While antidepressant drugs are widely prescribed to treat depression and anxiety disorders, only one-third of patients will respond to antidepressant treatment and only one-third of patients experience a full remission of symptoms. The identification of genetic biomarkers that predict antidepressant-treatment response can improve current clinical practice. This is an emerging field known as pharmacogenetics, which comprises of genetic studies on both the pharmacokinetics and pharmacodynamics of treatment response. Recent studies on antidepressant-treatment response have focused on both aspects of pharmacogenetics research, identifying new candidate genes that may predict better treatment response for patients. This paper reviews recent findings on the pharmacogenetics of antidepressant drugs and future clinical applications. Ultimately, these studies should lead to the use of genetic screening to guide the use of antidepressants in clinical practice.

KEYWORDS: antidepressants, anxiety disorders, bipolar disorder, depression, pharmacogenetics, treatment response

While antidepressants are widely prescribed to treat depression and anxiety disorders, only one-third of drug-treated patients exhibit a beneficial therapeutic response [1]. Response and tolerability to medication are highly variable, with some patients responding to one treatment but not another. There are several potential explanations for these poor drug-response rates, including clinical heterogeneity and diagnostic uncertainty, environmental and social factors, and genetics factors. If it were possible to isolate variables that could predict a greater likelihood of positive response to the medication, it would be possible to use the medication with greater certainty and efficiency. This forms the basis of much of the contemporary effort in the field of personalized medicine. Thus, a critical question remains: for which patients will antidepressant therapy have the greatest benefit?

Early studies suggested that specific clinical phenotypes, such as melancholic or anxious depression, might predict differential responses to antidepressants; however, the clinical phenotypes were often variable and difficult to translate into clinical practice [2]. Pharmacogenetics, which is the identification and development of genetic biomarkers that predict therapeutic response and the risk of side effects, takes a different approach to ultimately help the practitioner in choosing effective and safe treatment for patients suffering from psychiatric disorders.

The discovery of monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) in the 1950s spurred on research into developing new antidepressant medications with a better safety and tolerability profile [3]. Following a serotonin (5-HT) hypothesis of depression, the selective 5-HT reuptake inhibitors (SSRIs) were discovered to be more effective antidepressants, with their improved safety and tolerability profile [3]. More recently, dual-acting antidepressants such as 5-HT–norepinephrine (NE) reuptake inhibitors (SNRIs) have presented clinicians with a wider range of antidepressants that are effective, safe and easy to prescribe [3]. Currently, SSRIs are usually the first line of treatment, with dual-acting TCAs and SNRIs used as second-line treatment [3].

There has been a recent increase in the use of antidepressants across the USA, particularly for major depressive disorder (MDD), but also for other disorders such as anxiety, bipolar disorder and adjustment-related disorders [4]. Current clinical guidelines suggest antidepressants, particularly SSRIs, as treatment for anxiety disorders, chronic pain and bipolar depression [5–8]. With MDD affecting 10–15% of the population and anxiety disorders affecting approximately 25% of the population [9,10], a large percentage of the population use antidepressants for pharmacotherapy. However, response and tolerability to medication are highly variable, with some patients responding to one treatment but not another. Pharmacogenetics research attempts to use genetic factors to predict some of the variability in treatment response. Early studies showed a
correlation between relatives with depression in antidepressant-treatment responses [14]. One small study found pairs of related people with depression responded equally well to antidepressants [12], while another study found that depressed probands and depressed relatives had favorable responses to the same class of antidepressants [13]. Such studies indicated a role for genetics in antidepressant-treatment outcome, spurring on pharmacogenetic research in this field. This article will review current pharmacogenetic studies of antidepressants in mood and anxiety disorders and discuss the clinical future of the current research.

**Pharmacogenetics of antidepressant drugs in depression**

- Genetics of antidepressant drug pharmacokinetics

Pharmacogenetic studies are often subdivided into studies concerned with pharmacokinetics and those concerned with pharmacodynamics of antidepressant medications. Pharmacokinetics refers to the mechanisms controlling the absorption, distribution, metabolism and excretion of a drug. Here we discuss two systems that have been studied with respect to the influence of genetic traits on the pharmacokinetics of antidepressants.

**CYP450**

The variation in toxicity and tolerability of antidepressant drugs, particularly TCAs, is in part caused by differences in the activity in the CYP450 enzymes, by which these antidepressants are metabolized. CYP450 enzymes are drug-metabolizing hemoproteins present in multiple tissues, predominantly in the liver. More than 63 CYP450 genes encode over 50 enzymes; however, the main P450 enzymes involved in antidepressant drug metabolism are CYP2D6, CYP2C19, CYP3A4 and CYP1A2 [14]. The CYP2D6 system has been studied extensively and is the best characterized to date [15]. Early experiments with debrisoquine and nortriptyline documented that patients fall into different categories: poor, intermediate, extensive and ultra-rapid metabolizers. Cloning and characterization of the CYP2D6 gene led to the identification of over 75 CYP2D6 alleles, which determine metabolizer status [16,17]. Studies with nortriptyline showed that patients with no or only one functional copy of the gene reached therapeutic plasma levels with just starting doses, while high–normal doses would result in potentially toxic levels; on the other hand, patients with two to four copies required high–normal doses just to reach therapeutic plasma levels [18]. Similar CYP2D6-allele/plasma level concentration correlations have been reported for SSRIs and SNRIs, although more recent studies show these results are less conclusive (see below) [19–21]. A recent study also confirmed an association between CYP2D6-allele/plasma level concentrations of venlafaxine, although it did not find any such association for desvenlafaxine [22].

In addition to the CYP2D6 gene, variations in the CYP2C19 gene have also been shown to be associated with antidepressant metabolizer status. Different alleles of the CYP2C19 gene allow for the classification of poor, extensive and ultrarapid metabolizers, similar to the CYP2D6 alleles [23–25]. In addition, CYP2C19 alleles have been shown to affect escitalopram metabolism [26,27], including a positive association in the European consortium project Genome-Based Therapeutic Drugs for Depression (GENDEP) [28]. Furthermore, the side-effect profile of amitriptyline appears to be dependent on a combination of alleles coding for CYP2D6 and CYP2C19 [29].

Knowledge of the genetic metabolizer status of a patient may be helpful to the clinician in order to avoid potential side effects and to reach therapeutic levels faster. However, the well-documented correlations between CYP alleles and plasma concentrations of antidepressants do not translate well to differences in clinical response to the same antidepressants. Some small studies have found a significant association between CYP2D6 genotypes and antidepressant-treatment response [30,31]; a recent study combined samples from four studies and found an association between CYP2D6 alleles and treatment response to venlafaxine [32]. However, other studies have found no such association for either CYP2D6 or CYP2C19 alleles [33,34]. Most importantly, an analysis in the large STAR*D sample did not find an association with either CYP2D6 or CYP2C19 and response to citalopram [35]. This analysis did indicate a possible association between CYP2C19 genotypes and tolerance to citalopram; however, more studies are needed to fully elucidate this effect. These results suggest that there may be no relationship between metabolizer status and antidepressant clinical response; therefore, the efficacy of using these genotypes in clinical practice is limited.

**P-glycoprotein**

P-glycoprotein is an ATP-binding transporter protein that is involved in the blood–brain barrier. It is a plasma membrane transporter
encoded by the *ABCB1* gene. Animal studies have shown that most antidepressants are substrates of this transporter, and are thus removed from the brain due to P-glycoprotein activity \[36–40\]. Numerous studies have shown that variations in the *ABCB1* gene are associated with plasma levels of antidepressants and treatment response to antidepressants \[38,41–46\]. However, other studies have found no association with the same variants in antidepressant-treatment outcome \[35,47–51\]. Therefore, these findings require careful replication in larger treatment trials before *ABCB1* genotypes are used to prescribe antidepressants in the clinical practice.

### Genetics of antidepressant drug pharmacodynamics

The term pharmacodynamics is used to describe the effects a drug has on the body. Pharmacodynamics includes interactions of a drug with receptors, transporters and downstream targets. Although the primary mechanism of action for antidepressants is thought to involve predominantly monoaminergic neurotransmitter systems, the exact mechanisms by which antidepressant medications work remain unknown. Most pharmacogenetic studies in MDD to date have focused on candidate genes involved in monoaminergic neurotransmission. Here we highlight the pharmacodynamic candidate genes most commonly studied in antidepressant-treatment outcome \(\text{Table 1}\).

#### Monoamine metabolic enzymes

The three main metabolic enzymes involved in the monoamine pathways that have been implicated in depression are tryptophan hydroxylase (TPH), monoamine oxidase A (MAOA) and catechol-O-methyl transferase (COMT).

- **TPH** is involved in 5-HT biosynthesis. It has two isoforms: TPH1 and TPH2, the genes for both of which have been implicated in the pharmacogenetics of antidepressants. TPH1 is the main isoform in the pineal gland, while TPH2 is more widely expressed in the brain, including the striatum, hippocampus and mesencephalic tegmentum \[52\]. A functional SNP in the *TPHI* gene, rs1800532, has been associated with a worse response to SSRIs in Caucasians \[53–56\], although studies in other populations reported no association \[57–61\]. A meta-analysis of this SNP and antidepressant treatment efficacy showed an association with the C/C genotype and remission rate; however, this analysis did not include more recent pharmacogenetic studies \[62\].

- **MAOA** is a major degrading enzyme in the pathways of 5-HT, dopamine (DA) and NE. One polymorphism in the *MAOA* gene, a variable number tandem repeat (VNTR) upstream of the gene, has been shown to affect the transcription efficiency of *MAOA* \[67\]. This VNTR has also been implicated in pharmacogenetic studies of antidepressant medications in MDD. One study found a positive association with the long form of the VNTR and worse antidepressant-treatment response \[68\]. Some studies also found an association with the VNTR, but only in females \[69,70\], while others did not find significant associations \[71–73\]. Yoshida *et al.* reported that the *MAOA* VNTR might also play a role in SSRI-induced nausea, although this finding is yet to be replicated \[74\]. Another variant in the *MAOA* gene that has been associated with antidepressant-treatment outcome is rs6323, which is a functional coding SNP associated with decreased MAOA activity \[65,75,76\].

- **COMT** is involved in the catabolic pathway of both DA and NE, as well as indirectly in the 5-HT pathway. Several studies have investigated the role of variants in the *COMT* gene and antidepressant-treatment response. Perlis *et al.* investigated the role of 19 candidate genes in response to duloxetine and found the most significant associations for variants rs165599, rs165774 and rs174696 \(\text{Table 1}\) \[77\]. The authors found no significant association with the

Variation in the *TPH2* gene has also been associated with antidepressant-treatment response. Zhang *et al.* found an association between a nonsynonymous coding SNP, Arg441His, and poor-SSRI treatment response \[63\]. They also showed that this SNP was functional, resulting in 80% loss of function in *TPH2*. Other studies found an association between the intronic SNP rs10897346 and treatment response to various antidepressants in MDD \[64\]. The rs10897346 SNP is fully linked to the functional SNP Pro312Pro in the *TPH2* gene, which is known to affect expression levels of TPH2. Other SNPs with no known effect on function have also been associated with antidepressant-treatment response \(\text{Table 1}\) \[64–66\]. However, Uher *et al.* found no association between any *TPH2* SNPs and antidepressant-treatment response in the GENDEP sample \[60\]. Another study found no association between the *TPH2* rs1386494 SNP and response to SSRIs \[61\]. The pharmacogenetic role *TPH2* in MDD thus remains to be determined.

**Pharmacodynamics** includes interactions of a drug with receptors, transporters and downstream targets. Although the primary mechanism of action for antidepressants is thought to involve predominantly monoaminergic neurotransmitter systems, the exact mechanisms by which antidepressant medications work remain unknown. Most pharmacogenetic studies in MDD to date have focused on candidate genes involved in monoaminergic neurotransmission. Here we highlight the pharmacodynamic candidate genes most commonly studied in antidepressant-treatment outcome \(\text{Table 1}\).
## Table 1. Summary table of all pharmacodynamics candidate gene studies in major depressive disorder, showing both positive and negative associations with antidepressant-treatment outcome for each variation.

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<tbody>
<tr>
<td><strong>Monoamine metabolic enzymes</strong></td>
<td><strong>TPH1</strong></td>
<td>SNP rs1800532 (A218C)</td>
<td>Affects transcription, A allele associated with decreased 5-HT synthesis</td>
<td>Serretti et al. [53], Serretti et al. [54], Ham et al. [55], Viikki et al. [56]</td>
<td>Ham et al. [57], Hong et al. [58], Kato et al. [59], Uher et al. [60], Illi et al. [61]</td>
<td>Positive association with remission rate in meta-analysis Kato and Serretti [62]</td>
</tr>
<tr>
<td><strong>TPH2</strong></td>
<td>SNP Arg441His</td>
<td>Loss of function of TPH2</td>
<td>Zhang et al. [63]</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SNP rs10897346</td>
<td>Linked to functional SNP Pro312Pro</td>
<td>Tzvetkov et al. [64]</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SNPs rs1487278, rs1843809, rs1386492, rs1487276 and rs2171363</td>
<td>Intrinsic; no known function</td>
<td>Tzvetkov et al. [64], Peters et al. [65], Tsai et al. [66]</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SNP rs1386494</td>
<td>Intrinsic</td>
<td>Illi et al. [61]</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td><strong>MAOA</strong></td>
<td><strong>VNTR</strong></td>
<td>Affects transcription efficiency</td>
<td>Tzeng et al. [68], Domschke et al. [69], Yu et al. [70], Yoshida et al. [73]</td>
<td>Serretti et al. [71], Muller et al. [72], Yoshida et al. [74]</td>
<td>Association seen mainly in females Domschke et al. [69] Yu et al. [70]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SNP rs6323</td>
<td>Associated with decreased MAOA activity</td>
<td>Leuchter et al. [75], Tadic et al. [76]</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td><strong>COMT</strong></td>
<td>SNPs rs165599, rs165774 and rs174696</td>
<td>3’-UTR, intronic, intronic</td>
<td>Perlis et al. [77]</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SNP rs4680 Val158Met</td>
<td>Changes enzymatic levels of COMT</td>
<td>Benedetti et al. [79], Benedetti et al. [80], Leuchter et al. [75], Szegedi et al. [81], Tsai et al. [82], Baune et al. [83], Yoshida et al. [84]</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td><strong>Serotonin system</strong></td>
<td><strong>SLC6A4</strong></td>
<td>5-HTTLPR</td>
<td>Long form results in higher 5-HT reuptake</td>
<td>Smeraldi et al. [89], Zanardi et al. [90], Pollock et al. [91], Zanardi et al. [92], Joyce et al. [93], Perlis et al. [94], Arias et al. [95], Durham et al. [96], Serretti et al. [97], Wilkie et al. [98], Mrazek et al. [99], Huezo-Diaz et al. [100], Smits et al. [101], Kronenberg et al. [102], Murphy et al. [103], Yoshida et al. [111], Kim et al. [108,112], Kang et al. [113]</td>
<td>Serretti et al. [71], Minov et al. [105], Kirchheimer et al. [106], Dogan et al. [107], Ito et al. [109], Yoshida et al. [110,111]</td>
<td>Meta-analysis found no association with treatment response Taylor et al. [104]; possible gene–environment interaction Keers et al. [114] Mandelli et al. [115]</td>
</tr>
</tbody>
</table>

5-HT: Serotonin; BDNF: Brain-derived neurotrophic factor; COMT: Catechol-O-methyl transferase; GENDEP: Genome-Based Therapeutic Drugs for Depression; HPA: Hypothalamic–pituitary–adrenal; MAOA: Monoamine oxidase A; TESI: Treatment-emergent suicidal ideation; VNTR: Variable number tandem repeat.
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<tbody>
<tr>
<td>Serotonin system (cont.)</td>
<td>SLC6A4 (cont.)</td>
<td>SNP rs25531 (A/G)</td>
<td>Forms haplotype with 5-HTTLPR</td>
<td>Hu et al. [116], Kraft et al. [121], Serretti et al. [97]</td>
<td>Wilkie et al. [98]</td>
<td>In presence of G allele, L carriers associated with nonresponse</td>
</tr>
<tr>
<td>VNTR STin2</td>
<td>Intron 2</td>
<td>Peters et al. [65], Wilkie et al. [98], Yoshida et al. [111], Kim et al. [108], Kraft et al. [121], Smits et al. [123], Popp et al. [124]</td>
<td></td>
<td></td>
<td></td>
<td>Meta-analysis showed positive association with treatment outcome</td>
</tr>
<tr>
<td>5HTR1A</td>
<td>SNP rs6295</td>
<td>Associated with increased expression</td>
<td>Hong et al. [58], Arias et al. [127], Kato et al. [128], Parsey et al. [129], Serretti et al. [130], Lemonde et al. [131], Baune et al. [132]</td>
<td>Ili et al. [61], Lin et al. [133]</td>
<td></td>
<td>Meta-analysis showed significant association in Asian population</td>
</tr>
<tr>
<td>5HTR1B</td>
<td>Various SNPs</td>
<td>Xu et al. [137]</td>
<td></td>
<td></td>
<td>Associated with recent life stress</td>
<td></td>
</tr>
<tr>
<td>5HTR2A</td>
<td>SNPs rs6311 (102T/C), rs6313 (1438A/G) and rs6314</td>
<td>Coding</td>
<td>Wilkie et al. [98], Minov et al. [105], Choi et al. [138], Kato et al. [139], Cusin et al. [140], Kishi et al. [141], Murphy et al. [142], Suzuki et al. [143], Bishop et al. [144]</td>
<td>Ili et al. [61]</td>
<td></td>
<td>Meta-analysis of rs6313 found association with adverse events</td>
</tr>
<tr>
<td>5HTR3A</td>
<td>SNP C178T</td>
<td>Functional regulatory variant</td>
<td>Kato et al. [139]</td>
<td></td>
<td>Asian population</td>
<td></td>
</tr>
<tr>
<td>5HTR3B</td>
<td>Deletion 100–102 AAG del</td>
<td>Promoter</td>
<td>Kato et al. [139], Tanaka et al. [151]</td>
<td></td>
<td>Asian population</td>
<td></td>
</tr>
<tr>
<td>5HTR6</td>
<td>SNP rs1805054 (T267C)</td>
<td>Coding</td>
<td>Sugai et al. [152]</td>
<td></td>
<td>Associated with side-effect nausea</td>
<td></td>
</tr>
</tbody>
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</thead>
<tbody>
<tr>
<td>Dopamine system</td>
<td>DAT1</td>
<td>VNTR exon 15</td>
<td>Affects expression levels</td>
<td>Kirchheiner et al. [106]</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td>D5R2</td>
<td>Taq1A allele 1</td>
<td>Alternative splice isoform</td>
<td>Hedenmalm et al. [157]</td>
<td>–</td>
<td>Associated with antidepressant-induced extrapyramidal symptoms</td>
</tr>
<tr>
<td></td>
<td>D5R4</td>
<td>VNTR exon 3</td>
<td>Exonic</td>
<td>Garriock et al. [160]</td>
<td>Serretti et al. [158], Serretti et al. [159]</td>
<td>–</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>SLC6A2</td>
<td>SNP rs5569</td>
<td>Silent coding</td>
<td>Kim et al. [108]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>system</td>
<td></td>
<td>SNP T182C</td>
<td>Silent coding</td>
<td>Yoshida et al. [110]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SNPs rs36029 and rs1532701</td>
<td>Intrinsic</td>
<td>Uher et al. [60]</td>
<td>–</td>
<td>GENDEP-nominaly significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SNP rs5564</td>
<td>Intrinsic</td>
<td>Dong et al. [51]</td>
<td>–</td>
<td>Positive association (not after multiple testing correction)</td>
</tr>
<tr>
<td>ADRB1</td>
<td>SNP rs1801253 (Gly389Arg)</td>
<td>Enhancer region</td>
<td>Associated with enhanced coupling of receptor to G proteins</td>
<td>Baffa et al. [161]</td>
<td>–</td>
<td>Positive association</td>
</tr>
<tr>
<td>HPA axis/stress</td>
<td>CRHR1</td>
<td>SNP rs242941</td>
<td>Intrinsic</td>
<td>Liu et al. [164]</td>
<td>–</td>
<td>–</td>
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<tr>
<td>hormones</td>
<td></td>
<td>SNPs rs1876828 and rs242939</td>
<td>Intrinsic</td>
<td>Licinio et al. [165]</td>
<td>–</td>
<td>Haplotype associated with treatment response</td>
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<tr>
<td></td>
<td>CRHR2</td>
<td>SNP rs2270007</td>
<td>Intrinsic</td>
<td>Papiol et al. [166]</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td>NR3C1</td>
<td>SNPs ER22/23EK</td>
<td>Two linked nonsynonymous SNPs</td>
<td>van Rossum et al. [167]</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td></td>
<td>SNP BclI</td>
<td>Changes restriction enzyme site and is associated with hypersensitivity to glucocorticoids</td>
<td>van Rossum et al. [167], Brouwer et al. [168]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SNPs rs852977, rs10482633 and rs10052957</td>
<td>Intrinsic</td>
<td>Uher et al. [60]</td>
<td>–</td>
<td>GENDEP, nominal association</td>
</tr>
<tr>
<td>FKB5</td>
<td>SNP rs1360780</td>
<td>Intron 2; higher levels of protein</td>
<td>Binder et al. [169], Lekman et al. [170], Kircheiner et al. [171], Perroud et al. [175]</td>
<td>Sarginson et al. [45], Perlis et al. [77], Uher et al. [60], Papiol et al. [166], Tsai et al. [172]</td>
<td>–</td>
<td>Associated in multimarker analysis with GRIK4 and 5HT2A variants Horstmann et al. [174]; meta-analysis showed no association Zou et al. [173]</td>
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Pharmacogenetics of antidepressant drugs: current clinical practice & future directions

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<td>HPA axis/stress hormones</td>
<td>FKBP5 (cont.)</td>
<td>SNP rs3800373 and rs4713916</td>
<td>3’-UTR, intronic</td>
<td>Perlis et al. [77], Lekman et al. [79], Kirchheiner et al. [171], Brent et al. [176]</td>
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<td>Meta-analysis showed no association Zou et al. [173]</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Glutamatergic system</td>
<td>GRIK2</td>
<td>SNP rs2518224</td>
<td>Intrinsic</td>
<td>Laje et al. [182], Perlis et al. [183]</td>
<td>–</td>
<td>Associated with adverse events</td>
</tr>
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<td></td>
<td>GRIK4</td>
<td>SNP rs1954787</td>
<td>Intrinsic</td>
<td>Horstmann et al. [174], Paddock et al. [180], Laje et al. [181]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
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<td></td>
<td>SNP rs12800734</td>
<td>Intrinsic</td>
<td>Horstmann et al. [148]</td>
<td>–</td>
<td>Also interacts with variants in FKBP5 and 5HTR2A genes</td>
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<tr>
<td></td>
<td>GRIA1, GRIA3 and GRIN3A</td>
<td>Various</td>
<td>–</td>
<td>Paddock et al. [180], Laje et al. [182], Perlis et al. [183]</td>
<td>–</td>
<td>Associated with adverse events/side effects</td>
</tr>
<tr>
<td>Other systems</td>
<td>BDNF</td>
<td>SNP rs6265 (Val66Met)</td>
<td>Met allele changes secretion and localization of BDNF</td>
<td>Choi et al. [191], Yoshida et al. [192], Chi et al. [193], Perroud et al. [199]</td>
<td>Tsai et al. [194], Wilkie et al. [195], Gratacos et al. [196]</td>
<td>Meta-analysis found association with increased response rate Zou et al. [173]</td>
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<td></td>
<td>GNB3</td>
<td>SNP rs5443</td>
<td>Splice site variant that results in less active form of protein</td>
<td>Wilkie et al. [195], Zill et al. [201], Serretti et al. [202], Lee et al. [203]</td>
<td>Hong et al. [58], Kang et al. [205], Kato et al. [206]</td>
<td>Negative findings, mainly in Asian populations</td>
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<td></td>
<td>ACE</td>
<td>Indel</td>
<td>Higher plasma levels of ACE and substance P</td>
<td>Baghai et al. [210], Baghai et al. [211], Bondy et al. [212]</td>
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<td></td>
<td>CREB1</td>
<td>SNPs rs4675690 and rs7569963</td>
<td>3’-UTR</td>
<td>Perlis et al. [214]</td>
<td>–</td>
<td>Associated with TESI, only in men</td>
</tr>
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</table>

5-HT: Serotonin; BDNF: Brain-derived neurotrophic factor; COMT: Catechol-O-methyl transferase; GENDEP: Genome-Based Therapeutic Drugs for Depression; HPA: Hypothalamic–pituitary–adrenal; MAOA: Monoamine oxidase A; TESI: Treatment-emergent suicidal ideation; VNTR: Variable number tandem repeat.

Functional variant rs4680 (Val158Met), which is known to change enzymatic levels of COMT three- or four-fold [78]. However, other smaller studies have investigated the pharmacogenetic role of rs4680 in antidepressant treatment, with mixed results. Benedetti et al. found a positive association for treatment response to paroxetine and later reported a significant association to fluvoxamine treatment response in MDD [79,80]. Other studies supported this association with other antidepressant medications [75,81−83]. Yoshida et al. did not find an association between rs4680 and final therapeutic response to milnacipram [84], but noted an association between this variant and a faster therapeutic effect. Together, these studies document a possible role of the COMT gene and antidepressant-treatment response in MDD.
5-HT genes

Although the exact mechanism of action of antidepressants is unknown, most research focuses on the serotonergic pathway, particularly the 5-HT transporter (5-HTT) and the 5-HT receptors. One of the most widely studied genes in pharmacogenetic studies of antidepressants is the 5-HTT gene (SLC6A4). One polymorphism in the promoter region of the gene (5-HTT gene linked polymorphic region: 5-HTTLPR) consists of an insertion or deletion of a repetitive sequence, producing a short allele (S) or a long (L) allele [85]. The L allele version of 5-HTTLPR has been shown to affect transporter function, resulting in higher 5-HT reuptake by the transporter [85]. However, these functional findings have not been successfully translated into human studies; studies found no association with the 5-HTTLPR genotype and antidepressant-treatment response [86]. Thus, the exact functional effect of this polymorphism on 5-HTT expression and binding is unclear.

Based on this observation, several pharmacogenetic studies have investigated this polymorphism with regards to antidepressant-treatment response. Many studies have found an association between the L allele and better treatment outcome [89–103]. However, a recent meta-analysis did not find any association with this polymorphism and antidepressant-treatment response, possibly due to unexplained heterogeneity in effect sizes across studies [104]. Other studies, including an analysis of the STAR*D sample, also found no effect of the 5-HTTLPR genotype on antidepressant-treatment outcome [71,105–108], particularly in Asian populations [109,110]. In fact, many studies in Asian populations have found improved treatment outcome associated with the S allele, suggesting population stratification with this polymorphism that should be taken into account [108,111–113]. However, Taylor et al. did not find any effect of ethnicity on genotype effects in their meta-analysis [104]. One study described a model whereby use of a pretreatment test for the 5-HTTLPR genotype may lead to better antidepressant-treatment outcomes, giving support to the possible efficacy of this genotype in clinical practice [101]. However, randomized clinical trials with a pharmacogenetic component are needed before this genotype can be used widely in clinical practice.

Recent studies have also begun to investigate the interaction between genes and environment in antidepressant-treatment response. Two studies found a significant association between the 5-HTTLPR genotype and adverse life events and antidepressant-treatment outcome [114,115]. These studies indicate a possible need to investigate gene–environment interactions in future pharmacogenetic studies. The 5-HTTLPR genotype has also been associated with adverse events due to antidepressants. Studies have shown the S allele to be associated with worse tolerability to antidepressant medications [103]. Other studies have also found the S allele to be associated with SSRI-induced side effects [94,98,101,116–118]. A meta-analysis investigating the relationship between the 5-HTTLPR genotype and antidepressant side effects showed a significant association, with a trend in association with gastrointestinal side effects; however, this analysis did not include more recent pharmacogenetic studies [62]. Furthermore, additional studies have found no association with the 5-HTTLPR genotype and antidepressant-associated side effects [119,120].

The presence of an A/G SNP (rs25531) within the 5-HTT promoter region forms a haplotype with the 5-HTTLPR that may be associated with antidepressant-treatment outcome. Hu et al. showed that this haplotype is functional, with La carriers demonstrating the highest transcription of SLC6A4, and the Lg allele being equivalent to the S allele [116]. Studies have shown that in the presence of the g SNP, the L allele of 5-HTTLPR is associated with nonresponse to antidepressant treatment [121]. An analysis of the STAR*D sample showed an association between the 5-HTTLPR, rs25531 and an intron 2 VNTR and remission to citalopram [97]. However, an analysis in the GENEDEP sample did not find an effect of this SNP and antidepressant-treatment outcome [98]. The analysis did however, find an association with another SNP in intron 1, rs2020933, and treatment outcome [98]. One study also found an association with the S allele and the Lg allele and adverse effects from antidepressants [116]. However, the functional effect of rs25531 on in vivo 5-HTT expression is still controversial; one recent study found no association with the 5-HTTLPR rs25531 and 5-HTT availability in human brain [122]. Nonetheless, future pharmacogenetic studies with the 5-HTTLPR may need to consider this SNP in a haplotypic analysis.

Another VNTR polymorphism in intron 2 (STin2) of the SLC6A4 gene has been implicated in antidepressant response [65,98,111,121,123], although some studies did not find an association [58,109]. A meta-analysis of pharmacogenetic studies with this VNTR showed a significant association with antidepressant-treatment outcome;
However, this analysis does not include more recent pharmacogenetic studies [62]. Furthermore, Kim et al. showed that the haplotype of STIN2 12/12 and 5-HTTPLRS/S genotype had the highest response rate to antidepressants in an Asian population [108]. One study found an association between STIN2 10/10 genotype and increased side effects [124], but others did not support this association [98,125,126].

Various 5-HT receptor genes, including the 5HTR1A, 5HTR1B, 5HTR2A, 5HTR3A, 5HTR3B and 5HTR6 receptor genes, have also been studied in the pharmacogenetics of antidepressant treatment. The 5HTR1A receptor is located both pre- and post-synaptically. A functional SNP in the upstream regulatory region of the gene, rs6295, is associated with increased expression of the gene. Several studies have found a positive association with rs6295 and improved antidepressant-treatment outcome [58,127–131]. One study also found an association between this SNP and poorer treatment outcome in melancholic depression [132]. A meta-analysis of this SNP on antidepressant-treatment response did not find a significant association in all studies, but did report a significant outcome in studies with Asian populations; however, this analysis did not include more recent pharmacogenetic studies [62]. Other studies did not find an association with this SNP and antidepressant-treatment outcome [61,133]. Another SNP, which results in a change in amino acid at position 272 from glycine to aspartate, was found to be associated with better antidepressant-treatment response in one report [134]; however, this association could not be replicated in other studies [135,136]. Kato et al. also found significant associations between the rs10042486 and rs1364043 SNPs and improved antidepressant response (Table 1) [128]. One recent study also found a significant interaction between SNPs in the 5HTR1B gene and recent life stress in antidepressant-treatment outcome [137].

Several studies of various antidepressant drugs have indicated a potential role of the 5HTR2A gene and treatment response and/or adverse events. Three coding SNPs have been associated with antidepressant-treatment response in MDD in several studies: rs6311 (1438G/A), rs6313 (1027C/T) and rs6314 [98,105,138–141]. The rs6311 and rs6313 variants were also found to be associated with adverse drug reactions, including nausea, gastrointestinal side effects and sexual dysfunction [139,142–144]. These two SNPs are in linkage disequilibrium and can be considered together [145]. A meta-analysis of 1438A/G did not find a significant association with antidepressant-treatment outcome, but did report a significant association with adverse events. However, this analysis did not include more recent pharmacogenetic studies [62]. However, another study did not find an association with either rs6311 or 6313 [61]. In addition, a major pharmacogenetic study of the large STAR*D sample found a robust association between the intronic SNP rs7997012 and citalopram-treatment response [146], with other studies later replicating this association [147–150]. One study did not find an association with rs7997012 and antidepressant-treatment outcome [61].

Two genes for subunits of the 5HT3 receptor have been implicated in treatment outcome and side effects of antidepressant medications in MDD: 5HTR3A and 5HTR3B. The 5HTR3A SNP 178C/T (rs1062613) was associated with treatment outcome in an Asian sample, although there was no association with side effects [139]. An AAG deletion in the 5HTR3B gene (100–102 AAG del) was found to be associated with better treatment outcome [139]. This deletion and another nonsynonymous coding SNP, 129Tyr/Ser, was also found to be associated with nausea induced by antidepressant medication (Table 1) [151,152]. One variant in the 5HTR6 gene, rs1805054, may also play a role in antidepressant-treatment outcome. It is a silent polymorphism in exon 1 (267T/C) that has been associated with greater efficacy of antidepressant medications [153]; however, other studies did not report an association [61,98,154]. More studies on this gene are needed to elucidate its role in the pharmacogenetics of antidepressant-treatment response.

**DA genes**

The DA system is also highly involved in depressive symptomatology, with the proposed pathophysiology of melancholic depression involving decreased dopaminergic transmission [155]. A VNTR in exon 15 of the DA transporter gene (SLC6A3), which affects the expression levels of the transporter [156], is associated with a faster onset of antidepressant-treatment response [106]. The DA receptors have also been implicated in pharmacogenetic studies of antidepressants in depression. The dopamine receptor 2 has two isoforms due to alternative splicing, with the DRD2 Taq1A allele 1 (rs1800497) associated with SSRI-induced extrapyramidal symptoms [157]. The exon 3 VNTR of the DRD4 gene was also investigated in antidepressant drug response, with some studies finding no association [158,159].
and one study finding a significant modulation of this polymorphism on various antidepressant drugs [160].

**NE genes**

The NE system has also been studied in depression, particularly the action of NE reuptake inhibitors and SNRIs, which act at the NE transporter. One study found an association with the rs5569 SNP and response to NE reuptake inhibitors [108], and another found an association with the T-182C SNP and milnacipram response [110]. Another study found an association with the rs5564 SNP and response to desipramine, although this association did not stand up to correction for multiple testing [51]. However, a candidate gene study in the GENDEP sample only found nominally significant associations with the NE transporter SNPs rs36029 and rs1532701, which did not stand up to gene- or hypothesis-wide corrections [60]. Another study investigated seven polymorphisms across the gene and found no association with antidepressant-treatment response in depression; however, it did find a possible impact of an insertion/deletion in the enhancer region of the NE transporter gene (SLC6A2) and treatment response in melancholic depression [161]. A few pharmacogenetic studies have also focused on adrenoreceptors, particularly the β1 adrenoreceptors. One nonsynonymous coding SNP in the ADRB1 gene, rs1801253 (Gly389Arg), which is associated with enhanced coupling of the receptor to the stimulatory Gs protein and increased adenylyl cyclase activation, was reported to be associated with faster response to antidepressant treatment [162].

**Other candidate genes**

One of the other systems to be implicated in the etiology and treatment of MDD is the hypothalamic–pituitary–adrenal (HPA) axis. Dysfunction of the HPA axis is common in patients with MDD [163]. Recently, more pharmacogenetic studies in antidepressants have been published on HPA-axis candidates than monoamine-related genes. Several receptors in this pathway have been implicated in the pathophysiology of depressive disorders, including corticotropin-releasing hormone receptors and glucocorticoid receptors (GR). Corticotropin-releasing hormone is the main neuroregulator of the HPA axis; it has two receptors encoded by separate genes, CRHRI and CRHR2. One SNP in the CRHRI gene, rs242941, has been associated with antidepressant-treatment outcome in MDD, particularly in anxious patients with depression [164]. Furthermore, a haplotype with this SNP and two others, rs1876828 and rs242939, was also associated with therapeutic response to fluoxetine in highly anxious MDD patients [165]. One SNP in the CRHR2 gene, rs2270007, has been associated with response to citalopram [166]. However, further studies are needed to replicate these association studies and to determine the functional relevance of these SNPs in antidepressant-treatment outcome.

The GR has also been highly studied in antidepressant pharmacogenetic studies. A functional polymorphism in the GR gene (NR3C1) that consists of two linked nonsynonymous SNPs known as ER22 and 23EK has been associated with rapid response to antidepressant treatment [167]. Another functional SNP in this gene, BcII, which changes a restriction enzyme site and is associated with hypersensitivity to glucocorticoids also showed a trend in association with worse antidepressant-treatment outcome [167,168]. GENDEP also found nominal associations with antidepressant response and SNPs rs852977, rs10482633 and rs10052957 in the NR3CI gene [60].

Another gene that has been implicated in antidepressant-treatment response is the gene coding for FKBP5, an hsp90 co-chaperone that is a part of the GR heterocomplex. One initial study found significant associations with three SNPs in this gene and antidepressant-treatment outcome: rs1360780, rs3800373 and rs4713916 (Table 1) [169]. The association of rs1360780 was replicated in another sample in the same study, and was also found to be associated with higher lymphocyte levels of the FKBP5 protein [169]. Some studies replicated this result [170,171], although others found no association [45,60,77,166,172]. Other studies also found an association between rs4713916 and rs3800373 and antidepressant-treatment outcome in MDD [77,170,171]. A recent meta-analysis of these studies found an association with rs4713916 and antidepressant-treatment response, but no association with either rs1360780 or rs3800373 [173]. The SNPs in the FKBP5 gene have also been associated with multilocus pharmacogenetic studies, particularly with SNPs in the 5HTRA2 gene and the GRIK4 gene (the glutamate receptor gene) [174]. This multimarker analysis appeared to explain more of the antidepressant-treatment variance than single-marker analysis, perhaps indicating a need for more multimarker analyses [174]. However, to identify appropriate combinations of genes and markers, large samples or pooled analyses...
are necessary in future pharmacogenetic studies. Two SNPs in the FKBP5 gene, rs1360780 and rs3800373, have also been associated with treatment-emergent suicidal ideation (TESI), an adverse consequence of antidepressant treatment in one study [172], and treatment-emergent suicidal events in another [174], although further replication is necessary [175,176]. Although several variants in the genes of the HPA axis have been implicated in antidepressant pharmacogenetic studies, it is possible that these variants are more predictive of inherent pathophysiological differences in depressed patients rather than the mechanism of action of therapeutic drugs [174]. However, more studies are needed in this system before this can be determined.

The glutamatergic system has been implicated in both the acute response and maintenance of response to antidepressant medications in depression [177]. Particularly, the ionotropic glutamate receptors have been studied with respect to antidepressant mechanism of action [178,179]. Several glutamate receptor genes have been studied in antidepressant-treatment outcome. Variations in two glutamate receptor ionotropic kainate subtype genes, GRIK2 and GRIK4, have been studied in the STAR*D sample. One SNP in GRIK4, rs1954787, was associated with citalopram response in the STAR*D sample [180], and later replicated in other studies [174,181]. Another SNP in this gene, rs12800783, was associated with remission in antidepressant treatment, and was also shown to interact with SNPs in the FKBP5 and 5HT2A genes in a multivariate analysis [182]. This study also found significant associations with SNPs rs2276319, rs1621211, rs2156603 and rs1944522 in the GRIK4 gene and antidepressant-treatment response or remission [182]. One SNP in the GRIK2 gene, rs2518224, was associated with side effects to antidepressant medications in the STAR*D sample, including TESI and sexual dysfunction [182,183]. Variations in other glutamate receptor genes have also been associated with side effects resulting from antidepressant treatment, including the GRIA3 gene (coding for an AMPA-type glutamate receptor subunit) and TESI [180,183], GRIA1 (also coding for an AMPA-type receptor subunit), GRIN3A (coding for an N-Methyl-d-aspartate-type subunit) and the GRIA3 gene and sexual dysfunction (Table 1) [182].

Several studies have reported increased brain-derived neurotrophic factor (BDNF) expression after antidepressant administration in animal models [184–189]; thus, pharmacogenetic studies of antidepressant-treatment outcome in the BDNF gene have been conducted. One variant that has been highly studied is rs6265, which is a functional SNP that changes Val (G) to Met (A) at position 66 in the 5’ region of pro-BDNF, the precursor to mature BDNF. The Met allele results in decreased secretion of BDNF and failure to localize BDNF to secretory granules or synapses in neuronal culture [190]. While some studies found an association between rs6265 and treatment response [191–193], others found no association [194–196]. A recent meta-analysis found an association with this polymorphism and increased antidepressant response rate, specifically in the Asian population [173]. Domschke et al. found one SNP, rs7124442, to be associated with antidepressant-treatment outcome in patients with anxious depression, and rs7103411 to be associated with worse outcome in melancholic depression patients [197]. Other SNPs in BDNF that have been associated with antidepressant-treatment outcome include rs61888800, and a haplotype of rs12273363, rs908867 and rs1491850 (Table 1) [196,198]. An analysis in the GENEDEP sample found an association between rs10835210 and response to escitalopram [60]. BDNF variants have also been associated with antidepressant-induced adverse events. GENEDEP also found several variants associated with TESI (Table 1) [199]. It also reported an association between two haplotypes in the NTRK2 gene (the BDNF receptor gene) and TESI, and an interaction between polymorphisms in BDNF and NTRK2 and TESI (Table 1) [199].

Other candidate genes that have been studied in antidepressant-treatment outcome in MDD include the G-protein β3 subunit gene (GNβ3), the ACE gene, and the CREB1 gene. A functional variant in GNβ3, rs5443, results in a splice variant called Gβ3s that results in a less active form of this G protein [200]. This variant has been shown to predict improved antidepressant-treatment response in several studies [195,201–204], although other studies have reported no association, particularly in Asian populations [58,205,206]. ACE is an enzyme that degrades neuropeptides, including substance P, which has been implicated in the action of antidepressants [207]. An insertion-deletion polymorphism in ACE, which results in higher plasma levels of both ACE and substance P [208,209], has been associated with better antidepressant-treatment response and a faster onset of therapeutic effects, particularly in women [210–212]. Studies have shown that
cAMP response element binding 1 (CREB1) levels are associated with MDD and antidepressant treatment, with low levels of CREB1 found in MDD patients, and an increase in CREB1 levels in MDD patients on antidepressants [213]. Two SNPs in the 3’-UTR of the CREB1 gene, rs4675690 and rs7569963, have been associated with antidepressant-induced TESI, but only in men [214].

**Genome-wide studies of antidepressant-treatment response**

Pharmacogenetics research has recently turned away from single candidate gene studies towards hypothesis-free, genome-wide approaches, with some promising results. While single candidate genes often have low-gene coverage and minimally account for variability in treatment outcomes, genome-wide association studies (GWAS) have greater coverage to find novel variations that may predict antidepressant-treatment response. Ising et al. used a multilocus analysis across 328 SNPs to show that individuals with a high number of response alleles (based on individual associations with each SNP) had better antidepressant-treatment outcome [215]. Furthermore, they found an association between comorbid anxiety and a low number of response alleles and worse treatment outcome [215].

Other studies have also taken genome-wide approaches to find novel candidate genes that may be associated with treatment response to antidepressants. Uher et al. found strongest associations with treatment outcome on regions of chromosome 1 and 10 in the GENDEP sample [216]. They identified the IL11 gene as a possible new candidate in response to escitalopram, and the USTI gene as a possible new candidate in nortriptyline response [216]. However, due to the small sample size and low power for a GWAS, they did not find strong associations that held up to multiple testing [216]. Gartriock et al. conducted a similar analysis in the STAR*D sample, and also did not find any SNPs that reached genome-wide significance [217]. However, they did find nominally significant markers, such as rs6966038 (an SNP near the UBE3C and MNX1 genes) and rs809736 (an intronic SNP in the RORA gene) [217]. Together, these studies indicate the need for more GWAS studies to identify genes that have previously not been investigated in candidate gene studies and may play a role in predicting antidepressant-treatment response in MDD.

**Pharmacogenetics of antidepressant drugs in anxiety disorders**

- **Use of antidepressant medications in anxiety disorders**

There is a clear overlap of symptoms between depression and anxiety disorders, which often occur with a high comorbidity that may be explained by shared genetic factors [218]. Initially, benzodiazepines were used in the treatment of anxiety disorders; however, they do not treat comorbid depression, so drugs that would treat both depression and anxiety symptoms were needed [219]. In the 1960s, the anxiolytic properties of antidepressant drugs, particularly TCAs and MAOIs, were first discovered [219]. With the introduction of SSRIs, the treatment of anxiety disorders changed greatly, as they are now recommended as the first-line medications for generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder, obsessive-compulsive disorder (OCD) and post-traumatic stress disorder. While antidepressants such as SSRIs may be the most efficacious method of long-term treatment in anxiety disorders, the variability in drug response seen in depression still remains in anxiety patients [220]. Although depression and anxiety may have a shared genetic susceptibility, it remains unclear whether the results from pharmacogenetic studies in depression also apply to the treatment of anxiety disorders. Therefore, pharmacogenetic studies of antidepressant medications in anxiety disorders are of equal importance for the better clinical treatment of these patients.

- **Candidate genes in pharmacogenetic studies in anxiety disorders**

**5-HT genes**

With the discovery of the anxiolytic properties of certain antidepressants, it was hypothesized that the serotonergic system might be responsible for the efficacy of antidepressants in anxiety disorders [219]. The most highly studied candidate gene is the SLC6A4 gene, with the 5-HTTLPR polymorphism being investigated in various anxiety disorders. Some studies in OCD have found positive associations with 5-HTTLPR, with one study reporting a positive association with L/S heterozygotes and better response to venlafaxine [221], and another showing a trend in association with the L allele and poorer antidepressant-treatment response [222]. However, other studies have reported no association between this polymorphism and antidepressant treatment in OCD patients [223–225].
One study also reported an association between L allele carriers and better treatment response in PD, an association that appeared to be driven by females and did not appear to be a result of clinical or demographical differences in the population [226]. However, another study could not replicate these findings [227]. Stein et al. also showed an association of the S allele of 5-HTTLPR and poorer antidepressant response in social anxiety disorder [228]; they also investigated the haplotype of rs25531 and 5-HTTLPR and found a trend in association, although their results have yet to be replicated. Another recent study in GAD did find an association with this haplotype and antidepressant-treatment outcome, with La carriers showing better response to escitalopram [229].

A few studies in OCD have also investigated variants in the 5HTR2A gene and antidepressant-treatment outcome. Some found a positive association with rs6313 (102T/C) [179,183], although another study did not find an association [230]. One study investigated another variant, rs6311 (1438G/A) in OCD, but did not find an association [230]. We investigated the role of the 5HTR2A SNP rs7997012 in GAD and found an association with this polymorphism and response to venlafaxine [231]. It appears that the serotonergic system does play a role in antidepressant-treatment outcome in anxiety disorders, although more studies are needed with other candidate genes to elucidate this role (Table 2).

Other candidate genes

Other systems that have been investigated in pharmacogenetic studies of MDD have also begun to be investigated in anxiety disorders. All three monoamine metabolic enzymes have been studied in various anxiety disorders. One study investigated the 218A/C SNP in the TPH1 gene in a PD population, but did not find an association [227]. No studies have yet looked at any variations in the TPH2 gene in anxiety disorders. Variations in both COMT and MAOA have been studied in OCD disorder, but with no positive findings [220]. The dopamine receptor genes DRD2 and DRD4 have been briefly studied in anxiety disorder treatment. One study found no association with Taq1, a polymorphism in the DRD2 gene and antidepressant-treatment outcome in post-traumatic stress disorder [232], and another

<table>
<thead>
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<td>[221]</td>
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<td>[227]</td>
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<td>CNR1</td>
<td>SNP rs1049353</td>
<td>Anxious depression</td>
<td>Associated with poor response</td>
<td>Domschke et al.</td>
<td>[233]</td>
</tr>
<tr>
<td>BDNF</td>
<td>SNP rs7124442</td>
<td>Anxious depression</td>
<td>Positive association with response</td>
<td>Domschke et al.</td>
<td>[233]</td>
</tr>
<tr>
<td></td>
<td>SNP rs6265</td>
<td>GAD</td>
<td>No association</td>
<td>Narasimhan et al.</td>
<td>[234]</td>
</tr>
</tbody>
</table>

GAD: Generalized anxiety disorder; OCD: Obsessive-compulsive disorder; PD: Panic disorder; PTSD: Post-traumatic stress disorder; SAD: Social anxiety disorder.
study in OCD also did not find an association with this polymorphism [225]. One study investigated variations in the \textit{DRD4} gene and antidepressant-treatment response in OCD but reported no association [225]. Other genes have been investigated in pharmacogenetic studies with anxiety phenotypes: one study found an association with a SNP in the \textit{CNR1}, rs1049353, and association with poor treatment response in depressed patients with high levels of anxiety [235]; another study also found an association between \textit{BDNF} SNP rs7124442 and antidepressant-treatment outcome in anxious depression patients [197]. We did not find an association between the \textit{BDNF} variant rs6265 (Val166Met) and antidepressant-treatment outcome in GAD [234]. Collectively, these studies illustrate the importance of antidepressant pharmacogenetic studies in anxiety disorders, and the need for more replication and novel candidate gene studies (Table 2).

### Pharmacogenetics of antidepressant drugs in bipolar disorder

#### Use of antidepressants in bipolar disorder

Antidepressants are often used to treat depressive episodes in bipolar disorder (BPD), usually in conjunction with mood stabilizers. Although the neurobiological processes underlying depression may be common to both unipolar and bipolar depression, some pharmacogenetic studies combine both MDD and BPD populations, which may confound the results. However, as antidepressant treatment is associated with particular neurological systems, some of the same candidate genes considered in MDD pharmacogenetic studies could also be considered in BPD studies. Here, we review these candidate gene studies in both mixed populations (MDD and BPD) and BPD populations only (Table 3).

#### Candidate gene studies

There have been several reports of G-protein changes in mood disorders, and thus, the \textit{GNB3} gene has been studied in both MDD and BPD for antidepressant-treatment response [235]. The main SNP that has been investigated is rs5443; however, the results have been mixed, with some studies finding a positive association [201,202], and others finding no association [236,237]. However, all of these studies have been in mixed populations of both MDD and BPD patients, so perhaps future studies in BPD-only populations will yield more promising results. The other gene that may play a role in antidepressant response in BPD is the \textit{TPH1} gene, in which the functional rs1800532 SNP has been associated with decreased response in MDD/BPD mixed populations [53,54].

Other candidate genes that have been investigated in antidepressant-treatment outcome in BPD include the dopamine receptor genes \textit{DRD2} and \textit{DRD4} [158], the \textit{5HTR2A} gene and the \textit{MAOA} gene [140]. However, none of these studies found a positive association, again possibly due to mixed patient populations. These results clearly indicate the need for more pharmacogenetic studies in BPD-only populations or more studies in mixed populations with a higher BPD patient load before any of these results can become clinically applicable.

One antidepressant-treatment outcome that has been studied extensively in pharmacogenetic studies is antidepressant-induced mania (AIM). AIM is often considered a side effect following antidepressant use in depressed patients, although it can lead to the diagnosis of BPD.

<table>
<thead>
<tr>
<th>Author</th>
<th>Gene</th>
<th>Variant</th>
<th>Study</th>
<th>Finding</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zill et al.</td>
<td>GNB3</td>
<td>SNP rs5443</td>
<td>MDD/BPD</td>
<td>Positive association with response</td>
<td>[201]</td>
</tr>
<tr>
<td>Serretti et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[202]</td>
</tr>
<tr>
<td>Lin et al.</td>
<td></td>
<td></td>
<td>MDD/BPD</td>
<td>No association</td>
<td>[236]</td>
</tr>
<tr>
<td>Kunugi et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[237]</td>
</tr>
<tr>
<td>Serretti et al.</td>
<td>TPH1</td>
<td>SNP rs1800532</td>
<td>MDD/BPD</td>
<td>Associated with decreased response</td>
<td>[53,54]</td>
</tr>
<tr>
<td>Mundo et al.</td>
<td>SLC6A4</td>
<td>5-HTTLPR</td>
<td>BPD</td>
<td>Positive association with AIM</td>
<td>[239]</td>
</tr>
<tr>
<td>Masoliver et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[240]</td>
</tr>
<tr>
<td>Ferreira et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[241]</td>
</tr>
<tr>
<td>Rousseva et al.</td>
<td></td>
<td></td>
<td>BPD</td>
<td>No association with AIM</td>
<td>[242]</td>
</tr>
<tr>
<td>Serretti et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[243]</td>
</tr>
<tr>
<td>Baumer et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[244]</td>
</tr>
</tbody>
</table>

AIM: Antidepressant-induced mania; BPD: Bipolar disorder; MDD: Major depressive disorder.
The occurrence of AIM in BPD patients is anywhere between 20 and 40%, and is one of the reasons why antidepressants are usually only used as conjunctive therapy with an antimanic agent [8,238]. However, it is unclear which patients may experience this adverse outcome and which may not. Several studies have investigated the role of 5-HTTLPR in the 5-HTT gene in the occurrence of AIM in BPD, finding a positive association with the S allele and AIM [239–241]. However, a few studies have also found no association with this polymorphism [242–244]. A recent meta-analysis of these studies found a significant association of the 5-HTTLPR genotype and AIM occurrence in BPD [245]. Other candidate genes that have been studied in AIM include TPH, GBN3, MAOA, COMT, SHTR2A, DRD2, DRD4, and BDNF, although none have found a positive association thus far [243,246]. Despite AIM being the most extensively studied condition in the pharmacogenetics of antidepressant-treatment outcome in BPD, further studies are needed before the results can be incorporated into clinical practice.

Future perspective
While the field of psychiatric pharmacogenetics is rapidly developing, and it is thought that genetic patient information will likely revolutionize clinical practice in the very near future, most of the pharmacogenetic findings for antidepressants have been inconclusive and controversial. This review has shown that while many candidate gene studies have been conducted on antidepressant use in MDD, anxiety disorders and BPD, the results are not yet readily usable in clinical practice.

The one pharmacogenetic finding that has been translated to the clinic is the effect of CYP450 enzymes on pharmacokinetics of antidepressant use. Currently, there is only one commercial, US Food and Drug Administration-approved, pharmacogenetic test available (AmpliChip CYP450, Roche Diagnostic, Basel, Switzerland), which can be ordered through a few selected commercial and academic laboratories. This test provides genotypes for the two CYP2D6 alleles CYP2D6*4 and CYP2D6*10A. By genotyping patients for variation in these genes, the clinician should be able to predict metabolizer status of a patient, which might influence medication choice and dosing. While these genotypes clearly affect plasma concentrations of the drug and its metabolites, their effect on clinical response is inconclusive (see ‘Genetics of antidepressant drug pharmacodynamics’). Therefore, the use of this genotyping test in clinical practice is limited.

The FDA has approved several drug labels to contain information about pharmacogenetic biomarkers. Currently, approximately 17% of these pharmacogenetic labels are for psychiatric drugs, and most of them contain information about the CYP450 enzymes [247]. However, most of these labels only provide pharmacogenetic information for each drug, and do not offer any clinical recommendations or require the use of this information before treatment prescription. The ultimate goal of future studies is to expand the pharmacogenetic information on antidepressant labels and incorporate them into wide clinical use. However, there are several limitations that need to be considered before the field can advance to this stage.

The main problem with current pharmacogenetic studies is the lack of standardization, making it difficult to distinguish between positive and negative findings in the same candidate gene. Current studies often have very different inclusion criteria, use of medications, outcome measures, recording of side effects, ethnicity of study population and genetic coverage. Furthermore, many of these studies have small sample sizes with limited power and a short-term follow-up of patients, leading to possible false negative or false positive results. Thus, much of the future research will be devoted to replication of these results in large prospective trials with standardized designs, such as the GENDEP project [60]. In addition, those studies showing positive correlations often have small effect sizes, making them ill suited for clinical adaptation. Furthermore, more clinical trials focused solely on the pharmacogenetics of antidepressant medications will also be forthcoming, in order to incorporate genetic profiling into wide clinical use. Genome-wide approaches are also becoming more prevalent, although this is due to the inconsistent findings in traditional candidate genes. It should be noted that these GWAS will still need to address the above limitations while searching for novel candidates.

As discussed in this review, most of the antidepressant pharmacogenetic studies have focused on MDD, despite the fact that antidepressants are widely used in other disorders as well. In the future, more studies will be conducted on antidepressant use in other disorders, particularly anxiety disorders, which is just emerging as a new branch in this field. These new studies will require the same standardization that is currently lacking in MDD pharmacogenetic studies, with large, prospective clinical trials being the ultimate goal of this research; however, it is unlikely that these trials will occur in the very near future.
While it is clear that the pharmacogenetics of antidepressants in various psychiatric disorders deserves greater attention in both future research and clinical practice, it is important to remember that genetic information is only one aspect of the complex history of psychiatric patients. Future clinical practice will also need to consider all internal and external factors that may influence the pathology of these disorders.

Executive summary

Pharmacogenetics of antidepressant drugs in depression

- Genetics of antidepressant drug pharmacokineti
cs:
  - Pharmacokinetic candidate gene studies have mainly focused on CYP450 enzymes, which metabolize antidepressants, with CYP2D6 alleles conferring the metabolizer status that determines efficacy and tolerability of medications.
- Genetics of antidepressant drug pharmacodynamics:
  - The majority of pharmacodynamic candidate gene studies have been conducted on the monoaminergic system, including monoamine metabolic enzymes, the serotonin system and the dopamine and norepinephrine systems.
  - Pharmacogenetic studies in other candidate genes require more replication to determine the true effect of each gene in antidepressant-treatment outcome.

Pharmacogenetics of antidepressant drugs in anxiety disorders

- Use of antidepressant medications in anxiety disorders:
  - Although depression and anxiety disorders share a common genetic susceptibility, it is unclear whether pharmacogenetic-study results in major depressive disorder (MDD) are applicable to anxiety disorders; therefore, separate pharmacogenetic studies in anxiety disorders are necessary.
  - The most highly studied candidate gene system in antidepressant treatment of anxiety disorders is the serotonin system, with the most robust associations being with the 5-HTTLPR.
  - Other candidate gene studies in anxiety disorders have generally reported no association or require further replication in larger populations or prospective trials.

Pharmacogenetics of antidepressant drugs in bipolar disorder

- Use of antidepressants in bipolar disorder:
  - Antidepressant medications are often used as conjunctive therapy with mood stabilizers in bipolar disorder (BDP).
  - Most antidepressant pharmacogenetic studies in BPD have been conducted in mixed populations of MDD and BPD, thereby possibly confounding the results; future studies need to focus solely on BPD populations.
  - The most robust association has been between the 5-HTTLPR and antidepressant-induced mania, although other candidate genes have also been studied for the possible association with the occurrence of antidepressant-induced mania.

Future perspective

- Only the CYP450 pharmacogenetic data has been incorporated into clinical practice with the US FDA-approved AmpliChip CYP450 test; however, its efficacy in determining appropriate antidepressant treatment remains controversial.
- All other pharmacogenetic studies in MDD require replication in large, prospective clinical trials before the genetic data can be used by clinicians.

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Papers of special note have been highlighted as:
* of interest

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.
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*Summarizes findings from the Genome-Based Therapeutic Drugs for Depression (GENDEP) project, a large, prospective clinical trial that investigated many candidate genes and found promising results in some, while finding no associations with others.*


*Major review and meta-analysis paper that investigates most of the pharmacodynamic candidate genes studied in major depressive disorder (MDD); however, it was initially published in 2008 and its findings do not include more recent studies.*


Pharmacogenetics of antidepressant drugs: current clinical practice & future directions


- *Recent meta-analysis of the 5-HTTLPR in antidepressant-treatment response that did not find an association with this polymorphism, despite many documented studies showing positive association.*


Review


et al. 2010. }


Recent meta-analysis of hypothalamic–pituitary–adrenal axis genes that found a significant association with FKBP5 polymorphisms and antidepressant-treatment response in MDD.


Pharmacogenetics of antidepressant drugs: current clinical practice & future directions


Recent approaches in pharmacogenetics of antidepressants drugs have focused on genome-wide association studies that find positive associations in novel candidate genes, such as this one in the GENDEP sample.


