* **2012**, *22*, 239–258. [\[CrossRef\]](#)
97. Zou, Z.; Huang, Y.; Wang, J.; Min, W.; Zhou, B. The Association between Serotonin-Related Gene Polymorphisms and Susceptibility and Early Sertraline Response in Patients with Panic Disorder. *BMC Psychiatry* **2020**, *20*, 388. [\[CrossRef\]](#)

98. Stäuble, C.K.; Meier, R.; Lampert, M.L.; Mikoteit, T.; Hatzinger, M.; Allemann, S.S.; Hersberger, K.E.; Meyer Zu Schwabedissen, H.E. Case Report: Non-Response to Fluoxetine in a Homozygous 5-HTTLPR S-Allele Carrier of the Serotonin Transporter Gene. *Front. Psychiatry* **2022**, *13*, 942268. [\[CrossRef\]](#)
99. Maron, E.; Tammiste, A.; Kallassalu, K.; Eller, T.; Vasar, V.; Nutt, D.J.; Metspalu, A. Serotonin Transporter Promoter Region Polymorphisms Do Not Influence Treatment Response to Escitalopram in Patients with Major Depression. *Eur. Neuropsychopharmacol.* **2009**, *19*, 451–456. [\[CrossRef\]](#)
100. Kato, M.; Fukuda, T.; Wakeno, M.; Fukuda, K.; Okugawa, G.; Ikenaga, Y.; Yamashita, M.; Takekita, Y.; Nobuhara, K.; Azuma, J.; et al. Effects of the Serotonin Type 2A, 3A and 3B Receptor and the Serotonin Transporter Genes on Paroxetine and Fluvoxamine Efficacy and Adverse Drug Reactions in Depressed Japanese Patients. *Neuropsychobiology* **2006**, *53*, 186–195. [\[CrossRef\]](#)
101. Zhu, J.; Klein-Fedyshin, M.; Stevenson, J.M. Serotonin Transporter Gene Polymorphisms and Selective Serotonin Reuptake Inhibitor Tolerability: Review of Pharmacogenetic Evidence. *Pharmacotherapy* **2017**, *37*, 1089–1104. [\[CrossRef\]](#)
102. Sarmiento-Hernández, E.I.; Ulloa-Flores, R.E.; Camarena-Medellín, B.; Sanabrais-Jiménez, M.A.; Aguilar-García, A.; Hernández-Muñoz, S. Association between 5-HTTLPR Polymorphism, Suicide Attempt and Comorbidity in Mexican Adolescents with Major Depressive Disorder. *Actas Esp. Psiquiatr.* **2019**, *47*, 1–6.
103. Gonda, X.; Fountoulakis, K.N.; Harro, J.; Pompili, M.; Akiskal, H.S.; Bagdy, G.; Rihmer, Z. The Possible Contributory Role of the S Allele of 5-HTTLPR in the Emergence of Suicidality. *J. Psychopharmacol.* **2011**, *25*, 857–866. [\[CrossRef\]](#)
104. Antypa, N.; Serretti, A.; Rujescu, D. Serotonergic Genes and Suicide: A Systematic Review. *Eur. Neuropsychopharmacol.* **2013**, *23*, 1125–1142. [\[CrossRef\]](#) [\[PubMed\]](#)
105. Nemoda, Z.; Angyal, N.; Tarnok, Z.; Birkas, E.; Bogнар, E.; Sasvari-Szekely, M.; Gervai, J.; Lakatos, K. Differential Genetic Effect of the Norepinephrine Transporter Promoter Polymorphisms on Attention Problems in Clinical and Non-Clinical Samples. *Front. Neurosci.* **2018**, *12*, 1051. [\[CrossRef\]](#) [\[PubMed\]](#)
106. Ochi, T.; Vyalova, N.M.; Losenkov, I.S.; Paderina, D.Z.; Pozhidaev, I.V.; Loonen, A.J.M.; Simutkin, G.G.; Bokhan, N.A.; Wilffert, B.; Ivanova, S.A. Polymorphisms in the Adrenergic Neurotransmission Pathway Impact Antidepressant Response in Depressed Patients. *Neurosci. Appl.* **2023**, *2*, 101016. [\[CrossRef\]](#)
107. Porcelli, S.; Drago, A.; Fabbri, C.; Gibiino, S.; Calati, R.; Serretti, A. Pharmacogenetics of Antidepressant Response. *J. Psychiatry Neurosci.* **2011**, *36*, 87–113. [\[CrossRef\]](#)
108. Zhou, Z.; Zhen, J.; Karpowich, N.K.; Goetz, R.M.; Law, C.J.; Reith, M.E.A.; Wang, D.-N. LeuT-Desipramine Structure Reveals How Antidepressants Block Neurotransmitter Reuptake. *Science* **2007**, *317*, 1390–1393. [\[CrossRef\]](#)
109. Lavretsky, H.; Siddarth, P.; Kumar, A.; Reynolds, C.F., 3rd. The Effects of the Dopamine and Serotonin Transporter Polymorphisms on Clinical Features and Treatment Response in Geriatric Depression: A Pilot Study. *Int. J. Geriatr. Psychiatry* **2008**, *23*, 55–59. [\[CrossRef\]](#)
110. Kirchheiner, J.; Nickchen, K.; Sasse, J.; Bauer, M.; Roots, I.; Brockmöller, J. A 40-Basepair VNTR Polymorphism in the Dopamine Transporter (DAT1) Gene and the Rapid Response to Antidepressant Treatment. *Pharmacogenomics J.* **2007**, *7*, 48–55. [\[CrossRef\]](#)
111. Yohn, C.N.; Gergues, M.M.; Samuels, B.A. The Role of 5-HT Receptors in Depression. *Mol. Brain* **2017**, *10*, 28. [\[CrossRef\]](#)
112. Alqahtani, A.M.; Kumarappan, C.; Kumar, V.; Srinivasan, R.; Krishnaraju, V. Understanding the Genetic Aspects of Resistance to Antidepressants Treatment. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 7784–7795. [\[CrossRef\]](#) [\[PubMed\]](#)
113. Dong, Z.-Q.; Li, X.-R.; He, L.; He, G.; Yu, T.; Sun, X.-L. 5-HT_{1A} and 5-HT_{2A} Genetic Polymorphisms and SSRI Antidepressant Response in Depressive Chinese Patients. *Neuropsychiatr. Dis. Treat.* **2016**, *12*, 1623–1629. [\[CrossRef\]](#) [\[PubMed\]](#)
114. Ochi, T.; Vyalova, N.M.; Losenkov, I.S.; Paderina, D.Z.; Pozhidaev, I.V.; Loonen, A.J.M.; Simutkin, G.G.; Bokhan, N.A.; Ivanova, S.A.; Wilffert, B. Limited Associations between 5-HT Receptor Gene Polymorphisms and Treatment Response in Antidepressant Treatment-Free Patients with Depression. *Front. Pharmacol.* **2019**, *10*, 1462. [\[CrossRef\]](#) [\[PubMed\]](#)
115. Zhao, X.; Huang, Y.; Li, J.; Ma, H.; Jin, Q.; Wang, Y.; Wu, L.; Zhu, G. Association between the 5-HT_{1A} Receptor Gene Polymorphism (Rs6295) and Antidepressants: A Meta-Analysis. *Int. Clin. Psychopharmacol.* **2012**, *27*, 314–320. [\[CrossRef\]](#)
116. Scutt, G.; Overall, A.; Scott, R.; Patel, B.; Hachoumi, L.; Yeoman, M.; Wright, J. Does the 5-HT_{1A} Rs6295 Polymorphism Influence the Safety and Efficacy of Citalopram Therapy in the Oldest Old? *Ther. Adv. Drug Saf.* **2018**, *9*, 355–366. [\[CrossRef\]](#)
117. Villafuerte, S.M.; Vallabhaneni, K.; Sliwerska, E.; McMahon, F.J.; Young, E.A.; Burmeister, M. SSRI Response in Depression May Be Influenced by SNPs in HTR1B and HTR1A. *Psychiatr. Genet.* **2009**, *19*, 281–291. [\[CrossRef\]](#)
118. Kato, M.; Fukuda, T.; Wakeno, M.; Okugawa, G.; Takekita, Y.; Watanabe, S.; Yamashita, M.; Hosoi, Y.; Azuma, J.; Kinoshita, T.; et al. Effect of 5-HT_{1A} Gene Polymorphisms on Antidepressant Response in Major Depressive Disorder. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **2009**, *150B*, 115–123. [\[CrossRef\]](#)
119. Kao, C.-F.; Kuo, P.-H.; Yu, Y.W.-Y.; Yang, A.C.; Lin, E.; Liu, Y.-L.; Tsai, S.-J. Gene-Based Association Analysis Suggests Association of HTR2A with Antidepressant Treatment Response in Depressed Patients. *Front. Pharmacol.* **2020**, *11*, 559601. [\[CrossRef\]](#)
120. Sun, Y.; Tao, S.; Tian, S.; Shao, J.; Mo, Z.; Wang, X.; Wang, H.; Zhao, P.; Chen, Z.; Yao, Z.; et al. Serotonin 2A Receptor Polymorphism Rs3803189 Mediated by Dynamics of Default Mode Network: A Potential Biomarker for Antidepressant Early Response. *J. Affect. Disord.* **2021**, *283*, 130–138. [\[CrossRef\]](#)
121. Gassó, P.; Blázquez, A.; Rodríguez, N.; Boloc, D.; Torres, T.; Mas, S.; Lafuente, A.; Lázaro, L. Further Support for the Involvement of Genetic Variants Related to the Serotonergic Pathway in the Antidepressant Response in Children and Adolescents after a 12-Month Follow-up: Impact of the HTR2A Rs7997012 Polymorphism. *J. Child Adolesc. Psychopharmacol.* **2018**, *28*, 711–718. [\[CrossRef\]](#)

122. Kang, R.-H.; Choi, M.-J.; Paik, J.-W.; Hahn, S.-W.; Lee, M.-S. Effect of Serotonin Receptor 2A Gene Polymorphism on Mirtazapine Response in Major Depression. *Int. J. Psychiatry Med.* **2007**, *37*, 315–329. [CrossRef]
123. Oz, M.D.; Baskak, B.; Uckun, Z.; Artun, N.Y.; Ozdemir, H.; Ozel, T.K.; Ozguven, H.D.; Suzen, H.S. Association between Serotonin 2A Receptor (HTR2A), Serotonin Transporter (SLC6A4) and Brain-Derived Neurotrophic Factor (BDNF) Gene Polymorphisms and Citalopram/Sertraline Induced Sexual Dysfunction in MDD Patients. *Pharmacogenomics J.* **2020**, *20*, 443–450. [CrossRef]
124. Wan, Y.-S.; Zhai, X.-J.; Tan, H.-A.; Ai, Y.-S.; Zhao, L.-B. Associations between the 1438A/G, 102T/C, and Rs7997012 G/A Polymorphisms of HTR2A and the Safety and Efficacy of Antidepressants in Depression: A Meta-Analysis. *Pharmacogenomics J.* **2021**, *21*, 200–215. [CrossRef]
125. Wang, Y.; Liu, X.; Yu, Y.; Han, Y.; Wei, J.; Collier, D.; Li, T.; Ma, X. The Role of Single Nucleotide Polymorphism of D2 Dopamine Receptor Gene on Major Depressive Disorder and Response to Antidepressant Treatment. *Psychiatry Res.* **2012**, *200*, 1047–1050. [CrossRef]
126. Perlis, R.H.; Adams, D.H.; Fijal, B.; Sutton, V.K.; Fahren, M.; Breier, A.; Houston, J.P. Genetic Association Study of Treatment Response with Olanzapine/Fluoxetine Combination or Lamotrigine in Bipolar I Depression. *J. Clin. Psychiatry* **2010**, *71*, 599–605. [CrossRef]
127. Serretti, A.; Artioli, P.; Zanardi, R.; Lorenzi, C.; Rossini, D.; Cusin, C.; Arnoldi, A.; Catalano, M. Genetic Features of Antidepressant Induced Mania and Hypo-Mania in Bipolar Disorder. *Psychopharmacology* **2004**, *174*, 504–511. [CrossRef]
128. Benedetti, F.; Serretti, A.; Colombo, C.; Lilli, R.; Lorenzi, C.; Smeraldi, E. Dopamine receptor D2 and D3 gene variants are not associated with the antidepressant effect of total sleep deprivation in bipolar depression. *Psychiatry Res.* **2003**, *118*, 241–247. [CrossRef]
129. Tiwari, A.K.; Souza, R.P.; Müller, D.J. Pharmacogenetics of Anxiolytic Drugs. *J. Neural Transm.* **2009**, *116*, 667–677. [CrossRef]
130. Meech, R.; Hu, D.G.; McKinnon, R.A.; Mubarakah, S.N.; Haines, A.Z.; Nair, P.C.; Rowland, A.; Mackenzie, P.I. The UDP-Glycosyltransferase (UGT) Superfamily: New Members, New Functions, and Novel Paradigms. *Physiol. Rev.* **2019**, *99*, 1153–1222. [CrossRef]
131. Court, M.H.; Hao, Q.; Krishnaswamy, S.; Bekaii-Saab, T.; Al-Rohaimi, A.; von Moltke, L.L.; Greenblatt, D.J. UDP-Glucuronosyltransferase (UGT) 2B15 Pharmacogenetics: UGT2B15 D85Y Genotype and Gender Are Major Determinants of Oxazepam Glucuronidation by Human Liver. *J. Pharmacol. Exp. Ther.* **2004**, *310*, 656–665. [CrossRef]
132. Mijderwijk, H.; Klimek, M.; van Beek, S.; van Schaik, R.H.N.; Duivenvoorden, H.J.; Stolker, R.J. Implication of UGT2B15 Genotype Polymorphism on Postoperative Anxiety Levels in Patients Receiving Lorazepam Premedication. *Anesth. Analg.* **2016**, *123*, 1109–1115. [CrossRef] [PubMed]
133. Chung, J.-Y.; Cho, J.-Y.; Yu, K.-S.; Kim, J.-R.; Jung, H.-R.; Lim, K.-S.; Jang, I.-J.; Shin, S.-G. Effect of the UGT2B15 Genotype on the Pharmacokinetics, Pharmacodynamics, and Drug Interactions of Intravenous Lorazepam in Healthy Volunteers. *Clin. Pharmacol. Ther.* **2005**, *77*, 486–494. [CrossRef] [PubMed]
134. Jackson, A.; Stephens, D.; Duka, T. Gender Differences in Response to Lorazepam in a Human Drug Discrimination Study. *J. Psychopharmacol.* **2005**, *19*, 614–619. [CrossRef] [PubMed]
135. Court, M.H. Interindividual Variability in Hepatic Drug Glucuronidation: Studies into the Role of Age, Sex, Enzyme Inducers, and Genetic Polymorphism Using the Human Liver Bank as a Model System. *Drug Metab. Rev.* **2010**, *42*, 209–224. [CrossRef]
136. He, X.; Hesse, L.M.; Hazarika, S.; Masse, G.; Harmatz, J.S.; Greenblatt, D.J.; Court, M.H. Evidence for Oxazepam as Anin Vivoprobe of UGT2B15: Oxazepam Clearance Is Reduced By UGT2B15 D85Y Polymorphism but Unaffected By UGT2B17 deletion. *Br. J. Clin. Pharmacol.* **2009**, *6*, 721–730. [CrossRef]
137. Liu, W.; Ramírez, J.; Gamazon, E.R.; Mirkov, S.; Chen, P.; Wu, K.; Sun, C.; Cox, N.J.; Cook, E., Jr.; Das, S.; et al. Genetic Factors Affecting Gene Transcription and Catalytic Activity of UDP-Glucuronosyltransferases in Human Liver. *Hum. Mol. Genet.* **2014**, *2*, 5558–5569. [CrossRef]
138. Dinis-Oliveira, R.J. Metabolic Profile of Oxazepam and Related Benzodiazepines: Clinical and Forensic Aspects. *Drug Metab. Rev.* **2017**, *49*, 451–463. [CrossRef]
139. Uzun, S.; Kozumplik, O.; Jakovljević, M.; Sedić, B. Side Effects of Treatment with Benzodiazepines. *Psychiatr. Danub.* **2010**, *22*, 90–93.
140. Dean, L. Diazepam Therapy and CYP2C19 Genotype. In *Medical Genetics Summaries*; Pratt, V.M., Scott, S.A., Pirmohamed, M., Esquivel, B., Kattman, B.L., Malheiro, A.J., Eds.; National Center for Biotechnology Information: Bethesda, MD, USA, 2012. Available online: <https://www.ncbi.nlm.nih.gov/books/NBK546789/> (accessed on 15 April 2023).
141. Zubiaur, P.; Figueiredo-Tor, L.; Villapalos-García, G.; Soria-Chacartegui, P.; Navares-Gómez, M.; Novalbos, J.; Matas, M.; Calleja, S.; Mejía-Abril, G.; Román, M.; et al. Association between CYP2C19 and CYP2B6 phenotypes and the pharmacokinetics and safety of diazepam. *Biomed. Pharmacother.* **2022**, *155*, 113747. [CrossRef]
142. Skryabin, V.Y.; Zastrozhin, M.S.; Torrado, M.V.; Grishina, E.A.; Ryzhikova, K.A.; Shipitsyn, V.V.; Galaktionova, T.E.; Sorokin, A.S.; Bryun, E.A.; Sychev, D.A. How Do CYP2C19*2 and CYP2C19*17 Genetic Polymorphisms Affect the Efficacy and Safety of Diazepam in Patients with Alcohol Withdrawal Syndrome? *Drug Metab. Pers. Ther.* **2020**, *35*. [CrossRef]
143. Skryabin, V.Y.; Zastrozhin, M.; Torrado, M.; Grishina, E.; Ryzhikova, K.; Shipitsyn, V.; Galaktionova, T.; Bryun, E.; Sychev, D. Effects of CYP2C19*17 Genetic Polymorphisms on Plasma and Saliva Concentrations of Diazepam in Patients with Alcohol Withdrawal Syndrome. *Psychiatr. Genet.* **2022**, *32*, 67–73. [CrossRef]

144. Ho, T.T.; Noble, M.; Tran, B.A.; Sunjic, K.; Gupta, S.V.; Turgeon, J.; Crutchley, R.D. Clinical Impact of the CYP2C19 Gene on Diazepam for the Management of Alcohol Withdrawal Syndrome. *J. Pers. Med.* **2023**, *13*, 285. [\[CrossRef\]](#)
145. Garmén, A.K.; Pettersson, N.; Unge, C.; Lindh, J.D. Extreme Duration of Diazepam-Associated Sedation in a Patient with Alcohol Delirium and CYP2C19 Polymorphisms. *J. Clin. Psychopharmacol.* **2015**, *35*, 475–477. [\[CrossRef\]](#)
146. Skryabin, V.Y.; Zastrozhin, M.; Torrado, M.; Grishina, E.; Ryzhikova, K.; Shipitsyn, V.; Galaktionova, T.; Sorokin, A.; Bryun, E.; Sychev, D. Effects of CYP2C19*17 Genetic Polymorphisms on the Steady-State Concentration of Diazepam in Patients with Alcohol Withdrawal Syndrome. *Hosp. Pharm.* **2021**, *56*, 592–596. [\[CrossRef\]](#)
147. Saruwatari, J.; Ogusu, N.; Shimomasuda, M.; Nakashima, H.; Seo, T.; Tanikawa, K.; Tsuda, Y.; Nishimura, M.; Nagata, R.; Yasui-Furukori, N.; et al. Effects of CYP2C19 and P450 Oxidoreductase Polymorphisms on the Population Pharmacokinetics of Clobazam and N-Desmethyloclobazam in Japanese Patients with Epilepsy. *Ther. Drug Monit.* **2014**, *36*, 302–309. [\[CrossRef\]](#)
148. Hashi, S.; Yano, I.; Shibata, M.; Masuda, S.; Kinoshita, M.; Matsumoto, R.; Ikeda, A.; Takahashi, R.; Matsubara, K. Effect of CYP2C19 Polymorphisms on the Clinical Outcome of Low-Dose Clobazam Therapy in Japanese Patients with Epilepsy. *Eur. J. Clin. Pharmacol.* **2015**, *71*, 51–58. [\[CrossRef\]](#)
149. Boels, D.; Chhun, S.; Meyer, G.; Lelièvre, B.; Souday, V. Clinical Consequences Related to a Defective Elimination of Clobazam Caused by Homozygous Mutated CYP2C19 Allele. *Clin. Toxicol.* **2019**, *57*, 743–747. [\[CrossRef\]](#)
150. Hamilton, K.E.; Shelton, C.M.; Wheless, J.; Phelps, S.J. Persistent Hypersomnolence Following Clobazam in a Child with Epilepsy and Undiagnosed CYP2C19 Polymorphism. *J. Pediatr. Pharmacol. Ther.* **2020**, *25*, 320–327. [\[CrossRef\]](#)
151. Spina, E.; de Leon, J. Clinical Applications of CYP Genotyping in Psychiatry. *J. Neural Transm.* **2015**, *122*, 5–28. [\[CrossRef\]](#)
152. Tolle-Sander, S. Midazolam Exhibits Characteristics of a Highly Permeable P-Glycoprotein Substrate. *Pharm. Res.* **2003**, *20*, 757–764. [\[CrossRef\]](#)
153. Venkatakrishnan, K.; Gibbs, M.A. CYP3A5 Polymorphism and Alprazolam Pharmacokinetics/Pharmacodynamics. *Clin. Pharmacol. Ther.* **2006**, *80*, 719–720. [\[CrossRef\]](#) [\[PubMed\]](#)
154. Park, J.; Kim, K.; Park, P.; Lee, O.; Kang, D.; Shon, J.; Liu, K.; Shin, J. Effect of CYP3A5*3 Genotype on the Pharmacokinetics and Pharmacodynamics of Alprazolam in Healthy Subjects. *Clin. Pharmacol. Ther.* **2006**, *79*, 590–599. [\[CrossRef\]](#) [\[PubMed\]](#)
155. Elens, L.; van Gelder, T.; Hesselink, D.A.; Haufroid, V.; van Schaik, R.H.N. CYP3A4*22: Promising Newly Identified CYP3A4 Variant Allele for Personalizing Pharmacotherapy. *Pharmacogenomics* **2013**, *14*, 47–62. [\[CrossRef\]](#) [\[PubMed\]](#)
156. Mulder, T.A.M.; van Eerden, R.A.G.; de With, M.; Elens, L.; Hesselink, D.A.; Matic, M.; Bins, S.; Mathijssen, R.H.J.; van Schaik, R.H.N. CYP3A4*22 Genotyping in Clinical Practice: Ready for Implementation? *Front. Genet.* **2021**, *12*, 711943. [\[CrossRef\]](#)
157. Fukasawa, T.; Suzuki, A.; Otani, K. Effects of Genetic Polymorphism of Cytochrome P450 Enzymes on the Pharmacokinetics of Benzodiazepines. *J. Clin. Pharm. Ther.* **2007**, *32*, 333–341. [\[CrossRef\]](#)
158. Zastrozhin, M.S.; Skryabin, V.Y.; Smirnov, V.V.; Petukhov, A.E.; Pankratenko, E.P.; Zastrozhina, A.K.; Grishina, E.A.; Ryzhikova, K.A.; Bure, I.V.; Golovinskii, P.A.; et al. Effects of Plasma Concentration of Micro-RNA Mir-27b and CYP3A4*22 on Equilibrium Concentration of Alprazolam in Patients with Anxiety Disorders Comorbid with Alcohol Use Disorder. *Gene* **2020**, *739*, 144513. [\[CrossRef\]](#)
159. Zubiaur, P.; Abad-Santos, F. Use of Pharmacogenetics for Benzodiazepine Prescription: State of the Art and Expectations. *Pharmacogenomics* **2022**, *23*, 949–952. [\[CrossRef\]](#)
160. Engin, E. GABA_A Receptor Subtypes and Benzodiazepine Use, Misuse, and Abuse. *Front. Psychiatry* **2022**, *13*, 1060949. [\[CrossRef\]](#)
161. Park, J.Y.; Kim, B.J.; Lee, S.W.; Kang, H.; Kim, J.W.; Jang, I.-J.; Kim, J.G. Influence of Midazolam-Related Genetic Polymorphism on Conscious Sedation during Upper Gastrointestinal Endoscopy in a Korean Population. *Sci. Rep.* **2019**, *9*, 16001. [\[CrossRef\]](#)
162. Byon, H.-J.; Park, K.-S.; Park, Y.-H.; Kim, J.-T.; Jung, C.-W.; Kim, H.-S. The Influence of DNA Polymorphism of Multidrug Resistant 1 (MDR1) on the Effect of Midazolam Pretreatment in Children. *Korean J. Anesthesiol.* **2012**, *62*, 332–336. [\[CrossRef\]](#)
163. Flores-Pérez, C.; Flores-Pérez, J.; de Jesús Castillejos López, M.; Chávez-Pacheco, J.L.; Tejada-Gutiérrez, K.M.; Aquino-Gálvez, A.; Torres-Espindola, L.M. Sex and Age Influence on Association of CYP450 Polymorphism with Midazolam Levels in Critically Ill Children. *Diagnostics* **2022**, *12*, 2797. [\[CrossRef\]](#)
164. Ghit, A.; Assal, D.; Al-Shami, A.S.; Hussein, D.E.E. GABA_A Receptors: Structure, Function, Pharmacology, and Related Disorders. *J. Genet. Eng. Biotechnol.* **2021**, *19*, 123. [\[CrossRef\]](#)
165. Chen, X.; Broeyer, F.; Kam, M.; Baas, J.; Cohen, A.; Gerven, J. Pharmacodynamic Response Profiles of Anxiolytic and Sedative Drugs: Pharmacodynamics of Anxiolytic and Sedative Drugs. *Br. J. Clin. Pharmacol.* **2017**, *83*, 1028–1038. [\[CrossRef\]](#)
166. Kelly, M.D.; Smith, A.; Banks, G.; Wingrove, P.; Whiting, P.W.; Attack, J.; Seabrook, G.R.; Maubach, K.A. Role of the Histidine Residue at Position 105 in the Human Alpha 5 Containing GABA(A) Receptor on the Affinity and Efficacy of Benzodiazepine Site Ligands: BZ Pharmacology at Mutant GABAA receptors. *Br. J. Pharmacol.* **2002**, *135*, 248–256. [\[CrossRef\]](#)
167. Petrou, S.; Reid, C.A. The GABA_Aγ2(R43Q) Mouse Model of Human Genetic Epilepsy. In *Jasper's Basic Mechanisms of the Epilepsies*, 4th ed.; Noebels, J.L., Avoli, M., Rogawski, M.A., Olsen, R.W., Delgado-Escueta, A.V., Eds.; National Center for Biotechnology Information: Bethesda, MD, USA, 2012; pp. 731–739.
168. Smith, K.S.; Rudolph, U. Anxiety and Depression: Mouse Genetics and Pharmacological Approaches to the Role of GABA(A) Receptor Subtypes. *Neuropharmacology* **2012**, *62*, 54–62. [\[CrossRef\]](#)
169. Günther, U.; Benson, J.; Benke, D.; Fritschy, J.M.; Reyes, G.; Knoflach, F.; Crestani, F.; Aguzzi, A.; Arigoni, M.; Lang, Y.; et al. Benzodiazepine-Insensitive Mice Generated by Targeted Disruption of the Gamma 2 Subunit Gene of Gamma-Aminobutyric Acid Type A Receptors. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 7749–7753. [\[CrossRef\]](#)

170. Chandra, D.; Korpi, E.R.; Miralles, C.P.; De Blas, A.L.; Homanics, G.E. GABA_A Receptor Gamma 2 Subunit Knockdown Mice Have Enhanced Anxiety-like Behavior but Unaltered Hypnotic Response to Benzodiazepines. *BMC Neurosci.* **2005**, *6*, 30. [\[CrossRef\]](#)
171. Uygun, D.S.; Ye, Z.; Zecharia, A.Y.; Harding, E.C.; Yu, X.; Yustos, R.; Vyssotski, A.L.; Brickley, S.G.; Franks, N.P.; Wisden, W. Bottom-up versus Top-down Induction of Sleep by Zolpidem Acting on Histaminergic and Neocortex Neurons. *J. Neurosci.* **2016**, *36*, 11171–11184. [\[CrossRef\]](#)
172. Stephens, D.N.; King, S.L.; Lambert, J.J.; Belelli, D.; Duka, T. GABA_A Receptor Subtype Involvement in Addictive Behaviour: GABA_A Receptor Subtypes and Addiction. *Genes Brain Behav.* **2017**, *16*, 149–184. [\[CrossRef\]](#)
173. Lind, P.A.; Macgregor, S.; Agrawal, A.; Montgomery, G.W.; Heath, A.C.; Martin, N.G.; Whitfield, J.B. The Role of GABRA2 in Alcohol Dependence, Smoking, and Illicit Drug Use in an Australian Population Sample. *Alcohol. Clin. Exp. Res.* **2008**, *32*, 1721–1731. [\[CrossRef\]](#)
174. Strac, D.S.; Erjavec, G.N.; Perkovic, M.N.; Sviglin, K.N.; Borovecki, F.; Pivac, N. Association of GABA_A receptor $\alpha 2$ subunit gene (GABRA2) with alcohol dependence-related aggressive behavior. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2015**, *63*, 119–125. [\[CrossRef\]](#) [\[PubMed\]](#)
175. Engin, E.; Liu, J.; Rudolph, U. A2-Containing GABA(A) Receptors: A Target for the Development of Novel Treatment Strategies for CNS Disorders. *Pharmacol. Ther.* **2012**, *136*, 142–152. [\[CrossRef\]](#) [\[PubMed\]](#)
176. Tsai, J.-H.; Yang, P.; Lin, H.-H.; Cheng, K.-H.; Yang, Y.-H.; Wu, M.-T.; Chen, C.-C. Association between GABA(A) Receptor Subunit Gene Cluster and Zolpidem-Induced Complex Sleep Behaviors in Han Chinese. *Sleep* **2013**, *36*, 197–202. [\[CrossRef\]](#) [\[PubMed\]](#)
177. Choi, Y.-J.; Lee, S.Y.; Yang, K.-S.; Park, J.-Y.; Yoon, S.Z.; Yoon, S.M. Polymorphism Rs4263535 in GABRA1 Intron 4 Was Related to Deeper Sedation by Intravenous Midazolam. *J. Int. Med. Res.* **2015**, *43*, 686–698. [\[CrossRef\]](#) [\[PubMed\]](#)
178. Bowser, D.N.; Wagner, D.A.; Czajkowski, C.; Cromer, B.A.; Parker, M.W.; Wallace, R.H.; Harkin, L.A.; Mulley, J.C.; Marini, C.; Berkovic, S.F.; et al. Altered Kinetics and Benzodiazepine Sensitivity of a GABA_A Receptor Subunit Mutation [Gamma 2(R43Q)] Found in Human Epilepsy. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 15170–15175. [\[CrossRef\]](#)
179. Chakraborty, A.; Dey, S.; Kumar, K.; Dixit, A.B.; Tripathi, M.; Sharma, M.C.; Chandra, P.S.; Banerjee, J. Novel Variants in GABA_A Receptor Subunits: A Possible Association with Benzodiazepine Resistance in Patients with Drug-Resistant Epilepsy. *Epilepsy Res.* **2023**, *189*, 107056. [\[CrossRef\]](#)
180. Engelmann, J.; Zillich, L.; Frank, J.; Wagner, S.; Cetin, M.; Herzog, D.P.; Müller, M.B.; Tadic, A.; Foo, J.C.; Sirignano, L.; et al. Epigenetic Signatures in Antidepressant Treatment Response: A Methyloome-Wide Association Study in the EMC Trial. *Transl. Psychiatry* **2022**, *12*, 268. [\[CrossRef\]](#)
181. Stefanska, B.; MacEwan, D.J. Epigenetics and Pharmacology. *Br. J. Pharmacol.* **2015**, *172*, 2701–2704. [\[CrossRef\]](#)
182. Takeuchi, N.; Nonen, S.; Kato, M.; Wakeno, M.; Takekita, Y.; Kinoshita, T.; Kugawa, F. Therapeutic Response to Paroxetine in Major Depressive Disorder Predicted by DNA Methylation. *Neuropsychobiology* **2017**, *75*, 81–88. [\[CrossRef\]](#)
183. Powell, T.R.; Smith, R.G.; Hackinger, S.; Schalkwyk, L.C.; Uher, R.; McGuffin, P.; Mill, J.; Tansey, K.E. DNA methylation in interleukin-11 predicts clinical response to antidepressants in GENDEP. *Transl. Psychiatry* **2013**, *3*, e300. [\[CrossRef\]](#)
184. Duclot, F.; Kabbaj, M. Epigenetic Mechanisms Underlying the Role of Brain-Derived Neurotrophic Factor in Depression and Response to Antidepressants. *J. Exp. Biol.* **2015**, *218*, 21–31. [\[CrossRef\]](#)
185. Lopez, J.P.; Mamdani, F.; Labonte, B.; Beaulieu, M.-M.; Yang, J.P.; Berlim, M.T.; Ernst, C.; Turecki, G. Epigenetic Regulation of BDNF Expression according to Antidepressant Response. *Mol. Psychiatry* **2013**, *18*, 398–399. [\[CrossRef\]](#)
186. Wang, P.; Zhang, C.; Lv, Q.; Bao, C.; Sun, H.; Ma, G.; Fang, Y.; Yi, Z.; Cai, W. Association of DNA Methylation in BDNF with Escitalopram Treatment Response in Depressed Chinese Han Patients. *Eur. J. Clin. Pharmacol.* **2018**, *74*, 1011–1020. [\[CrossRef\]](#)
187. Tadić, A.; Wagner, S.; Schlicht, K.F.; Peetz, D.; Borysenko, L.; Dreimüller, N.; Hiemke, C.; Lieb, K. The early non-increase of serum BDNF predicts failure of antidepressant treatment in patients with major depression: A pilot study. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2011**, *35*, 415–420. [\[CrossRef\]](#)
188. Gassen, N.C.; Fries, G.R.; Zannas, A.S.; Hartmann, J.; Zschocke, J.; Hafner, K.; Carrillo-Roa, T.; Steinbacher, J.; Preißinger, S.N.; Hoeijmakers, L.; et al. Chaperoning epigenetics: FKBP51 decreases the activity of DNMT1 and mediates epigenetic effects of the antidepressant paroxetine. *Sci. Signal.* **2015**, *8*, ra119. [\[CrossRef\]](#)
189. Zannas, A.; Wiechmann, T.; Gassen, N.; Binder, E.B. Gene–Stress–Epigenetic Regulation of FKBP5: Clinical and Translational Implications. *Neuropsychopharmacology* **2016**, *41*, 261–274. [\[CrossRef\]](#)
190. Mourtzi, N.; Sertedaki, A.; Charmandari, E. Glucocorticoid Signaling and Epigenetic Alterations in Stress-Related Disorders. *Int. J. Mol. Sci.* **2021**, *22*, 5964. [\[CrossRef\]](#)
191. Anacker, C.; Zunszain, P.A.; Carvalho, L.A.; Pariante, C.M. The glucocorticoid receptor: Pivot of depression and of antidepressant treatment? *Psychoneuroendocrinology* **2011**, *36*, 415–425. [\[CrossRef\]](#)
192. Elliott, E.; Ezra-Nevo, G.; Regev, L.; Neufeld-Cohen, A.; Chen, A. Resilience to social stress coincides with functional DNA methylation of the Crf gene in adult mice. *Nat. Neurosci.* **2010**, *13*, 1351–1353. [\[CrossRef\]](#)
193. Schiele, M.A.; Zwanzger, P.; Schwarte, K.; Arolt, V.; Baune, B.T.; Domschke, K. Serotonin Transporter Gene Promoter Hypomethylation as a Predictor of Antidepressant Treatment Response in Major Depression—A Replication Study. *Int. J. Neuropsychopharmacol.* **2020**, *24*, 191–199. [\[CrossRef\]](#)
194. Domschke, K.; Tidow, N.; Schwarte, K.; Deckert, J.; Lesch, K.-P.; Arolt, V.; Zwanzger, P.; Baune, B.T. Serotonin Transporter Gene Hypomethylation Predicts Impaired Antidepressant Treatment Response. *Int. J. Neuropsychopharmacol.* **2014**, *17*, 1167–1176. [\[CrossRef\]](#) [\[PubMed\]](#)

195. Lisoway, A.; Zai, C.; Tiwari, A.K.; Harripaul, R.; Freeman, N.; French, L.; Kaminsky, Z.; Kennedy, J.L. DNA methylation and 5-HTTLPR genotype of the serotonin transporter gene (SLC6A4) in antidepressant treatment response of major depressive disorder. *Eur. Neuropsychopharmacol.* **2019**, *29*, S1001–S1002. [[CrossRef](#)]
196. Ziegler, C.; Wolf, C.; Schiele, M.A.; Feric Bojic, E.; Kucukalic, S.; Sabic Dzananovic, E.; Goci Uka, A.; Hoxha, B.; Haxhibeqiri, V.; Haxhibeqiri, S.; et al. Monoamine Oxidase a Gene Methylation and Its Role in Posttraumatic Stress Disorder: First Evidence from the South Eastern Europe (SEE)-PTSD Study. *Int. J. Neuropsychopharmacol.* **2017**, *21*, 423–432. [[CrossRef](#)] [[PubMed](#)]
197. Domschke, K.; Tidow, N.; Schwarte, K.; Ziegler, C.; Lesch, K.-P.; Deckert, J.; Arolt, V.; Zwanzger, P.; Baune, B.T. Pharmacoeigenetics of Depression: No Major Influence of MAO-A DNA Methylation on Treatment Response. *J. Neural Transm.* **2014**, *122*, 99–108. [[CrossRef](#)] [[PubMed](#)]
198. Checknita, D.; Ekström, T.J.; Comasco, E.; Nilsson, K.W.; Tiihonen, J.; Hodgins, S. Associations of Monoamine Oxidase a Gene First Exon Methylation with Sexual Abuse and Current Depression in Women. *J. Neural Transm.* **2018**, *125*, 1053–1064. [[CrossRef](#)]
199. Tsankova, N.M.; Berton, O.; Renthal, W.; Kumar, A.; Neve, R.L.; Nestler, E.J. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat. Neurosci.* **2006**, *9*, 519–525. [[CrossRef](#)]
200. Chen, E.S.; Ernst, C.; Turecki, G. The epigenetic effects of antidepressant treatment on human prefrontal cortex BDNF expression. *Int. J. Neuropsychopharmacol.* **2011**, *14*, 427–429. [[CrossRef](#)]
201. Belzeaux, R.; Lin, R.; Ju, C.; Chay, M.A.; Fiori, L.M.; Lutz, P.E.; Turecki, G. Transcriptomic and epigenomic biomarkers of antidepressant response. *J. Affect. Disord.* **2018**, *233*, 36–44. [[CrossRef](#)]
202. Fiori, L.M.; Lin, R.; Ju, C.; Belzeaux, R.; Turecki, G. Using Epigenetic Tools to Investigate Antidepressant Response. *Prog. Mol. Biol. Transl. Sci.* **2018**, *158*, 255–272. [[CrossRef](#)]
203. Fiori, L.M.; Lopez, J.P.; Richard-Devantoy, S.; Berlim, M.; Chachamovich, E.; Jollant, F.; Foster, J.; Rotzinger, S.; Kennedy, S.H.; Turecki, G. Investigation of miR-1202, miR-135a, and miR-16 in Major Depressive Disorder and Antidepressant Response. *Int. J. Neuropsychopharmacol.* **2017**, *20*, 619–623. [[CrossRef](#)]
204. Lopez, J.P.; Fiori, L.M.; Cruceanu, C.; Lin, R.; Labonte, B.; Cates, H.M.; Heller, E.A.; Vialou, V.; Ku, S.M.; Gerald, C.; et al. MicroRNAs 146a/b-5 and 425-3p and 24-3p are markers of antidepressant response and regulate MAPK/Wnt-system genes. *Nat. Commun.* **2017**, *8*, 15497. [[CrossRef](#)]
205. Auta, J.; Gatta, E.; Davis, J.M.; Pandey, S.C.; Guidotti, A. Potential Role for Histone Deacetylation in Chronic Diazepam-Induced Downregulation of α 1-GABAA Receptor Subunit Expression. *Pharmacol. Res. Perspect.* **2018**, *6*, e00416. [[CrossRef](#)]
206. Pathak, S.; Gupta, G.; Gilhotra, R.M. The Role of Diazepam in Epigenetics: From the Molecular Level to Clinical Implications. *Adv. Mind-Body Med.* **2021**, *35*, 25–33.
207. Peedicayil, J. The Potential Role of Epigenetic Drugs in the Treatment of Anxiety Disorders. *Neuropsychiatr. Dis. Treat.* **2020**, *16*, 597–606. [[CrossRef](#)]
208. Swen, J.J.; van der Wouden, C.H.; Manson, L.E.; Abdullah-Koolmees, H.; Blagec, K.; Blagus, T.; Böhringer, S.; Cambon-Thomsen, A.; Cecchin, E.; Cheung, K.C.; et al. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: An open-label, multicentre, controlled, cluster-randomised crossover implementation study. *Lancet* **2023**, *401*, 347–356. [[CrossRef](#)]

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