Supplement to:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6*, *CYP2C19*, *CYP2B6*, *SLC6A4* and *HTR2A* Genotypes and Serotonin Reuptake Inhibitor Antidepressants

Chad A. Bousman[1,2,3]*, James M. Stevenson[4]*, Laura B. Ramsey[5,6], Katrin Sangkuhl[7], J. Kevin Hicks[8], Jeffrey R. Strawn[9,10], Ajeet B Singh[11], Gualberto Ruaño[12, 13], Daniel J. Mueller[14,15], Evangelia Eirini Tsermpini[16], Jacob T. Brown[17], Gillian C. Bell[18], J. Steven Leeder[19,20], Andrea Gaedigk[19,20], Stuart A. Scott[21,22], Teri E. Klein[7], Kelly E. Caudle[23], Jeffrey R. Bishop[24,25]
*Shared first author

[1]Departments of Medical Genetics, Psychiatry, and Physiology & Pharmacology, University of Calgary, Alberta, Canada
[2]Alberta Children's Hospital Research Institute, University of Calgary, Alberta, Canada
[3]Mathison Centre for Mental Health Research and Education, Hotchkiss Brain Institute, University of Calgary, Alberta, Canada
[4]Departments of Medicine and Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[5]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA
[6]Divisions of Clinical Pharmacology and Research in Patient Services, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[7]Department of Biomedical Data Science, Stanford University, Stanford, CA, USA
[8]Department of Individualized Cancer Management, Moffitt Cancer Center, Tampa, FL, USA
[9]Department of Psychiatry & Behavioral Neuroscience, University of Cincinnati, Cincinnati, OH, USA
[10]Divisions of Child & Adolescent Psychiatry and Clinical Pharmacology Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[11]School of Medicine, Deakin University, Australia
[12]Institute of Living at Hartford Hospital, Hartford, CT, USA
[13]Department of Psychiatry, University of Connecticut School of Medicine, Hartford, CT, USA
[14]Pharmacogenetics Research Clinic, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada
[15]Department of Psychiatry, University of Toronto, Ontario, Canada
[16] Pharmacogenetics Laboratory, Institute of Biochemistry and Molecular Genetics, Faculty of Medicine, University of Ljubljana, 1000 Ljubljana, Slovenia
[17]Department of Pharmacy Practice & Pharmaceutical Sciences, University of Minnesota College of Pharmacy, Duluth, MN, USA
[18]Genome Medical, South San Francisco, CA, USA
[19]Division of Clinical Pharmacology, Toxicology & Therapeutic Innovation, Children's Mercy Research Institute (CMRI), Kansas City, Kansas City, MO, USA
[20]School of Medicine, University of Missouri-Kansas City, Kansas City, MO, USA
[21]Department of Pathology, Stanford University, Palo Alto, CA, USA
[22]Stanford Medicine Clinical Genomics Program, Stanford Medicine, Stanford, CA, USA
[23]Department of Pharmacy and Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA
[24]Department of Experimental and Clinical Pharmacology, University of Minnesota College of Pharmacy, Minneapolis, MN, USA

[25]Department of Psychiatry and Behavioral Sciences, University of Minnesota Medical School, Minneapolis, MN, USA

TABLE OF CONTENTS

GUIDELINE UPDATES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6*, *CYP2C19*, *CYP2B6*, *SLC6A4* and *HTR2A* Genotypes and Serotonin Reuptake Inhibitor Antidepressants is published in full on the CPIC website (https://cpicpgx.org/guidelines/cpic-guideline-for-ssri-and-snri-antidepressants/) (1). Relevant information will be periodically reviewed, and guidelines will be updated online.

LITERATURE REVIEW

The PubMed® database was searched for associations between *CYP2D6, CYP2C19, CYP2B6, HTR2A,* or *SLC6A4* genotypes and metabolism, drug-related adverse drug events or clinical outcomes using the following keywords:

SSRIs - *CYP2D6*, *CYP2C19*, *CYP2B6*

January 2015 to June 20, 2022: for (cytochrome P450 2D6 or CYP2D6) OR (cytochrome P450 2C19 or CYP2C19) AND (SSRI OR selective serotonin reuptake inhibitors OR fluoxetine OR paroxetine OR citalopram OR escitalopram OR sertraline OR fluvoxamine OR paroxetine)
1966 to June 20, 2022: (cytochrome P450 2B6 or CYP2B6) AND (SSRI OR selective serotonin reuptake inhibitors OR fluoxetine OR paroxetine OR citalopram OR escitalopram OR sertraline OR fluvoxamine OR paroxetine)
The PubMed search retrieved 324 articles of which 44 were added in addition to the references of the prior published SSRI guideline.

SNRIs and 5HT Modulators - *CYP2D6*, *CYP2C19*, *CYP2B6*

1966 to June 20, 2022: for (cytochrome P450 2D6 or CYP2D6) OR (cytochrome P450 2C19 or CYP2C19) OR (cytochrome P450 2B6 or CYP2B6) AND (SNRI OR serotonin norepinephrine reuptake inhibitors OR venlafaxine OR desvenlafaxine OR duloxetine OR vortioxetine OR vilazodone OR levomilnacipran OR milnacipran)
The PubMed search retrieved 310 articles of which 59 were included in the evidence tables.

SSRI/SNRI/5HT Modulators - *HTR2A*

1966 to June 20, 2022: for (5-hydroxytryptamine receptor 2A OR HTR2A OR HTR2 OR 5-HTR2A OR 5-HT2A) AND (SSRI OR selective serotonin reuptake inhibitors OR fluoxetine OR

paroxetine OR citalopram OR escitalopram OR sertraline OR fluvoxamine OR paroxetine OR SNRI OR serotonin norepinephrine reuptake inhibitors OR venlafaxine OR desvenlafaxine OR duloxetine OR vortioxetine OR vilazodone OR levomilnacipran OR milnacipran) AND (polymorphism OR variant OR allele OR genotype)
The PubMed search retrieved 163 articles of which 67 were included in the evidence tables.

SSRI/SNRI/5HT Modulators – *SLC6A4*

1966 to June 20, 2022 for (SLC6A4 OR serotonin transporter OR 5-HTT OR 5-HTTLPR OR 5HTT OR HTT OR OCD1 OR SERT OR SERT1 OR hSERT OR solute carrier family 6 member 4) AND (SSRI OR selective serotonin reuptake inhibitors OR fluoxetine OR paroxetine OR citalopram OR escitalopram OR sertraline OR fluvoxamine OR paroxetine OR SNRI OR serotonin norepinephrine reuptake inhibitors OR venlafaxine OR desvenlafaxine OR duloxetine OR vortioxetine OR vilazodone OR levomilnacipran OR milnacipran) AND (polymorphism OR variant OR allele OR genotype)
The PubMed search retrieved 579 articles of which 148 were included in the evidence tables.

GENES: *CYP2D6*, *CYP2C19,* AND *CYP2B6*

Genetic Test Interpretation

CYP2D6, *CYP2C19,* and *CYP2B6* genetic variants are typically reported as haplotypes, which are defined by a specific combination of single nucleotide polymorphisms (SNPs) and/or other sequence variants including insertions and deletions that are interrogated during genotyping analysis. Haplotypes are described using star (*) allele nomenclature to allow for the standardization of genetic polymorphism annotation (2). A complete list of *CYP2D6*, *CYP2C19* and *CYP2B6* star (*) alleles along with the genetic variants that define each star (*) allele is available at https://www.pharmvar.org/gene/CYP2D6, https://www.pharmvar.org/gene/CYP2C19, and https://www.pharmvar.org/gene/CYP2B6, respectively (3-5), and the allele definition tables at https://cpicpgx.org/guidelines/cpic-guideline-for-ssri-and-snri-antidepressants/. Knowing which SNPs or other genetic variants a particular pharmacogenetic test interrogates is important as the inclusion or exclusion of certain variants in the test could affect the reported star (*) allele result (i.e., genotype or diplotype call).

Clinical laboratories typically report a diplotype (often also referred to as genotype), which is the summary of inherited maternal and paternal star (*) alleles (e.g., *CYP2C19*1/*2*, where an individual inherited a **1* allele and a **2* allele). Commonly reported *CYP2D6*, *CYP2C19,* and *CYP2B6* star (*) alleles are categorized into functional groups (e.g., increased function, normal function, decreased function, or no function) based on the predicted activity of the encoded enzyme (***CYP2D6*, *CYP2C19* and *CYP2B6* Allele Functionality Tables** (https://cpicpgx.org/guidelines/cpic-guideline-for-ssri-and-snri-antidepressants/). The predicted phenotype (**Table 1, main manuscript**) is influenced by the expected function of each reported allele in the diplotype.

CYP2D6 Genetic Test Interpretation

Calculating* CYP2D6 *Activity Score. Gaedigk *et al*. developed a scoring system to provide a uniform approach for assigning a predicted CYP2D6 phenotype based on genotype (6). The activity values assigned to each allele are added together to calculate the CYP2D6 activity score for the reported diplotype. For example, to calculate the activity score of a *CYP2D6*1/*17* diplotype, the activity values of **1* (activity value = 1) and **17* (activity value = 0.5) are totaled to provide the CYP2D6 activity score of 1.5. Note that a value of 0.5 indicates decreased activity and not that the activity conveyed by the allele is half of that encoded by a normal function allele. For this guideline, an updated method to translate *CYP2D6* genotype into phenotype is utilized (7). CYP2D6 activity scores translate genotype into phenotype as follows: activity score of 0 = poor metabolizer (PM), activity scores of $0 < x < 1.25$ = intermediate metabolizer (IM), activity scores of $1.25 \leq x \leq 2.25$ = normal metabolizer (NM), and activity scores greater than 2.25 = ultrarapid metabolizer (UM). Therefore, a pharmacogenetic test result of *CYP2D6*1/*17* results in a CYP2D6 activity score of 1.5 and a predicted phenotype of NM. The "indeterminate" phenotype is assigned when the individual carries one or two uncertain function alleles.

CYP2D6 Structural and Gene Copy Number Variants. Given that *CYP2D6* is subject to copy number variation (gene duplications, multiplications, or deletions), clinical laboratories may report gene copy number if tested. Most patients will have a normal copy number of 2, with one gene copy inherited maternally and one gene copy inherited paternally. When two *CYP2D6* gene copies are present, the diplotype may be reported as follows: *CYP2D6*1/*1* or *CYP2D6 (*1/*1)2N*, where "*2N*" represents the patient's total number of gene copies. A copy number of

"1" indicates the presence of a *CYP2D6* gene deletion (the patient possesses only one gene copy), and a copy number of "0" indicates that both *CYP2D6* gene copies are deleted. Of note, *CYP2D6* gene deletion alleles are designated as *CYP2D6*5*. A gene deletion that is present on one chromosome may be reported as follows: *CYP2D6*2/*5* or *CYP2D6 (*2/*2)1N*, where "*1N*" represents gene copy number and the *CYP2D6*5* allele is inferred. Typically, clinical laboratories will report a homozygous gene deletion as *CYP2D6*5/*5* or *CYP2D6 (*5/*5)0N*. A copy number greater than two indicates the presence of a *CYP2D6* gene duplication or multiplication. When a *CYP2D6* gene duplication is present, the diplotype may be reported as *CYP2D6 (*1/*2)3N*, where "*3N*" represents gene copy number. A clinical laboratory may not report an exact copy number or which allele has the duplication, but rather indicate that an additional gene copy or copies are present, e.g., *CYP2D6 (*1/*2)3N* or *CYP2D6 (*1/*2)xN*. In instances where a duplication or multiplication is present, and the exact copy number is not reported, most patients will likely have a *CYP2D6* gene copy number of 3. However, individuals carrying as many as 13 *CYP2D6* gene copies have been reported (8). Some clinical laboratories may not determine which allele is duplicated; therefore, when calculating CYP2D6 activity score the duplication must be considered for each allele reported in the diplotype (9). For example, a genotype result of *CYP2D6 (*1/*4)3N* indicates a patient has three copies of the *CYP2D6* gene, with either two copies of the *CYP2D6*1* allele and one copy of the *CYP2D6*4* allele (*CYP2D6*1x2/*4*), or one copy of the *CYP2D6*1* allele and two copies of the *CYP2D6*4* allele (*CYP2D6*1/*4x2*). If *CYP2D6*1* is duplicated, the CYP2D6 activity score of this diplotype will be 2 (NM), whereas if *CYP2D6*4* is duplicated, the activity score will be 1 (IM). Likewise, if the number of gene copies is not determined and it remains unknown which allele carries the duplication or multiplication, a *CYP2D6 (*1/*10)xN* genotype, for example, can be consistent with a NM phenotype (*CYP2D6*1/*10x2*; activity score of 1.5 or *CYP2D6*1x2/*10,* activity score of 2.25) or UM phenotype (or *CYP2D6*1x2/*10x2*; activity score of 2.5 or *CYP2D6*1x3/*10*; activity score of 3.25). As these examples illustrate, phenotype prediction will be more accurate if testing determines which allele is duplicated and the number of gene copies present. Consequences of *CYP2D6* copy number variation on pharmacotherapy has been reviewed by Jarvis *et al*. 2019 (10).

Note that a duplication may not be detected by copy number assays when paired with the *CYP2D6*5* allele (gene deletion). A *CYP2D6*2x2/*5* diplotype, for example, has a gene

duplication on one allele and a gene deletion on the other for a total number of two gene copies. This diplotype may also be reported as *CYP2D6*2/*2*.

Other structural variants include gene copies that consist of *CYP2D6* and *CYP2D7*-derived sequences (5, 11, 12). An overview of these variants can also be found in the "Structural Variation" document at https://www.pharmvar.org/gene/CYP2D6. The no function *CYP2D7-2D6* hybrid genes, collectively assigned as *CYP2D6*13* (13), may not be detected by a particular genotype test or gene copy number testing. In such cases the test may detect only the allele present on the second chromosome and report the diplotype as homozygous for that allele. For example, a test that does not detect *CYP2D6*13* may report a *CYP2D6*1/*13* diplotype as *CYP2D6*1/*1*. Hybrid genes can also occur in duplication configurations and cause positive gene duplication test results that may lead to an overestimation of activity and false-positive prediction of ultrarapid metabolism (12, 14). For example, a *CYP2D6*1/*13+*2* diplotype (activity score = 2 predicting normal metabolism) may be assigned as *CYP2D6*1/*2xN* (activity score ≥ 3 predicting ultrarapid metabolism).

Limitations of the Star (*) Nomenclature and Allele Assignments. The Pharmacogene Variation (PharmVar) Consortium star (*) allele nomenclature provides suballele definitions (e.g., *CYP2D6*1.001, CYP2D6*4.002*), but these are typically not distinguished by current testing. This is of no consequence for *CYP2D6*4*, as all **4* suballeles share the 1847G>A variant causing aberrant splicing and absence of functional protein. However, for *CYP2D6*1* it is unknown whether any of the sequence variations defining the suballeles convey a functional consequence. Also, there is no, or little, information regarding their frequencies because most laboratories do not discriminate between the suballeles. In addition, there are likely numerous known variants and suballeles that have not been designated by PharmVar at this time (investigators and clinical laboratories are encouraged to submit novel information to PharmVar (www.pharmavar.org).

The accuracy of a pharmacogenetic test depends on the number of sequence variations/allelic variants tested. If no variation is found, a *CYP2D6*1* will be the 'default' assignment. Depending on which sequence variations are interrogated, the allele assignment may vary. For example, if 2851C>T is present, but 1022C>T is not, the assignment is *CYP2D6*2*. In contrast,

if 1022C>T is also present, the allele would be assigned as **17*. Additional examples are provided in the PharmVar *CYP2D6* GeneFocus review (5). Also see 'CYP2D6 Other Considerations' below.

Note that the SNP positions provided above and below are according to the NG_008376.4 reference sequence (RefSeq). The M33388 "legacy" RefSeq contains errors causing certain variant positions to shift by 1-base when mapped to the NG_008376.4 RefSeq. PharmVar uses NG_008376.4 for allele definitions and strongly encourages the use and reporting of positions in respect to NG_008376.4 RefSeq. To facilitate variant mapping, PharmVar cross-references positions between NG_008376.4 and M33388 (https://www.pharmvar.org/gene/CYP2D6). Of note, NG_008376.4 corresponds to the sequence present in the GRCh38 genome build.

Findings indicate that a variant in a distal enhancer region impacts allele activity on the transcriptional level (15, 16). Specifically, it was reported that *CYP2D6*2* alleles lacking the "enhancer" SNP (NM_152613.3:c.63-2604G>A; rs5758550) have decreased function. However, one subsequent study found that this SNP did not lead to improved prediction of endoxifen concentrations in breast cancer patients (17) while another concluded that it remains inconclusive whether the small observed effects were indeed caused by the enhancer SNP or were due to its incomplete linkage with other variants within the gene. Furthermore, it was also reported (18) that this variant can occur on many other star alleles besides *CYP2D6*2,* and that the portion of an allele with and without rs5758550 may considerably vary among biogeographical groups. Thus, it remains uncertain whether the effect of this variant on CYP2D6 activity *in vivo* is of clinical significance. Rs5758550 is currently not included in common *CYP2D6* genotyping panels, nor is it included in star allele definitions.

CYP2C19 Genetic Test Interpretation

Table 1 (main manuscript) defines each CYP2C19 phenotype based on genotype and provides examples of diplotypes. Of note, the predicted phenotype for a patient carrying the *CYP2C19*17* increased function allele in combination with a no function allele (e.g., *CYP2C19*2*) is less clear than for other allele combinations. Limited data suggest that *CYP2C19*17* may not compensate for no function alleles such as *CYP2C19*2* (19) and these combinations (increased function plus a no function allele) have been categorized as a CYP2C19 IM. CYP2C19 PMs are characterized

by the presence of two no function alleles. Diplotypes characterized by one normal function allele and one increased function allele (i.e., *CYP2C19*1/*17)* are classified as rapid metabolizers (RMs), and diplotypes characterized by two increased function alleles (i.e., *CYP2C19*17/*17*) are classified as UMs. There are limited data available for decreased function alleles (e.g., *CYP2C19*9*); therefore, individuals who have one normal function and one decreased function allele, or one increased function and one decreased function allele, or two decreased function alleles, are currently classified as "likely IM" Individuals with one no function and one decreased function allele are currently classified as "likely PM." The "indeterminate" phenotype is assigned when the individual carries one or two uncertain function alleles. See the ***CYP2C19* Diplotype-Phenotype Table** online for a complete list of possible diplotypes and the corresponding predicted phenotype assignments (1, 20).

Of note, two recent publications report findings that a haplotype within the *CYP2C* gene cluster may affect escitalopram (21) and sertraline (22) metabolism. The haplotype described as "*CYP2C:TG"* is defined by the presence of rs11188059G (*CYP2C18* intron 5) and rs2860840T (*CYP2C18* 3'UTR); the two variants appear to be in near-100% linkage disequilibrium. The *CYP2C:TG* haplotype was only detected on a subgroup of *CYP2C19*1* alleles which were associated with lower levels of escitalopram and sertraline comparable to levels found for the *CYP2C19*17* allele. However, this *CYP2C:TG* haplotype is not currently interrogated by clinical genotyping platforms. Another study reporting on omeprazole treatment failure further corroborates the potential importance of this haplotype (23).

CYP2B6 Genetic Test Interpretation

CYP2B6 alleles are categorized into functional groups as follows: normal function (e.g., *CYP2B6*1*), decreased function (e.g., *CYP2B6*6* and **9*), no function (e.g., *CYP2B6*18*), and increased function (e.g., *CYP2B6*4*). Allele function assignments, as described in the ***CYP2B6* Allele Functionality Table** (https://cpicpgx.org/guidelines/cpic-guideline-for-ssri-and-snri-antidepressants/), have been made based on *in vitro* data with or without *in vivo* data. *CYP2B6*6* (p.Q172H, p.K262R) is the most frequent decreased function allele (15% to 60% minor allele frequency depending on ancestry) and has been the most extensively studied variant of this gene. While reduced protein expression due to aberrant splicing caused by the c.516G>T (rs3745274, p.Q172H) variant contributes to substantially decreased function of *CYP2B6*6*, *in vitro* studies

also suggest complex substrate-dependent catalytic effects (reviewed in: (3)). Therefore, it is challenging to assign function to *CYP2B6* alleles, as function may be substrate specific.

Table 1 (main manuscript) defines each CYP2B6 phenotype based on genotype and provides examples of diplotypes. The phenotype categories of CYP2B6 RM (one normal function allele and one increased function allele) and CYP2B6 UM (two increased function alleles) allow for the possibility that these may be clinically relevant for other CYP2B6 substrates such as bupropion, efavirenz, and methadone. See the ***CYP2B6* Diplotype-Phenotype Table** https://cpicpgx.org/guidelines/cpic-guideline-for-ssri-and-snri-antidepressants/) for a complete list of possible diplotypes and phenotype assignments.

Many clinical laboratories report *CYP2B6* genotype results using the star-allele (*) nomenclature. The star-allele nomenclature for CYP2B6 alleles is found at the PharmVar website (https://www.pharmvar.org/gene/CYP2B6). Some laboratories test and report only on specific variants that have been most extensively studied, such as c.516G>T and c.983T>C. These variants are the only defining variants for *CYP2B6*9* and **18*, respectively. Of importance, c.516G>T is also found in combination with other variants that are defined as *CYP2B6*6, *7, *13, *19, *20, *26, *29, *34, *36, *37,* and **38*. In cases where only c.516G>T is tested, it is not possible to distinguish between the (*) alleles containing this variant. However, all alleles with c.516G>T are considered decreased function, and result in the same CYP2B6 phenotypes based on diplotypes. In contrast, c.983T>C is unique to *CYP2B6*18*. Tables on the CPIC website contain a list of *CYP2B6* alleles, the combinations of variants that define each allele, allele functional status, and allele frequency across major ancestral populations as reported in the literature (1).

Available Genetic Test Options

Commercially available genetic testing options change over time. The Genetic Testing Registry provides a central location for voluntary submission of genetic test information by laboratories and is available at http://www.ncbi.nlm.nih.gov/gtr. Desirable characteristics of pharmacogenetic tests, including the naming of alleles and test report contents, have been extensively reviewed by an international group, including CPIC members (24) as well as the American College of Medical Genetics and Genomics (ACMG) (25). CPIC recommends that clinical laboratories

adhere to these test reporting standards. CPIC gene-specific tables adhere to these allele nomenclature standards. Moreover, these tables (**Allele Definition Tables**, **Allele Functionality Tables**, and **Allele Frequency Tables**) may be used to assemble lists of known functional and actionable genetic variants and their population frequencies, which may inform decisions as to whether pharmacogenetic tests are adequately comprehensive with the interrogated alleles (26, 27). Further, the Association for Molecular Pathology (AMP) has published recommendations for the key attributes of alleles recommended for clinical testing and a minimum set of variants that should be included in clinical genotyping assays for *CYP2C19* (28) and *CYP2D6* (29).

Incidental Findings

A concern about genetic testing in clinical settings is that an individual's genotype may be predictive of an unrelated disease risk; however, variants in pharmacogenes related to drug metabolism are not generally strongly associated with disease risk. A large candidate gene association study has identified a correlation between *CYP2C19* no function alleles (e.g., *CYP2C19*2*) and lower depressive symptoms in European twins (30). A subsequent study of transgenic mice suggested that *CYP2C19* overexpression in the brain was associated with reduced hippocampal volume and behavioral markers of anxiety (31). *CYP2D6* has been investigated in candidate gene studies of depression as well as personality traits (32-44). Although some nominal associations were identified, *CYP2D6* genetic variants are not currently considered to be predictive of depression or personality traits. Notably, a recent meta-analysis of genome wide association studies for major depressive disorder did not identify any significant association between depression risk and *CYP2C19* or *CYP2D6* (45). Small isolated studies on cancer susceptibility have been reported for *CYP2C19* and *CYP2D6*, yet neither gene is currently considered to be significantly predictive of cancer risk (46, 47).

Genetic variants in *SLC6A4* and *HTR2A* have also been associated with numerous psychiatric and medical conditions or phenotypes (48-59). However, evidence is inconsistent and larger studies revealed no evidence of an association between *SLC6A4* genotype and depression (60) and variants in these genes are not considered to be clinically useful in predicting disease likelihood or course of illness.

***CYP2D6* Other Considerations**

There are several factors that cause potential uncertainty in *CYP2D6* genotyping results and phenotype predictions as follows: **1)** Given that it is currently impractical to test for every variation in the *CYP2D6* gene, genotyping assays may not detect rare or *de novo* variants resulting in patients being assigned a default genotype. Depending on the sequence variants (or alleles present) in a given patient, the default genotype may be *CYP2D6*1/*1* (or wild-type) or another diplotype. If the rare or *de novo* variant adversely affects CYP2D6 enzyme function, then the patient's actual phenotype may differ from the predicted phenotype. **2)** Suballeles of *CYP2D6*4* and other star alleles have been identified that harbor additional variants which have no added functional consequence (e.g., *CYP2D6*4.001*, **4.002*, **4.003*, and **4.004*). Therefore, only analyzing for the defining, or core variant of *CYP2D6*4* (1846G>A) is usually sufficient to determine a CYP2D6 phenotype. **3)** There are multiple gene units involved in duplication and other major rearrangements. Additionally, rearranged gene structures involving *CYP2D7*-derived sequences may be misinterpreted as functional duplications (61). If the specific gene units involved in the duplication or other rearrangements are not specifically tested for, the phenotype prediction may be inaccurate and CYP2D6 activity over-estimated. **4)** Alleles are typically assigned based on the most likely scenario of variant linkage. For example, most *CYP2D6*4* alleles carry the 1846G>A 'core' variants, but also 100C>T. If a patient is heterozygous for these two variants, a *CYP2D6*1/*4* is typically assigned. However, the rare *CYP2D6*4.012* subvariant does not carry 100C>T, which in isolation defines the *CYP2D6*10* decreased function allele. Therefore, a *CYP2D6*4.012/*10* assignment constitutes a valid, albeit unlikely, diplotype assignment. Taking the presence or absence of additional variants into consideration can distinguish the two possibilities. As such, to unequivocally assign *CYP2D6* alleles/haplotypes, testing for multiple variants or full gene sequencing may be required. **5)** The majority of laboratories assign the most likely diplotype and do not provide information regarding alternate diplotypes; if laboratories report alternate diplotypes, it may not be accompanied by information regarding the probability of the patient having the alternate diplotype. **6)** Allele frequencies vary considerably among individuals of different ancestries (biogeographical groups). For instance, *CYP2D6*10* is common in Asian populations while *CYP2D6*17* is common in people of sub-Saharan African ancestry. These alleles, however, have a considerably lower prevalence in other groups such as Europeans. Moreover, *CYP2D6*114* (formerly **14A*) is present in Asian populations and the variant defining this allele (1758G>A) is typically incorporated into Asian genotyping panels (62). Thus, the alleles that should be tested for a given population may vary

considerably. **7)** Certain alleles carry genes in tandem arrangements. One such example is *CYP2D6*36+*10* (one copy of the no function *CYP2D6*36* allele and one copy of the decreased function *CYP2D6*10* allele). This tandem is frequently found in East Asians and is typically defaulted as *CYP2D6*10* due to limitations of many test platforms identifying this structural variant. The complexity of the *CYP2D6* locus is detailed in the PharmVar CYP2D6 GeneFocus review (5). Additional information regarding gene analysis, interpretation, and phenotype assignment are summarized by Hicks *et al*., Gaedigk, and Jarvis et al. (10, 12, 63) and the complexity of testing is commented on by Nofziger & Paulmichl (64).

CYP2C19 Other Consideration

There are several factors to consider when genotyping *CYP2C19*. Some of these factors may cause potential uncertainty in *CYP2C19* genotyping results and phenotype predictions and are listed as follows: **1)** Currently, over 35 *CYP2C19* star alleles have been defined by PharmVar with many having a growing number of suballeles. Notably, *CYP2C19*1* is defined by a variant (c.991A>G, p.I331V), while *CYP2C19*38* matches the genomic reference sequence NG_008384.3 and the sequence in the GRCh38genome build (4). Based on current knowledge, c.991A>G does not appear to impact function. *CYP2C19*2* is the most common no function allele. More than ten suballeles of *CYP2C19*2* have been defined which harbor additional variants with no known added functional consequence (e.g., *CYP2C19*2.001*, **2.002*, **2.003*, and **2.004*). Three variants, c.332-23A>G, c.681G>A, and c.991A>G are present in all *CYP2C19*2* suballeles and therefore define the *CYP2C19*2* core allele. The splice variant c.681G>A is unique to *CYP2C19*2* and is thus used to detect *CYP2C19*2*. **2)** Because it is currently impractical to test for every variant in the *CYP2C19* gene, genotyping assays do not typically interrogate rare or novel variants. Depending on the sequence variants (or alleles present) in a given patient, the default genotype may be *CYP2C19*1/*1* (or wild-type) or another diplotype. If the rare or novel variant adversely affects CYP2C19 enzyme function, then the patient's actual phenotype may differ from the predicted phenotype. **3)** *CYP2C19* allele frequencies vary considerably among individuals of different ancestries (biogeographical groups). For example, *CYP2C19*3* has a low prevalence among most ethnic groups, but has an allele frequency of approximately 15% in some Asian populations (***CYP2C19* Allele Frequency Table**) (65). Thus, the alleles that should be tested for a given population may vary. **4)** The

variant defining the no function *CYP2C19*4* allele has been found in linkage with the SNP defining the *CYP2C19*17* allele. This haplotype is designated *CYP2C19*4.002* and may occur more frequently in certain ethnic groups, in particular the Ashkenazi Jewish population (65-67). *CYP2C19*17* is an increased function allele, while *CYP2C19*4.002* is a no function allele. Testing for *CYP2C19*4* in addition to *CYP2C19*17* may improve CYP2C19 phenotype prediction accuracy. It is noted that discrimination between *CYP2C19*4.001/*17* and **1/*4.002* requires additional testing to determine the phase of the variants (i.e., in *cis* or *trans*) in addition to genotyping for both c.-806C>T and 1A>G (68). **5)** A recent study identified a novel allelic variant that carries the *CYP2C19*17*-defining increased activity -806C>T SNP, but also a nonsynonymous variant, c.463G>T, that introduces a premature stop codon (p.E155X) (67). While this variant appears to be rare, it may lead to considerable overestimation of activity in *CYP2C19*17* carriers if not interrogated. **6**) Certain genotyping platforms interrogate many *CYP2C19* star alleles, some of which are rare and not well characterized. Therefore, uncertainty exists when translating a genotype result into a predicted CYP2C19 phenotype in instances where a patient is found to carry a poorly characterized allele. Bioinformatic tools can computationally predict the effect of these rare and poorly characterized alleles on CYP2C19 enzymatic function (69, 70). These data may assist in diplotype interpretation in instances where a poorly characterized allele is reported, but these methods are not a substitute for *in vitro* and *in vivo* analyses. In addition, rare alleles with full and partial *CYP2C19* gene deletions have been reported and designated as *CYP2C19*36* and **37,* respectively; however, most clinical laboratories do not currently interrogate *CYP2C19* copy number (71).

CYP2B6 Other Considerations

The limitations of genetic testing as described here include: (1) known star alleles not tested for will not be reported, and instead, the allele will be reported as **1* by default; (2) in cases where only c.516G>T is interrogated, it will not be known if the variant exists in combination with other variants, and may be reported as *CYP2B6*9* by default or as **6* since the latter is considerably more frequent compared than **9*; (3) rare variants may not be genotyped; (4) tests are not designed to detect unknown or *de novo* variants; (5) *CYP2B6* structural variations exist (hybrids, duplications), but little is known of their frequencies and clinical relevance.

DRUGS: OTHER CONSIDERATIONS

Other Considerations

CYP2D6 inhibition by other drugs may not impact patients predicted to be CYP2D6 PMs because the enzyme activity cannot be further reduced (72). Paroxetine is an example of auto-inhibition; the extent to which UM, NM or IM individuals are affected is not fully understood, however. Paroxetine concentrations were low or undetectable in some CYP2D6 UMs (**Table S1**) signifying that these individuals may not undergo extensive phenoconversion (e.g., from UM to PM) (72-74). Paroxetine exposure at steady state has also been observed to vary significantly between CYP2D6 phenotype groups (**Table S1**). In contrast, chronically administered paroxetine may progressively decrease CYP2D6 activity resulting in oral clearance values that were similar among the phenotype groups (**Table S1**). Higher paroxetine doses (i.e., >30 mg/day) were associated with greater CYP2D6 inhibition. Therefore, paroxetine-induced phenoconversion (from extensive to lower metabolism due to auto-inhibition) may be dose-dependent.

Individuals taking medications that are CYP2D6, CYP2C19, and/or CYP2B6 substrates along with a CYP2D6, CYP2C19, and/or CYP2B6 inhibitor may experience higher than expected drug concentrations, and the individuals' predicted phenotypes may need to be adjusted accordingly. For example, it is common practice in research studies for patients taking strong CYP2D6 inhibitors to have their CYP2D6 activity score adjusted to 0 and the predicted phenotype converted to poor metabolizer (75). For patients taking a moderate CYP2D6 inhibitor, the activity score is multiplied by 0.5 and then converted to the corresponding predicted phenotype (76, 77). Based on FDA drug interaction studies, there does not appear to be any clinically relevant induction of CYP2D6 activity by any medications; however, accumulating data show that CYP2D6 enzyme activity increases during pregnancy (78).

LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE

The evidence summarized in **Tables S1-S4** is graded on a scale of high, moderate, and weak based upon the level of evidence:

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality or consistency of the individual studies, generalizability to routine practice, or the indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

STRENGTH OF RECOMMENDATIONS

CPIC's therapeutic recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are considered in evaluating the evidence supporting therapeutic recommendations include *in vivo* pharmacokinetic and pharmacodynamic data, *in vitro* enzyme activity of tissues expressing wild-type/reference or variants, *in vitro* enzyme activity from tissues isolated from individuals of known genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

Overall, the therapeutic recommendations are presented in a way that allows for rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for rating recommendations adopted from the rating scale for evidence-based guidelines on the use of antiretroviral agents (79):

- **Strong** recommendation for the statement: The evidence is high quality, and the desirable effects clearly outweigh the undesirable effects.
- **Moderate** recommendation for the statement: There is a close or uncertain balance as to whether the evidence is high quality, and the desirable effects clearly outweigh the undesirable effects.
- **Optional** recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
- **No recommendation**: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN ELECTRONIC HEALTH RECORD WITH CLINICAL DECISION SUPPORT

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (80-84). Resources to support the adoption of CPIC guidelines within an EHR are available on the CPIC website (https://cpicpgx.org/guidelines/cpic-guideline-for-ssri-and-snri-antidepressants/). Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating *CYP2D6, CYP2C19,* and/or *CYP2B6* genotype results in an EHR to guide antidepressant use.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (85). To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main manuscript; *CYP2D6*, *CYP2C19*, and *CYP2B6* Diplotype to Phenotype Tables** (https://cpicpgx.org/guidelines/cpic-guideline-for-ssri-and-snri-antidepressants/). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient summary section; these phenotypes are best stored in the EHR at the "person level" rather than at the date-centric "encounter level". Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (see **Pre- and Post-Test Alerts and Flow Chart** for example CDS alerts (https://cpicpgx.org/guidelines/cpic-guideline-for-ssri-and-snri-antidepressants/).

Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include full diplotype to phenotype tables, diagram(s) that illustrate how *CYP2D6, CYP2C19,* and/or *CYP2B6* pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems (see

https://cpicpgx.org/guidelines/cpic-guideline-for-ssri-and-snri-antidepressants/). Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC is also providing gene-drug specific tables that provide guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for relevant drugs (https://cpicpgx.org/guidelines/cpic-guideline-for-ssri-and-snri-antidepressants/).

TABLE S1. EVIDENCE LINKING *CYP2D6*, *CYP2C19* AND *CYP2B6* GENOTYPE TO SSRI PHENOTYPE

Type of Experimental Model	Major Findings	References	Level of Evidence
Es-/citalopram-CYP2C19			
Metabolism			
Clinical	Higher CYP2C19 activity (determined by phenotyping) was associated with lower concentration of escitalopram.	Lloret-Linares, *et al.* (2018) (86)	Weak
Clinical	Genotypic CYP2C19 PMs (patients) had significantly higher racemic citalopram or escitalopram plasma concentrations at steady state as compared to the median dose-corrected plasma concentrations of all study participants.	Grasmader, *et al.* (2004) (87) Rudberg, *et al.* (2008) (88) Tsai, *et al.* (2010) (89) de Vos, *et al.* (2011) (90) Huezo-Diaz, *et al.* (2012) (91)	High
Clinical	Healthy volunteers (92, 93) and patients (94) determined to be CYP2C19 PMs by genotyping or phenotyping had significantly different pharmacokinetic parameters (e.g., higher citalopram or escitalopram plasma concentrations, higher AUC, longer half-life, or slower clearance) at steady state as compared to NMs.	Herrlin, *et al.* (2003) (93) Yin, *et al.* (2006) (94) Noehr-Jensen, *et al.* (2009) (92)	High
Clinical	Healthy volunteers determined to be CYP2C19	Yu, *et al.* (2003) (95) Noehr-Jense, *et al.* (2009) (92)	Moderate

	PMs by genotyping or phenotyping had significantly higher escitalopram AUC, half-life, or lower clearance after a single dose of escitalopram as compared to NMs.	Fudio, *et al.* (2010) (96) Huang, et al. (2021) (97)	
Clinical	Healthy volunteers determined to be CYP2C19 IMs by genotyping had significantly lower escitalopram AUC and half-life after a single dose as compared to PMs.	Huang, et al. (2021) (97)	Weak
Clinical	Genotypic CYP2C19 IMs (patients (88, 98, 99)) and healthy volunteers (96, 100) had significantly higher citalopram or escitalopram plasma concentrations or AUC or log concentration/dose ratios when compared to NMs.	Rudberg, *et al.* (2008) (88) Fudio, *et al.* (2010) (96) Chen, *et al.* (2013) (100) Uckun, *et al.* (2015) (101) Shelton, *et al.* (2020) (99) Zastrozhin, et al. (2021) (98)	High
Clinical	CYP2C19 genotype is associated with increased dose-corrected steady-state plasma or serum concentration of escitalopram with increased number of variant alleles *(*2, *3*).	Tsuchimine, *et al.* (2018) (102) Jukic, *et al.* (2018) (103)	High
Clinical	Escitalopram AUC0-24 significantly decreased with	Strawn, *et al.* (2020) (104)	Weak

	increased CYP2C19 metabolism at 15mg/day.		
Clinical	Patients carrying a *CYP2C19*17* allele had significantly lower levels of citalopram or escitalopram.	Rudberg, *et al.* (2008) (88) de Vos, *et al.* (2011) (90) Huezo-Diaz, *et al.* (2012) (91) Hodgson, *et al.* (2014) (105) Uckun, *et al.* (2015) (13) Jukic, *et al.* (2018) (103)	Moderate
Clinical	Patients with the *CYP2C19*1/*17* genotype had a small but statistically significant lower dose-harmonized serum concentration of citalopram or escitalopram compared to *CYP2C19*1/*1*.	Rudberg, *et al.* (2008) (88) de Vos, *et al.* (2011) (90) Huezo-Diaz, *et al.* (2012) (91) Jukic, *et al.* (2018) (103) Shelton, *et al.* (2020) (99) Branten, et al (2021) (21)	Moderate
Clinical	Patients with a *CYP2C19*17/*17* genotype had significantly lower citalopram or escitalopram plasma concentrations at steady state when compared to NMs.	Ohlsson Rosenborg, *et al.* (2008) (106) Rudberg, *et al.* (2008) (3) Huezo-Diaz, *et al.* (2012) (91) Hodgson, *et al.* (2014) (105) Jukic, *et al.* (2018) (103)	High
Clinical	Patients carrying the CYP2C:TG/CYP2C:TG or *CYP2C19*17*/CYP2C:TG diplotypes had significantly lower escitalopram serum concentrations compared to CYP2C:CG or TA carriers.	Bråten, et al. (2021) (21)	Moderate
Dose			
Clinical	Patients with a *CYP2C19*1/*17* genotype	Bernini de Brito, *et al.* (2020) (107)	Weak

	had significantly higher escitalopram dose when compared to patients with the **1/*1* and **1/*2* genotype and received co-treatment with either mirtazapine or bupropion to achieve remission.		
Clinical	CYP2C19 RMs + UMs showed a slower rate of change in escitalopram dose over time.	Bishop, *et al.* (2015) (108)	Weak
Response			
Clinical	CYP2C19 PM (determined by genotyping) associated with better response or remission.	Peters, *et al.* (2008) (109) Tsai, *et al.* (2010) (89) Mrazek, *et al.* (2011) (110) Hodgson, *et al.* (2014) (111) Hodgson, *et al.* (2014) (105) He, *et al.* (2017) (112) He, *et al.* (2019) (113)	Weak
Clinical	Genotypic CYP2C19 IMs were associated with greater symptom response compared to CYP2C19 NMs.	Strawn, *et al.* (2020) (104)	Weak
Clinical	Heterozygous carriers of rs4244285 had significantly less reduction in HAMD, HADS, UKU scale scores at week 8 compared to non-carriers.	Zastrozhin, et al. (2021) (98)	Weak
Clinical	CYP2C19 metabolizer phenotype was not associated	Bishop, *et al.* (2015) (108) Aldrich, *et al.* (2019) (114) He, *et al.* (2019) (113)	Weak

	with differences in symptom response.	Campos, et al. (2022) (115)	
Clinical	CYP2C19 RMs and UMs responded more quickly than other metabolizer groups.	Aldrich, *et al.* (2019) (114)	Weak
Clinical	Time x group interaction showed that CYP2C19 PMs were associated with greater reduction in HAMA-14 score but not PDSS-CV score compared to IMs and NMs.	He, *et al.* (2019) (113)	Weak
Side effects			
Clinical	CYP2C19 PMs and IMs may be at greater risk of citalopram-induced prolonged QT interval. No association between escitalopram-induced prolonged QT interval and CYP2C19 phenotype.	Kumar, *et al.* (2014) (116) Petry, *et al.* (2019) (117)	Weak
Clinical	Side effects were observed in a patient determined by phenotyping to be both a CYP2D6 PM and CYP2C19 PM.	Herrlin, *et al.* (2003) (93)	Weak
Clinical	CYP2C19 PM (determined by genotyping or phenotyping) was associated with decreased tolerance.	Herrlin, *et al.* (2003) (93) Yin, *et al.* (2006) (94) Mrazek, *et al.* (2011) (110) Asakura, *et al.* (2016) (118)	Weak
Clinical	CYP2C19 phenotype (determined by genotyping) was associated with patient-reported side effects.	Campos, et al. (2022) (115)	Weak

Clinical	CYP2C19 PMs and IMs experienced more side effects during citalopram or escitalopram treatment compared to RMs and UMs.	Hodgson, *et al.* (2015) (119) Aldrich, *et al.* (2019) (114)	Weak
Clinical	CYP2C19 NMs had increased risk of side effects compared to CYP2C19 IMs and PMs	Rossow, et al. (2020) (120)	Weak
Clinical	Combined CYP2C19 PM and RM + UM phenotypes were significantly more frequent among suicide cases compared to controls.	Rahikainen, *et al.* (2019) (121)	Weak
Discontinuation			
Clinical	CYP2C19 IM/PMs were significantly more likely to discontinue es/citalopram treatment than NMs.	Hodgson, *et al.* (2015) (119) Jukic, *et al.* (2018) (103) Aldrich, *et al.* (2019) (114)	Moderate
Clinical	CYP2C19 RM/UMs were NOT significantly more likely to discontinue es/citalopram treatment than NMs.	Aldrich, *et al.* (2019) (114)	Moderate
Clinical	CYP2C19 PMs were significantly more likely to discontinue es/citalopram treatment than NMs.	Jukic, *et al.* (2018) (103)	High
Clinical	CYP2C19 IMs were NOT significantly more likely to discontinue es/citalopram treatment than NMs.	Jukic, *et al.* (2018) (103) Aldrich, *et al.* (2019) (114)	Moderate
Clinical	CYP2C19 RMs were significantly more likely to	Jukic, *et al.* (2018) (103) Aldrich, *et al.* (2019) (114) Campos, et al. (2022) 35094016	Moderate

	discontinue es/citalopram treatment than **1/*1*.		
Clinical	CYP2C19 UMs were significantly more likely to discontinue es/citalopram treatment than **1/*1*.	Jukic, *et al.* (2018) (103) Aldrich, *et al.* (2019) (114)	High
Clinical	CYP2C19 IM but not PM had increased risks of switching and/or dose reduction.	Bahar, et al. (2020) (122)	Weak
Es-citalopram-CYP2D6			
Metabolism			
In-vitro	*CYP2D6*2, *10, *87-*91, *93, *95, *97, *98* showed significantly reduced intrinsic clearance of citalopram in-vitro compared to CYP2D6*1.	Hu, *et al.* (2016) (123)	Weak
Clinical	Genotypic CYP2D6 PMs (patients) had significantly higher citalopram or escitalopram plasma concentrations at steady state when compared to NMs.	Herrlin, *et al.* (2003) (93) Grasmader, *et al.* (2004) (87) Tsai, *et al.* (2010) (89) Huezo-Diaz, *et al.* (2012) (91)	Weak
Clinical	Genotypic CYP2D6 IMs (patients) had significantly higher citalopram or escitalopram plasma concentrations at steady state when compared to NMs.	Huezo-Diaz, *et al.* (2012) (91)	Weak
Clinical	Log concentration/dose ratios for citalopram or escitalopram were significantly different	Shelton, *et al.* (2020) (99)	Weak

	across CYP2D6 phenotypes. But CYP2D6 phenotype was not a significant predictor of citalopram or escitalopram blood levels in a multivariate analysis adjusted for age and smoking status.		
Response			
Clinical	Relationship between genotypic CYP2D6 IM/PM status and better/faster response (tolerance and remission).	Tsai, *et al.* (2010) (89) Mrazek, *et al.* (2011) (110) Han, *et al.* (2013) (124)	Weak
Fluvoxamine-CYP2D6			
Response/Side effects			
Clinical	Patients with the *CYP2D6*1/*4* genotype (tested for rs3892097) had significantly higher efficacy and side effect rating scales within the first 3 weeks of treatment with fluvoxamine compared to patients not carrying the variant.	Zastrozhin, *et al.* (2018) (125) Zastrozhin, et al. (2021) (126)	Weak
Clinical	Higher risk of developing gastrointestinal side effects in patients with reduced CYP2D6 activity (**1/*5*; **10/*10*; **5/*10*) compared to normal metabolizers (**1/*1*; **1/*10*).	Suzuki, *et al.* (2006) (127)	Moderate
Metabolism			

Clinical	Patients with two variant CYP2D6 alleles (*CYP2D6*5/CYP2D6*10* and *CYP2D6*10/CYP2D6*10*) had significantly higher fluvoxamine plasma concentrations compared to patients with no variant alleles.	Suzuki, *et al.* (2011) (128)	Moderate
Clinical	Phenotypic CYP2D6 PMs (healthy volunteers and patients had significantly different fluvoxamine pharmacokinetic parameters (higher maximum plasma concentration, longer half-life, or lower oral clearance of fluvoxamine) following a single dose as compared to NMs.	Carrillo, *et al.* (1996) (129) Spigset, *et al.* (1997) (130)	Moderate
Clinical	Phenotypic CYP2D6 PMs (healthy volunteers) had a lower clearance than NMs following a single dose of fluvoxamine.	Spigset, *et al.* (2001) (131)	Weak
Clinical	Patients with at least one variant CYP2D6 allele had significantly higher fluvoxamine plasma levels than CYP2D6 wild-type patients under steady state conditions with lower doses of fluvoxamine (50mg) but	Watanabe, *et al.* (2008) (132)	Weak

	not higher doses (100-200mg).		
Clinical	The dose-adjusted steady-state plasma concentrations of fluvoxamine were not significantly different among patients with no, one, or two **10* alleles.	Ohara, et al. (2003) (133)	Weak
Clinical	The steady-state plasma concentrations of fluvoxamine and fluvoxamino acid were not significantly different among the *CYP2D6*1/*1*, *CYP2D6*1/*5 + *1/*10* and *CYP2D6*5/*10 + *10/*10* genotype groups. The fluvoxamino acid/fluvoxamine ratio was significantly lower in the patients with the *CYP2D6*1/*5 + *1/*10* and *CYP2D6*5/*10 + *10/*10* genotypes compared to non-**5* or **10* carriers.	Gerstenberg et al, (2003) (134)	Weak
Fluvoxamine-CYP2C19			
Metabolism			
Clinical	CYP2C19 variants were not significantly associated with fluvoxamine steady-state concentrations.	Zastrozhin, et al. (2021) (135)	Weak
Response/Side effects			

Clinical	CYP2C19 variants were not significantly associated with difference in HAMD, HADS, UKU scale scores during 8 weeks of fluvoxamine treatment.	Zastrozhin, et al. (2021) (135)	Weak
Fluoxetine-CYP2D6			
Metabolism			
Clinical	Higher CYP2D6 activity (determined by phenotyping) was associated with lower concentration of the parent compound for fluoxetine.	Lloret-Linares, *et al.* (2018) (86)	Weak
Clinical	Patients determined to be CYP2D6 PMs by genotyping or phenotyping had significantly higher fluoxetine plasma concentrations at steady as compared to NMs.	Eap, *et al.* (2001) (136) Charlier, *et al.* (2003) (137)	High
Clinical	Phenotypic CYP2D6 PMs (healthy volunteers) had significantly different fluoxetine pharmacokinetic parameters (lower clearance, greater AUC, and half-life) following a single dose as compared to NMs.	Hamelin, *et al.* (1996) (138) Fjordside, *et al.* (1999) (139)	High
Clinical	Steady-state fluoxetine dose-corrected plasma concentrations were significantly different among patients with 0, 1, 2, or >2	LLerena, *et al.* (2004) (140) Magalhaes, *et al.* (2020) (141)	High

	active CYP2D6 alleles. Subjects with the most active alleles had the lowest fluoxetine concentrations and those with no active alleles had the highest fluoxetine concentrations.		
Clinical	Genotype-predicted poor metabolizer phenotype was significantly associated with lower concentrations of norfluoxetine and norfluoxetine/fluoxetine ratio compared to other phenotypes.	Magalhaes, *et al.* (2020) (141)	Moderate
Clinical	No statistically significant predictors (*ABCB1*, *CYP2C9*, *CYP2C19*, and *CYP2D6*) were found for differences in fluoxetine + norfluoxetine concentrations.	Magalhaes, *et al.* (2020) (141)	Moderate
Clinical	Increasing CYP2D6 activity score and predicted CYP2D6 phenotype was negatively correlated with fluoxetine metabolic ratio. No significant differences were observed between mean metabolic ratios of most groups (phenotype or activity score) with mean metabolic ratios of their preceding groups. However, CYP2D6	Hinrich, *et al.* (2008) (142)	Weak

	PMs had a significantly lower metabolic ratio compared to IMs .		
Clinical	Fluoxetine/(S)-norfluoxetine ratio was negatively correlated with the number of normal function *CYP2D6* alleles	Gasso, *et al.* (2014) (143)	Moderate
Clinical	Patients with CYP2D6 AS 0.5 had significantly higher fluoxetine plasma concentrations and lower norfluoxetine/fluoxetine ratios compared to patients with CYP2D6 AS 1-2.	Sagahón-Azúa, et al. (2021) (144)	Weak
Clinical	Patients with the *CYP2D6*1/*4* genotype (tested for rs3892097) had significantly higher fluoxetine concentrations and concentration/dose ratio compared to non-carriers of the variant.	Zastrozhin, et al. (2021) (145)	Weak
Side effects			
Clinical	Suspected adverse effects and eventual death due to fluoxetine intoxication in a genotypic CYP2D6 PM.	Sallee, *et al.* (2000) (146)	Weak
Clinical	No significant relationship between fluoxetine-induced adverse drug reactions and CYP2D6 PMs and NMs determined by genotyping.	Roberts, *et al.* (2004) (147)	Moderate

Response			
Clinical	Patients with the *CYP2D6*1/*4* genotype (tested for rs3892097) had significantly worse efficacy and higher side effect rating scales scores at week 8 compared to non-carriers of the variant.	Zastrozhin, et al. (2021) (145)	Weak
Clinical	CYP2D6 metabolizer status was not significantly associated with categorical response (CGI-I score) or time to response.	Troy, et al. (2020) (148)	Weak
Fluoxetine-CYP2C19			
Metabolism			
In-vitro	*CYP2C19*29-*33* showed significantly reduced intrinsic clearance of fluoxetine in-vitro compared to CYP2C19*1.	Fang, *et al.* (2017) (149)	Weak
Paroxetine-CYP2D6			
Metabolism			
Clinical	Genotypic CYP2D6 UMs (patients and health volunteers) had significantly lower, or undetectable, paroxetine plasma concentrations at steady state when compared to genotypic NMs.	Lam, *et al.* (2002) (72) Charlier, *et al.* (2003) (137) Guzey, *et al.* (2006) (74) Gex-Fabry, *et al.* (2008) (73)	High

Clinical	Genotypic CYP2D6 UMs (patients) did not have an antidepressant response to paroxetine.	Guzey, *et al.* (2006) (74) Gex-Fabry, *et al.* (2008) (73)	Weak
Clinical	A subset of individuals determined to be CYP2D6 NMs by genotyping/phenotyping may phenoconvert to IMs or PMs after prolonged paroxetine treatment.	Sindrup, *et al.* (1992) (150) Alfaro, *et al.* (1999) (151) Lam, *et al.* (2002) (72) Solai, *et al.* (2002) (152) Zourkova, *et al.* (2003) (153)	Moderate
Clinical	CYP2D6 UMs may phenoconvert to NMs/IMs when administered paroxetine.	Laine, *et al.* (2001) (154) Lam, *et al.* (2002) (72)	Weak
Clinical	CYP2D6 IMs may covert to PMs when administered paroxetine.	Storelli, *et al.* (2018) (155)	Moderate
Clinical	Healthy volunteers determined to be CYP2D6 PMs by genotyping or phenotyping had significantly higher paroxetine plasma concentrations at steady state compared to NMs.	Lam, *et al.* (2002) (72) Charlier, *et al.* (2003) (137)	High
Clinical	Individuals (healthy volunteers and patients) determined to be CYP2D6 PMs or IMs by genotyping/phenotyping had significantly different pharmacokinetic parameters (e.g., lower clearance, greater	Sindrup, *et al.* (1992) (150) Findling, *et al.* (1999) Chen, *et al.* (2015) (156) Nishimura, *et al.* (2016) (157) Chen, *et al.* (2017) (158)	Moderate

	AUC and half-life) of paroxetine versus NMs.		
Clinical	Pharmacokinetic parameters of paroxetine at steady state were significantly different among those with 0, 1, 2, or >2 active CYP2D6 alleles. Those with the most active alleles had the lowest paroxetine concentrations and those with no active alleles had the highest paroxetine concentrations.	Sawamura, *et al.* (2004) (159) Feng, *et al.* (2006) (160) Findling, *et al.* (2006) (161) Van Neiuwerburgh, *et al.* (2009) (162) Saruwatari, *et al.* (2014) (163)	High
Response			
Clinical	Genotypic CYP2D6 UMs (patients) did not have an antidepressant response to paroxetine.	Guzey, *et al.* (2006) (74) Gex-Fabry, *et al.* (2008) (73)	Weak
Clinical	CYP2D6 poor metabolizers taking paroxetine had higher Hb1Ac than normal metabolizers	Austin-Zimmerman, *et al*. (2021)(164)	Weak
Side effects			
Clinical	A significant relationship between paroxetine-induced adverse drug reactions was observed when female CYP2D6 PMs were compared to female NMs.	Zourkova, *et al.* (2007) (165)	Weak
Clinical	Suspected adverse effects due to paroxetine intoxication in a genotypic CYP2D6 IM.	Sato, *et al.* (2004) (166)	Weak

Clinical	No significant relationship between paroxetine-induced adverse drug reactions was observed when genotypic CYP2D6 PMs and/or IMs were compared to NMs.	Stedman, *et al.* (2002) (167) Murphy, *et al.* (2003) (168) Sugai, *et al.* (2006) (169)	Weak
Sertraline-CYP2C19			
Metabolism			
Clinical	Higher CYP2C19 activity (determined by phenotyping) was associated with lower concentration of the parent compound for sertraline.	Lloret-Linares, *et al.* (2018) (86)	Weak
Clinical	Sertraline and N-desmethyl sertraline concentrations did not differ significantly among the CYP2C19 genotypes.	Yuce-Artun, *et al.* (2016) (170)	Weak
Clinical	Genotypic CYP2C19 PMs (patients carrying two no function CYP2C19 alleles) had higher sertraline plasma concentrations at steady state compared to NM patients with a *CYP2C19*1/*1* genotype.	Rudberg, *et al.* (2008) (171)	Moderate
Clinical	Healthy volunteers determined to be CYP2C19 PMs by phenotyping and genotyping had significantly different sertraline pharmacokinetic parameters (i.e., higher area under the	Wang, *et al.* (2001) (172)	Moderate

	plasma concentration versus time curve and longer half-life, lower clearance) after one dose of sertraline compared to NMs (*CYP2C19*1/*1* and **1*/null).		
Clinical	Healthy volunteers determined to be CYP2C19 IMs by genotyping had significantly different sertraline pharmacokinetic parameters (i.e., higher area under the plasma concentration versus time curve and longer half-life) after one dose of sertraline compared to NMs +UMs/RMs. CYP2C19 UMs/RMs had significantly lower area under the plasma concentration versus time curve values compared to NMs.	Saiz-Rodriguez, *et al.* (2018) (173)	Weak
Clinical	Genotypic CYP2C19 PMs and IMs had increased sertraline serum concentration and higher odds of having a sertraline concentration above the therapeutic reference range compared to CYP2C19 NMs. CYP2C19 UMs/RMs had marginal lower serum	Braten, *et al.* (2020) (174) Parikh, et al (2022) (175)	High

	concentration compared to NMs.		
Clinical	Genotypic CYP2C19 PMs, IMs, and IMs with the rs2860840T + rs11188059G (CYP2C:TG) haplotype had significantly increased sertraline serum concentration compared to NMs. *CYP2C19 *17/*17*, *CYP2C:TG/CYP2C:TG*, *CYP2C19 *17* + CYP2C:TG, and *CYP2C19 *1/*17* had significantly lower sertraline serum concentration compared to CYP2C19 NMs. No significant impact of *CYP2C19*1/ CYP2C:TG* genotype. CYP2C19 PMs had a 1.2-fold higher *N*-desmethylsertraline-to-sertraline metabolic ratio compared to NMs.	Bråten, et al. (2022) (22)	Moderate
Dose			
Clinical	The maximum sertraline dose was inversely associated with the number of CYP2C19 no function alleles *(*2-*8*) at 60 and 90 days.	Poweleit, *et al.* (2019) (176)	Moderate
Clinical	The number of CYP2C19 no function alleles (*2-*8*) was not associated with the sertraline dose at the time of	Poweleit, *et al.* (2019) (176)	Weak

	response or the total number of side effects.		
Clinical	No significant difference in initial weight-adjusted dose but a trend for higher dose was observed at the second dose change for RM/UMs compared to NMs.	Brown, et al. (2022) (177)	Weak
Response			
Clinical	CYP2C19 metabolizer phenotype was not associated with differences in response.	Campos, et al. (2022) (115)	Weak
Side effects			
Clinical	Sertraline-induced adverse effects were observed in CYP2C19 PMs (determined by phenotyping).	Wang, *et al*. (2001) (172)	Weak
Clinical	No differences in the mean QTc between *CYP2C19*1/*1* and *CYP2C19*1/*2* were observed in subjects treated with sertraline.	Petry, *et al.* (2019) (117)	Weak
Clinical	CYP2C19 IMs had greater odds of reporting side effects for sertraline compared to NMs.	Campos, et al. (2022) (115)	Weak
Clinical	CYP2C19 PMs showed greater tolerability (based on discontinuation due to side effects) compared to NMs.	Campos, et al. (2022) (115)	Weak
Clinical	CYP2C19 NMs had an increased risk of side effects	Rossow, et al. (2020) (120)	Weak

	compared to CYP2C19 IMs and PMs.		
Sertraline-CYP2D6			
Metabolism			
Clinical	No significant association between CYP2D6 phenotypes with pharmacokinetics of sertraline after a single dose.	Saiz-Rodriguez, *et al.* (2018) (173)	Weak
Clinical	No significant association between CYP2D6 phenotypes with sertraline concentrations.	Bråten, et al. (2022) (22)	Moderate
Sertraline-CYP2B6			
Metabolism			
Clinical	Carriers of TT genotype of *CYP2B6 G516T* (**9*, rs3745274) had a longer half-life time after a single dose of sertraline but all other pharmacokinetic parameters were not significantly different across genotype groups.	Saiz-Rodriguez, *et al.* (2018) (173)	Weak
Clinical	The mean N-desmethyl sertraline/sertraline ratio and dose normalized N-desmethyl sertraline values were significantly lower in all subgroups including the *CYP2B6*6* and *CYP2B6*9* variant alleles compared to *CYP2B6*1/*1*, and dose normalized sertraline values	Yuce-Artun, *et al.* (2016) (170)	Weak

	were significantly higher in all subgroups with *CYP2B6*6* and *CYP2B6*9* variant alleles compared to *CYP2B6*1/*1*.		
Clinical	CYP2C19 UMs (including CYP2C:TG haplotype) + CYP2B6 UMs had predicted sertraline serum concentrations 35.4% lower compared to CYP2B6 NMs +CYP2C19 NMs. CYP2C19 PMs + CYP2B6 PMs had a 2.89-fold increased predicted serum concentration compared to CYP2B6 NMs +CYP2C19 NMs.	Bråten, et al. (2022) (22)	Weak
Clinical	Patients carrying the *CYP2B6*4* allele had a 17.4% lower serum concentration of sertraline compared to NMs.	Bråten, et al. (2022) (22)	Weak
Clinical	CYP2B6 PMs had increased concentration/dose-ratios compared to NMs.	Parikh, et al (2022) (175) Bråten, et al. (2022) (22)	Moderate
Dose			
Clinical	No significant differences in dosing associated with CYP2B6 genotypes.	Brown, et al. (2022) (177)	Weak
Clinical	CYP2C19 IMs/PMs and CYP2B6 IMs/PMs received significantly higher doses of sertraline recorded as the last prescribed dose as compared	Brown, et al. (2022) (177)	Weak

	CYP2C19 and CYP2B6 NMs.		

[a]See Level of Evidence section for definitions.

TABLE S2. EVIDENCE LINKING *CYP2D6* GENOTYPE TO SNRI AND SEROTONIN MODULATOR PHENOTPE

Type of Experimental Model	Major Findings	References	Level of Evidence
Desvenlafaxine-CYP2D6			
Metabolism			
Clinical	Pharmacokinetic parameters of desvenlafaxine showed no significant differences between CYP2D6 NM/IMs (AS 1-2) and CYP2D6 PMs (AS 0).	Preskorm, *et al.* (2009) (178) Nichols, *et al.* (2011) (179)	Moderate
Duloxetine-CYP2D6/CYP2C19			
Metabolism			
Clinical	*CYP2C19*1/*2* and *CYP2D6*4/*4* patient had high dose-adjusted drug concentrations of duloxetine.	Kuzin, *et al.* (2020) (180)	Weak
Clinical	Patients with the rs3892097GA genotype had a lower level of drug equilibrium concentration of duloxetine than those with the GG genotype.	Zastrozhin, *et al.* (2020) (181)	Weak
Response/Side effects			
Clinical	*CYP2D6*4/*69* patient co-medicated with ciprofloxacin experienced CNS depression (RASS score).	Hoffmann, *et al*. (2022) (182)	Weak
Clinical	*CYP2D6*1/*5* patient experienced duloxetine-induced syndrome of inappropriate antidiuretic hormone secretion.	Kamei, *et al.* (2015) (183)	Weak
Clinical	Patients with the rs3892097GA genotype had higher HAMD and UKU scores after 8 weeks of	Zastrozhin, *et al.* (2020) (181)	Weak

	duloxetine treatment than those with the GG genotype.		
Clinical	In patients with no remission to citalopram or escitalopram treatment, duloxetine remission rates were not significantly different between CYP2D6 UM, IM/NM, or PM and CYP2C19 UM, IM/NM or PM.	Ahmed, *et al.* (2019) (184)	Weak
Milnacipran-CYP2D6/CYP2C19			
Metabolism			
Clinical	No differences were observed in pharmacokinetic parameters of milnacipran for phenotypic CYP2D6 PMs compared to NMs or for phenotypic CYP2C19 PMs compared to NMs.	Puozzo, *et al.* (2005) (185)	Weak
Clinical	CYP2D6 PM patient had 28% higher mean dose-adjusted plasma milnacipran concentrations compared to the drug-specific median. CYP2D6 UM patient (also taken zolpidem, olanzapine) had 4% higher mean dose-adjusted plasma venlafaxine concentrations compared to the drug- specific median.	Grasmader, *et al.* (2004) (87)	Weak
Venlafaxine-CYP2D6			
Metabolism			
In-vitro	*CYP2D6*2, *10, *87-*91, *93-*95, *97, *98* showed significantly reduced intrinsic clearance of	Zhan, *et al.* (2016) (186)	Moderate

	venlafaxine in-vitro compared to *CYP2D6*1*.		
Ex-vivo	The rate of venlafaxine O-demethylation in livers with high CYP2D6 activity was 3-200x times greater than in CYP2D6-deficient livers. O-demethylation and N-demethylation were similar in microsomes from CYP2D6-deficient livers.	Otton, *et al.* (1996) (187)	Moderate
Clinical	Positive correlation between CYP2D6 activity score and the ratio of O-desmethylvenlafaxine/venlafaxine.	Fukuda, *et al.* (2000) (188) Veefkind, *et al.* (2000) (189) Van der Weide, *et al.* (2005) (190) Shams, *et al.* (2006) (191) Hermann, *et al.* (2008) (192) Hinrichs, *et al.* (2008) (142) Arneth, *et al.* (2009) (193) Kandasamy, *et al.* (2010) (194) Launiainen, *et al.* (2011) (195) McAlpine, *et al.* (2011) (196) Nichols, *et al.* (2011) (179) Kingback, *et al.* (2012) (197) Jiang, *et al.* (2015) (198) Karlsson, *et al.* (2015) (199) Mannheimer, *et al.* (2016) (200) Montane, *et al.* (2018) (201) Komahashi-Sasaki, *et al*. (2020) (202) Sasaki, *et al.* (2021) (203) Van der Lee, *et al.* (2021) (204) Jukic, *et al*. (2021) (205) Ganesh, *et al*. (2021) (206)	High

Clinical	CYP2D6 PMs had significantly higher N-desmethylvenlafaxine/venlafaxine ratio or lower venlafaxine/N-desmethylvenlafaxine ratio compared to IMs (AS1) and NMs (AS2).	Launiainen, *et al.* (2011) (195) Kingback, *et al.* (2012) (197) Karlsson, *et al.* (2015) (199)	Moderate
Clinical	N-/O-desmethylvenlafaxine ratio >1 was observed to predict CYP2D6 PMs.	Mannheimer, *et al.* (2016) (200)	Weak
Clinical	O-/N-desmethylvenlafaxine metabolic ratio was significantly lower in CYP2D6 PMs compared to NMs (*1/*1).	Hole, *et al.* (2021) (207)	Moderate
Clinical	CYP2D6 PMs had a significantly lower S/R-venlafaxine ratio and higher S/R-O-desmethylvenlafaxine compared to CYP2D6 IMs and NMs. In CYP2D6 PMs, R-venlafaxine concentrations were higher, while S-venlafaxine concentrations were higher in CYP2D6 NM.	Eap, *et al.* (2003) (208) Kingback, *et al.* (2012) (197) Karlsson, *et al.* (2015) (199)	Moderate
Clinical	CYP2D6*10 carriers had a significantly lower S-ODV/S-VEN ratio and R-ODV/R-VEN ratio compared to *CYP2D6 *1/*1*, or **1/*2* or **2/*2*.	Sasaki, *et al*. (2021) (203)	Weak
Clinical	CYP2D6 PMs had significantly higher venlafaxine and lower O-desmethylvenlafaxine concentrations compared to IMs/NMs.	Lessard, *et al.* (1999) (209) Eap, *et al.* (2003) (208) Preskorn, *et al.* (2009) (178) Lobello, *et al.* (2010) (210) Nichols, *et al.* (2011) (179)	High

Clinical	CYP2D6 PMs/IMs (AS0-1) had significantly higher venlafaxine and lower O-desmethylvenlafaxine concentrations compared to NMs (AS2).	Whyte, *et al.* (2006) (211) Van Nieuwerburgh, *et al.* (2009) (162)	Weak
Clinical	CYP2D6 PMs (AS0) or IMs (AS0.5 or 1) had significantly higher venlafaxine and lower O-desmethylvenlafaxine concentrations compared to NMs (AS1.25 or 2).	Fukuda, *et al.* (1999) (212) Fukuda, *et al.* (2000) (188) Veefkind, *et al.* (2000) (189) Ciusani, *et al.* (2004) (213) Shams, *et al.* (2006) (191) Hermann, *et al.* (2008) (192) Kingback, *et al.* (2012) (197) Jiang, *et al.* (2015) (198) Komahashi-Sasaki, *et al*. (2020) (202)	High
Clinical	CYP2D6 NM (AS 1.25) had significantly higher venlafaxine concentrations compared to NM (AS 2) but no difference in O-desmethylvenlafaxine concentration (single dose or steady state).	Fukuda, *et al.* (1999) (212) Fukuda, *et al.* (2000) (188) Komahashi-Sasaki, *et al*. (2020) (202)	Moderate
Clinical	CYP2D6 UMs (AS3) had significantly lower venlafaxine concentrations compared to NMs (AS2), but no difference in O-desmethylvenlafaxine concentrations.	Shams, *et al.* (2006) (191)	Weak
Clinical	IncreasedCYP2D6 activity was associated with lower venlafaxine and higher O-desmethylvenlafaxine concentrations.	Grasmader, *et al.* (2004) (87) Haller-Gloor, *et al.* (2004) (214) Whyte, *et al.* (2006) (211) Wijnen, *et al.* (2009) (215) Kandasamy, et al. (2010) (194)	Moderate

		McAlpine, et al. (2011) (196) Gressier, *et al.* (2014) (216) Kuzin, *et al.* (2020) (180)	
Clinical	Increased CYP2D6 activity was associated with lower N-desmethylvenlafaxine concentrations.	Veefkind, *et al.* (2000) (189) Eap, *et al.* (2003) (208) Ciusani, *et al.* (2004) (213) Haller-Gloor, *et al.* (2004) (214) Shams, *et al.* (2006) (191) Hermann, *et al.* (2008) (192) Kingback, *et al.* (2012) (197)	High
Clinical	No significant difference in N,O-didesmethylvenlafaxine concentrations by CYP2D6 activity groups.	Lessard, *et al.* (1999) (209) Kingback, *et al.* (2012) (197)	Moderate
Clinical	Increased CYP2D6 activity was associated with lower venlafaxine + O-desmethylvenlafaxine concentrations.	Veefkind, *et al.* (2000) (189) Shams, *et al.* (2006) (191) Hermann, *et al.* (2008) (192) Lobello, *et al.* (2010) (210) McAlpine, *et al.* (2011) (196) Ganesh, *et al*. (2021) (206)	Weak
Clinical	CYP2D6 IMs (AS 0.5) had significantly higher venlafaxine + O-desmethylvenlafaxine concentrations compared to NMs (AS 2) (single dose).	Fukuda, *et al.* (1999) (212) Jiang, *et al.* (2015) (198)	Weak
Clinical	CYP2D6 PMs/IMs (AS0-1) had significantly higher venlafaxine + O-desmethylvenlafaxine concentrations compared to NMs (AS 2).	Van Nieuwerburg, *et al.* (2009) (162)	Weak
Clinical	No difference in proportion of venlafaxine concentrations in/out	Berm, *et al*. (2015) (217)	Weak

	of reference range across NMs, IMs, and PMs after 3, 5, and 12 weeks.		
Venlafaxine-CYP2C19			
Metabolism			
Clinical	Positive correlation between CYP2C19 activity and the ratio of O-desmethylvenlafaxine/venlafaxine.	McAlpine, *et al.* (2011) (196) Karlsson, *et al.* (2015) (199) Montane, *et al.* (2018) (201)	Weak
Clinical	Increased CYP2C19 activity was associated with lower venlafaxine but not associated with O-desmethylvenlafaxine concentrations.	Fukuda, *et al.* (2000) (188) McAlpine, *et al.* (2011) (196) Kringen, *et al.* (2020) (218)	Weak
Clinical	Increased CYP2C19 activity was associated with lower venlafaxine + O-desmethylvenlafaxine concentrations.	McAlpine, *et al.* (2011) (196)	Weak
Clinical	No difference in N-desmethylvenlafaxine/venlafaxine ratio by CYP2C19 activity.	Karlsson, *et al.* (2015) (199)	Weak
Venlafaxine-CYP2D6/CYP2C19			
Metabolism			
Clinical	CYP2D6NM/2C19IM or 2D6NM/2C19PM or 2D6IM (AS0.25-1)/2C19IM or 2D6IM/2C19PM or 2D6PM (AS0)/2C19NM or 2D6PM/2C19IM or 2D6PM/2C19PM had increased venlafaxine + O-desmethylvenlafaxine concentrations compared to	Kringen, *et al.* (2020) (218)	Weak

	CYP2D6 NMs (AS1.25-2)/CYP2C19 NMs (*1/*1 + *1/*17).		
Clinical	CYP2D6NM/2C19IM or 2D6NM/2C19PM or 2D6IM (AS0.25-1)/2C19NM or 2D6IM/2C19IM or 2D6IM/2C19PM or 2D6PM/2C19NM or 2D6PM/2C19IM or 2D6PM/2C19PM had increased venlafaxine concentrations compared to CYP2D6 NMs (AS1.25-2)/CYP2C19 NMs (*1/*1 + *1/*17).	Kringen, *et al.* (2020) (218)	Weak
Clinical	CYP2D6NM/2C19IM or 2D6IM/2C19NM or 2D6PM/2C19UM or 2D6PM/2C19NM or 2D6PM/2C19IM or 2D6PM/2C19PM had decreased O-desmethylvenlafaxine concentrations compared to CYP2D6 NMs (AS1.25-2)/CYP2C19 NMs (*1/*1 + *1/*17).	Kringen, *et al.* (2020) (218)	Weak
Dose			
Clinical	A lower median daily dose (75 mg/day) of venlafaxine was observed in combined CYP2D6 IM (AS0.25-1)/CYP2C19 PMs compared with other metabolizer subgroups.	Kringen, *et al.* (2020) (218)	Weak

Clinical	A lower median daily dose (75 mg/day) of venlafaxine was observed in combined CYP2D6 PMs (AS0)/CYP2C19 PMs compared with the other subgroups.	Kringen, *et al.* (2020) (218)	Moderate
Clinical	No significant differences in venlafaxine dose among CYP2D6 phenotypes.	Shams, *et al.* (2006) (191) McAlpine, *et al.* (2007) (219) Hermann, *et al.* (2008) (192) Lobello, *et al.* (2010) (210) Taranu, *et al.* (2017) (220)	Weak
Clinical	CYP2D6 PMs (AS0) and UMs (AS2.5-3) (part of the subjects who received phenotype-guided dosing) reached the adequate venlafaxine or nortriptyline dose faster compared to NMs (AS1.25-2).	van der Schans, *et al.* (2019) (221)	Weak
Venlafaxine-CYP2D6			
Response			
Clinical	CYP2D6 NMs had greater improvement and higher rates of response compared to PMs.	Shams, *et al.* (2006) (191) Whyte, *et al.* (2006) (211) Van Nieuwerburgh, *et al.* (2009) (162) Lobello, *et al.* (2010) (210) Ng, *et al.* (2013) (222) Brandl, *et al.* (2014) (223) Taranu, *et al.* (2017) (220)	Weak
Clinical	Higher CYP2D6 metabolism was associated with higher remission rate.	Lobello, *et al.* (2010) (210) Taranu, *et al.* (2017) (220) Ahmed, *et al.* (2019) (184)	Weak
Clinical	Improvement, response or remission scores or venlafaxine dose were not significantly	Brandl, *et al.* (2014) (223) Taranu, *et al.* (2017) (220) Ahmed, *et al.* (2019) (184)	Moderate

	different between CYP2C19 phenotypes.		
Side effects			
Clinical	No significant differences in venlafaxine treatment related side effects among CYP2D6 phenotypes.	Shams, *et al.* (2006) (191) Whyte, *et al.* (2006) (211) Lobello, *et al.* (2010) (210) Ng, *et al.* (2013) (222) Brandl, *et al.* (2014) (223) Rolla, *et al.* (2014) (224)	Weak
Clinical	Adverse drug reactions were reported in case studies of CYP2D6 IMs or PMs.	Lessard, *et al.* (1999) (209) Haller-Gloor, *et al.* (2004) (214) McAlpine, *et al.* (2007) (219) Wijnen, *et al.* (2009) (215) Chua, *et al.* (2013) (225) Jornil, *et al.* (2013) (226) Gressier, *et al.* (2014) (216) Garcia, *et al.* (2017) (227) Singh, *et al.* (2019) (228) Volon, *et al.* (2019) (229) Kuzin, *et al.* (2020) (180)	Weak
Clinical	CYP2D6 poor metabolizers participants with diabetes who were taking venlafaxine, had higher HbA1c levels compared to normal metabolizers	Austin-Zimmerman, et al. (2021)(164)	Weak
Meta-analyses			
Venlafaxine-CYP2D6			
Vortioxetine -CYP2D6/CYP2C19			
Clinical	CYP2D6 PMs and IMs had significantly increased dose-adjusted vortioxetine serum concentrations compared to NMs.	Frederiksen, *et al*. (2022) (230)	High

Clinical	No significant difference in vortioxetine serum concentrations was found for CYP2D6 UMs compared to NMs.	Frederiksen, *et al*. (2022) (230)	Weak
Clinical	Prescribed vortioxetine doses did not differ significantly between CYP2D6 phenotypes.	Frederiksen, *et al*. (2022) (230)	Moderate
Clinical	CYP2D6 PMs had a significantly higher frequency of switching to another antidepressant compared with NMs.	Frederiksen, *et al*. (2022) (230)	High
Clinical	No significant difference in switch rate between CYP2D6 IMs and NMs.	Frederiksen, *et al*. (2022) (230)	Moderate
Clinical	CYP2D6 UMs had a significantly higher frequency of switching compared to NMs.	Frederiksen, *et al*. (2022) (230)	Weak

[a]See Level of Evidence section for definitions.

TABLE S3. EVIDENCE LINKING *SLC6A4* GENOTYPE TO ANTIDEPRESSANT PHENOTYPE

Type of Experimental Model	Major Findings	References	Level of Evidence
Desvenlafaxine			
Clinical	The 5-HTTLPR was not associated with significant differences in response (HAMD) or remission (HAMD) in patients with depression receiving desvenlafaxine.	Ng, *et al.* (2016) (231)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in side effects (UKU) in patients receiving desvenlafaxine.	Ng, *et al.* (2016) (231)	Weak
Duloxetine			
Clinical	The 5-HTTLPR was not associated with significant differences in response (HAMD) in patients with depression receiving duloxetine.	Perlis, *et al.* (2010) (232)	Weak
Clinical (AMPS)	The 5-HTTLPR was not associated with significant differences in remission (QIDS-C16) in patients with depression receiving duloxetine.	Ahmed, *et al.* (2019) (184)	Weak
Clinical	The rs25531 variant was not associated with significant differences in response	Perlis, *et al.* (2010) (232)	Moderate

	(HAMD) in patients with depression receiving duloxetine.		
Clinical	The VNTR intron 2 was not associated with significant differences in response (HAMD) in patients with depression receiving duloxetine.	Perlis, *et al.* (2010) (232)	Moderate
Clinical (autopsy cases)	The S/S genotype was significantly associated with increased risk to commit violent suicide in male subjects using citalopram (violent suicides versus controls (males) with LA/LA as reference).	Rahikainen, *et al.* (2017) (233)	Weak
Es-/citalopram			
Clinical (autopsy cases)	The S/S genotype was significantly associated with increased risk to commit violent suicide in male subjects using citalopram (violent suicides versus controls (males) with LA/LA as reference).	Rahikainen, *et al.* (2017) (233)	Weak
Clinical	The S/S genotype was significantly associated with less response (yes: CDRS-R scores over time; no: SCARED scores over time or response based on CGI-I score) compared to the S/L + L/L	Kronenberg, *et al.* (2007) (234) Rotberg, *et al.* (2013) (235)	Weak

	genotype in patients with major depression and or anxiety disorder receiving citalopram.		
Clinical	The S/S + S/L genotype was significantly associated with increased HADS depression score and Mini-MAC fatalism score compared to the L/L genotype in cancer patients receiving citalopram.	Capozzo, *et al.* (2009) (236)	Weak
Clinical	The 5-HTTLPR + rs25531 was not associated with significant differences in response (HAMD) in patients with depression after traumatic brain injury receiving citalopram.	Lanctot, *et al.* (2010) (237)	Weak
Clinical (Star*D)	The S-A-12 and the S-12 haplotype were significantly associated with lower remission (QIDS-C16) in patients with depression receiving citalopram.	Mrazek, *et al.* (2009) (238) Shiroma, *et al.* (2014) (239)	Weak
Clinical (Star*D)	The rs25531 variant was not associated with significant differences in remission (QIDS-C16, QIDS-SR) in patients with depression receiving citalopram.	Kraft, *et al.* (2007) (240) Mrazek, *et al.* (2009) (238) Shiroma, *et al.* (2014) (239)	Moderate
Clinical (Star*D)	The rs25533, rs16965628, rs2020934, rs2066713, rs6354, rs140700, rs140701,	Kraft, *et al.* (2007) (240)	Moderate

	rs1042173 variants were not associated with significant differences in response or remission (QIDS-SR) in patients with depression receiving citalopram.		
Clinical	The 5-HTTLPR was not associated with significant differences in concentrations of prolactin or cortisol in healthy subjects receiving citalopram.	Smith, *et al.* (2004) (241)	Weak
Clinical (Star*D)	The rs25531 variant was not associated with significant differences in treatment discontinuation in patients receiving citalopram.	Mrazek, *et al.* (2009) (238)	Weak
Clinical (Star*D)	One or two copies of the LA allele and one copy of the VNTR 12 allele was significantly associated with a greater remission (QIDS-CR16) rate in patients receiving citalopram compared to other genotypes in patients with first depression episode at age 56 years or later but not in patients with earlier disease onset.	Shiroma, *et al.* (2014) (239)	Weak
Clinical (GENDEP)	The 5-HTTLPR was not associated with significant differences in es-/citalopram plasma levels.	Arias, *et al.* (2003) (242) Eichhammer, *et al.* (2003) (243) Smith, *et al.* (2004) (241)	High

		Kellner, *et al.* (2008) (244) Huezo-Diaz, *et al.* (2009) (245)	
Clinical (GENDEP)	The 5-HTTLPR + rs25531 was not associated with significant differences in escitalopram plasma levels.	Huezo-Diaz, *et al.* (2009) (245) Hinkelman, *et al.* (2010) (246) Garfield, *et al.* (2014) (247)	High
Clinical	The 5-HTTLPR was not associated with significant differences in escitalopram dose titration.	Ng, *et al.* (2013) (222)	Weak
Clinical	The S/S genotype was significantly associated with lower dose of escitalopram compared to the S/L genotype but not the L/L genotype.	Kronenberg, *et al.* (2007) (234) Huezo-Diaz, *et al.* (2009) (245) Ng, *et al.* (2013) (222)	Weak
Clinical (GENDEP)	The 5-HTTLPR + rs25531 was not associated with significant differences in escitalopram dose in patients with major depression disorder.	Huezo-Diaz, *et al.* (2009) (245)	Moderate
Clinical	The 5-HTTLPR + rs25531 was not associated with significant differences in escitalopram dose in patients with autism.	Najjar, *et al.* (2015) (248)	Weak
Clinical (Star*D)	The 5-HTTLPR was not associated with significant differences in treatment discontinuation in patients receiving es-/citalopram.	Kronenberg, *et al.* (2007) (234) Mrazek, *et al.* (2009) (238) Huezo-Diaz, *et al.* (2009) (245)	Moderate
Clinical (GENDEP)	The 5-HTTLPR + rs25531 was not associated with significant differences in treatment	Huezo-Diaz, *et al.* (2009) (245)	Moderate

	discontinuation in patients receiving escitalopram.		
Clinical	The S/S or S/L genotype was significantly associated with increased adverse effect burden compared to L/L genotype in patients receiving es-/citalopram.	Hu, *et al.* (2007) (249) Kronenberg, *et al.* (2007) (234) Kellner, *et al.* (2008) (244) Huezo-Diaz, *et al.* (2009) (245) Maron, *et al.* (2009) (250) Basu, *et al.* (2015) (251) Oz, *et al.* (2020) (252)	Weak
Clinical	The LA allele was significantly associated with reduced adverse effect burden in patients receiving es-/citalopram.	Hu, *et al.* (2007) (249) Huezo-Diaz, *et al.* (2009) (245) Maron, *et al.* (2009) (250) Perroud, *et al.* (2009) (253) Lanctot, *et al.* (2010) (237) Garfield, *et al.* (2014) (247)	Moderate
Clinical	In patients with depression receiving es-/citalopram: The S/L + L/L or L/L only genotype was significantly associated with better response (MADRS, HAMD), better and faster response (BDI) compared to the S/S genotype (19567893, 24130607, 24014145).	Arias, *et al.* (2003) (242) Hu, *et al.* (2007) (249) Kraft, *et al.* (2007) (240) Margoob, *et al.* (2008) (254) Lavretsky, *et al.* (2008) (255) Huezo-Diaz, *et al.* (2009) (245) Maron, *et al.* (2009) (250) Lewis, *et al.* (2011) (256) Won, *et al.* (2012) (257) Sahraian, *et al.* (2013) (258) Ng, *et al.* (2013) (222) Poland, *et al.* (2013) Ng, *et al.* (2013) (222) Shiroma, *et al.* (2014) (239)	Weak

		Basu, *et al.* (2015) (251) Tatham, *et al.* (2017) (259) Mandal, *et al.* (2020) (260) Brunoni, *et al.* (2020)	
Clinical	In patients with depression receiving es-/citalopram: The L/L genotype was significantly associated with greater remission (QIDS-C16, HAMD) compared to the S/S + S/L genotype (18618621, 19375170, 14624186).	Arias, *et al.* (2003) (242) Kraft, *et al.* (2007) (240) Hu, *et al.* (2007) (249) Mrazek, *et al.* (2009) (238) Alexopoulos, *et al.* (2009) (261) Won, *et al.* (2012) (257) Poland, *et al.* (2013) (262) Shiroma, *et al.* (2014) (239) Basu, *et al.* (2015) (251) Kang, *et al.* (2016) (263)	Weak
Clinical	The S/L + L/L genotype was significantly associated with better response (MADRS, BDI) compared to the S/S genotype in male but not female patients with depression receiving es-/citalopram.	Huezo-Diaz, *et al.* (2009) (245) Sahraian, *et al.* (2013) (258)	Weak
Clinical	The L/L genotype was significantly associated with better response (HAMD) compared to the S/S + S/L genotype in female but not male patients with depression receiving escitalopram.	Ng, *et al.* (2013) (222)	Weak
Clinical	The S/S genotype was significantly associated with less response to escitalopram	Keers, *et al.* (2011) (264)	Weak

	(MADRS) compared to the S/L + L/L genotype in subjects with at least one stressful life event, but not in those who reported no stressful life events.		
Clinical (Star*D)	The L/L genotype was significantly associated with a greater remission rate compared S/S + S/L genotype in patients taking citalopram with first depression episode at age 56 years or later but not in patients with earlier disease onset.	Shiroma, *et al.* (2014) (239)	Weak
Clinical	The L/L genotype was significantly associated with greater decrease in MADRS scores between 3 months and 6 months but not over the entire treatment and lower MARDS scores at 6 months compared to S/S + S/L genotype in patients with major depression and alcohol dependence receiving escitalopram.	Muhonen, *et al.* (2011) (265)	Weak
Clinical	In patients with generalized anxiety disorder receiving escitalopram: For response (CGI-I score ≤2) over time, a logistic regression including age, sex, time, CYP2C19 phenotype (normal or	Strawn, *et al.* (2020) (104)	Weak

	intermediate), HTR2A (G/G vs G/A or A/A), and SLC6A4 (S/S vs S/L or L/L) found that greater response was significantly associated with having at least one long allele of SLC6A4 (P = 0.005), being an intermediate CYP2C19 metabolizer (P=015), and having a G/G diplotype for the HTR2A rs6311 allele.		
Clinical	The S/S + S/L genotype was significantly associated with decreased HADS anxiety scores and increased Mini-MAC anxious preoccupation scores compared to the L/L genotype in cancer patients receiving escitalopram.	Schillani, *et al.* (2011) (266)	Weak
Clinical	The S/L + L/L genotype was significantly associated better response (CGI-I, PSWQ) in patients with generalized anxiety disorder receiving escitalopram versus placebo but no significant differences in response to escitalopram versus placebo in patients with the S/S genotype.	Lenze, *et al.* (2010) (267)	Weak
Clinical	The LA/LA genotype was significantly associated with better response (yes: HAMD, MADRS; no: QIDS-C16,	Hu, *et al.* (2007) (249) Maron, *et al.* (2009) (250) Mandal, *et al.* (2020) (260)	Weak

	MADRS) compared to non-LA/LA genotypes in patients with depression receiving es-/citalopram.		
Clinical	Carriers of the LA allele were significantly associated with greater remission (yes: HAMD; no: QIDS-C16) and lower HAMD exit scores compared to non- carriers of the LA alleles in patients with depression receiving es-/citalopram.	Hu, *et al.* (2007) (249) Alexopoulos, *et al.* (2009) (261)	Weak
Clinical	The 5-HTTLPR + rs25531 was not associated with significant differences in response (RBS-R-CRS or ABC-CV-IRR over 6 weeks' time) in patients with autism receiving escitalopram. The S/S genotype was significantly associated with greater reduction in irritability symptoms (ABC-CV-IRR) over first 3 weeks compared to non-S/S genotype.	Najjar, *et al.* (2015) (248)	Weak
Clinical (GENDEP)	The S/S (S= S or LG) genotype showed less response (MADRS) to escitalopram compared to the S/LA + LA/LA genotype in subjects with at least one stressful life event, but not in those who	Keers, *et al.* (2011) (264)	Weak

	reported no stressful life events.		
Clinical	Patients with generalized anxiety disorder receiving escitalopram versus placebo, with one or two LA alleles had a significantly better response (CGI-I, PSWQ) but no significant differences in response to escitalopram versus placebo in patients without the LA allele.	Lenze, *et al.* (2010) (267)	Weak
Clinical	The was 5-HTTLPR + rs25531 not associated with significant differences in response-drug concentration interaction in patients with generalized anxiety disorder receiving escitalopram.	Lenze, *et al.* (2010) (267)	Weak
Clinical (Star*D)	The rs25531 variant was not associated with significant differences in response (QIDS-CR16, QIDS-SR, MADRS) in patients with depression receiving es-/citalopram.	Kraft, *et al.* (2007) (240) Maron, *et al.* (2009) (250) Shiroma, *et al.* (2014) (239)	Moderate
Clinical	The VNTR intron 2 was not associated with significant differences in response (HAMD, QIDS-CR16, MADRS) in patients with depression receiving es-/citalopram.	Huezo-Diaz, *et al.* (2009) (245) Keers, *et al.* (2011) (264) Ng, *et al.* (2013) (222) Shiroma, *et al.* (2014) (239)	Moderate

Clinical	The VNTR intron 2 was not associated with significant differences in remission (HAMD, QIDS-C16) in patients with depression receiving es-/citalopram.	Mrazek, *et al.* (2009) (238) Shiroma, *et al.* (2014) (239) Kang, *et al.* (2016) (263)	Moderate
Clinical (GENDEP)	The VNTR intron 2 was not associated with significant differences in response (MADRS) - stressful life events interaction in patients with depression receiving escitalopram.	Keers, *et al.* (2011) (264)	Moderate
Clinical (GENDEP)	Neither the inclusion of rs25531 or rs2020933 to 5-HTTLPR provided an advantage over single marker analysis in patients with depression receiving escitalopram.	Huezo-Diaz, *et al.* (2009) (245)	Weak
Clinical	In patients with autism receiving escitalopram: The least reduction (baseline to last visit) in ABC-CV Irritability scores was found in the group of subjects with S/S genotype who did not have the rs2020936-rs2020937 TT/TT haplotype.	Owley, *et al.* (2010) (268)	Weak
Clinical (GENDEP)	The VNTR intron 4 was not associated with significant differences in response	Keers, et al (2011) (264) Huezo-Diaz, *et al.* (2009) (245)	Moderate

	(MADRS) in patients receiving escitalopram.		
Clinical (GENDEP)	Subjects with at least one stressful life event and homozygous for STin4 shorter alleles (5-7 repeats) were significantly associated with less response (MADRS) to escitalopram, but not in those who reported no stressful life events.	Keers, *et al.* (2011) (264)	Weak
Clinical	The rs2020933 T allele was associated with better response (yes: MADRS; no: QIDS-SR, MADRS) compared to the A allele in patients with depression receiving es-/citalopram.	Kraft, *et al.* (2007) (240) Huezo-Diaz, *et al.* (2009) (245) Keers, *et al.* (2011) (264)	Weak
Clinical (GENDEP)	The rs2066713, rs2020939, rs8076005, rs2020942, rs140700, rs4583306, rs140701, rs4325622, rs3813034 variants were not associated with significant differences in response (MADRS) in patients with depression receiving escitalopram.	Huezo-Diaz, *et al.* (2009) (245) Keers, *et al.* (2011) (264)	Moderate
Clinical (GENDEP)	The rs2020933, rs2066713, rs2020939, rs8076005, rs2020942, rs140700, rs4583306, rs140701, rs4325622, rs3813034 variants	Keers, *et al.* (2011) (264)	Weak

	were not associated with significant differences in response (MADRS) - stressful life event interaction in patients with depression receiving escitalopram.		
Clinical	The 5-HTTLPR + rs25531 was not associated with significant differences in attentional performance (digit span scores) in older adults with generalized anxiety disorder receiving escitalopram.	Lenze, *et al.* (2013) (269)	Weak
Fluvoxamine			
Clinical	The 5-HTTLPR was not associated with significant differences in fluvoxamine plasma levels.	Smeraldi, *et al.* (1998) (270) Di Bella, *et al.* (2002) (271) Yoshida, *et al.* (2002) (272) Kato, *et al.* (2005) (273)	Moderate
Clinical	The VNTR intron 2 was not significantly associated with differences in fluvoxamine plasma levels.	Ito, *et al.* (2002) (274)	Weak
Clinical	Significant time - genotype interaction was found with the YBOCS compulsion scores but not with the YBOCS obsession scores in patients receiving fluvoxamine. Considering patients without tic disorder co-diagnosis, a significant time - genotype interaction for both YBOCS total scores and compulsion scores was found.	Di Bella, *et al.* (2002) (271)	Weak

Clinical	The L allele was significantly more effective compared to the S allele but no significant difference was found for the genotype comparison S/S vs S/L + L/L in patients receiving fluvoxamine. Significant improvement with respect to poor emotional expression was observed in the L allele, and with respect to flighty eye movements and delayed speech or peculiar or inappropriate speech with the S allele.	Sugie, *et al.* (2005) (275)	Weak
Clinical	Subjects with L/L genotype that were not exposed to stressful life events at onset showed better response (HAMD) compared to exposed subjects with the L/L genotype in patients receiving fluvoxamine. Subjects with the S/S + S/L genotype showed the poorest outcome, particularly if they had been exposed to stressful life events.	Mandelli, *et al.* (2009) (276)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in treatment discontinuation in patients receiving fluvoxamine.	Kato, *et al.* (2006) (277)	Weak

Clinical	The 5-HTTLPR was not associated with significant differences in total side effects or nausea in patients receiving fluvoxamine.	Takahashi, *et al.* (2002) (278) Kato, *et al.* (2006) (277)	Weak
Clinical	The VNTR intron 2 was not associated with significant differences in nausea in patients receiving fluvoxamine.	Takahashi, *et al.* (2002) (278)	Weak
Clinical	The S/L + L/L genotype was significantly associated with better response (yes: HAMD; no: MADRS) compared to the S/S genotype in patients with depression receiving fluvoxamine.	Smeraldi, *et al.* (1998) (270) Yoshida, *et al.* (2002) (272) Kato, *et al.* (2006) (277)	Weak
Clinical	The S/L + L/ L genotype was significantly associated with better response (HAMD) compared to the S/S genotype in patients with depression receiving fluvoxamine only but not in patients receiving fluvoxamine plus pindolol.	Smeraldi, *et al.* (1998) (270)	Moderate
Clinical	The S/S or S/L genotype was significantly associated with less response (HAMD) compared to the L/L genotype and the S/S genotype was associated with slower decrease of the symptomatology in patients	Zanardi, *et al.* (2001) (279)	Weak

	with major/bipolar depressive disorder receiving fluvoxamine.		
Clinical	The 5-HTTLPR was not associated with significant differences in response (YBOCS) in patients with obsessive-compulsive disorder receiving fluvoxamine.	Di Bella, *et al.* (2002) (271)	Weak
Clinical	The LA allele was significantly associated with better response (HAMD) compared to non-LA containing genotypes in patients with depression receiving fluvoxamine.	Kato, *et al.* (2015) (280)	Weak
Clinical	The S/S + S/LG genotype was significantly associated with less response (HAMD) in patients receiving fluvoxamine compared to receiving paroxetine but no significant differences in the LA allele carrier (S/LA + LA/LA + LA/LG).	Kato, *et al.* (2013) (281)	Weak
Clinical	The VNTR intron 2 was not associated with significant differences in response (MADRS) in patients with depression receiving fluvoxamine.	Ito, *et al.* (2002) (274)	Weak
Clinical	The 5-HTTLPR was not associated with significant	Sugie, *et al.* (2005) (275)	Weak

	differences in the blood serotonin level before and after fluvoxamine treatment.		
Fluoxetine			
Clinical	The 5-HTTLPR was not associated with significant differences in treatment discontinuation in patients receiving fluoxetine.	Perlis, *et al.* (2003) (282)	Weak
Clinical	The S/S genotype was significantly associated with insomnia and agitation which emerged earlier in treatment and at lower dose compared to the S/L + L/L genotype but no significant association for the total number of adverse effects in patients receiving fluoxetine.	Perlis, *et al.* (2003) (282)	Weak
Clinical	In patients with depression receiving fluoxetine: The S/L or L/L genotype was significantly associated with better response or remission compared to the S/S + S/L genotype in patients taking fluoxetine.	Yu, *et al.* (2002) (283) Perlis, *et al.* (2003) (282) Peters, *et al.* (2004) (284) Hong, *et al.* (2006) (285) Manoharan, *et al.* (2016) (286)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in response (symptom severity rated with a simple three-point system) in patients with obsessive-	Billett, *et al.* (1997) (287)	Weak

	compulsive disorder receiving fluoxetine.		
Clinical	The L/L genotype was significantly associated with better response (Overt Aggression Scale–modified total and Aggression subscale but not Irritability and Suicidality subscale) compared to the S/S + S/L genotype in patients with personality disorder receiving fluoxetine.	Silva, *et al.* (2010) (288)	Weak
Clinical	The S/S was significantly associated with less response (MADRS) to fluoxetine compared to the S/L + L/L genotype in patients ≥ 25 years but not in patients under the age of 25.	Joyce, *et al.* (2003) (289)	Weak
Clinical	The 5-HTTLPR + rs25531 was not associated with significant differences in response (HAMD, MADRS) in patients with depression receiving fluoxetine.	Gudayol-Ferre, *et al.* (2010) (290) Camarena, *et al.* (2019) (291)	Weak
Clinical	Carriers of the LA allele were associated with greater probability of being remitters (HAMD) compared to non-carriers of the LA allele in patients with depression receiving fluoxetine.	Gudayol-Ferre, *et al.* (2012) (292)	Weak

Clinical	The rs25531 was not associated with significant differences in response (CGI-I) in patients with depression receiving fluoxetine.	Kraft, *et al.* (2005) (293)	Weak
Clinical	The VNTR intron 2 was not associated with significant differences in response (HAMD, CGI-I) in patients with depression receiving fluoxetine.	Peters, *et al.* (2004) (284) Hong, *et al.* (2006) (285)	Weak
Clinical	The haplotype containing rs25531-A , HTTLPR-S, and rs25533-T was more common in responder, whereas the haplotype containing rs25531-G , HTTLPR-L, and rs25533-C in nonresponder patients with depression receiving fluoxetine.	Kraft, *et al.* (2005) (293)	Weak
Clinical	The rs25533, rs2020934, rs2066713, rs2020936, rs2020937, rs2020938, rs2020939, rs25528, rs6354, rs6355, rs2020942, rs140699, rs140700, rs717742, rs140701, rs6353, rs1042173 variants were not associated with significant differences in response (CGI-I) in patients with depression receiving fluoxetine.	Peters, *et al.* (2004) (284)	Weak

Ex-vivo	The S/S genotype was associated with decreased and the L/L genotype with increased SERT immunoreactivity after exposure to fluoxetine compared with vehicle-treated platelets.	Little, *et al.* (2006) (294)	Weak
Milnacipran			
Clinical	The 5-HTTLPR was not significantly associated with differences in milnacipran plasma levels.	Yoshida, *et al.* (2004) (295)	Weak
Clinical	The VNTR intron 2 was not significantly associated with differences in milnacipran plasma levels.	Yoshida, *et al.* (2004) (295)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in nausea in patients receiving milnacipran.	Higuchi, *et al.* (2009) (296)	Weak
Clinical	The VNTR intron 2 was not associated with significant differences in nausea or excessive sweating in patients receiving milnacipran.	Higuchi, *et al.* (2009) (296)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in response (MADRS) or remission (MADRS) in patients with	Yoshida, *et al.* (2004) (295)	Weak

	depression receiving milnacipran.		
Clinical	The 5-HTTLPR + rs25531 was not associated with significant differences in response (HAMD) in patients with depression receiving milnacipran.	Kato, *et al.* (2015) (280)	Weak
Clinical	The VNTR intron 2 was not associated with significant differences in response or remission (MADRS) in patients with depression receiving milnacipran.	Yoshida, *et al.* (2004) (295)	Weak
Mirtazapine			
Clinical	The VNTR intron 2 was not associated with significant differences in response (CGI item 2) (cohort with > 50% of patients taking mirtazapine).	Popp, *et al.* (2006) (297)	Weak
Paroxetine			
Clinical	The S/S genotype was significantly associated with lower paroxetine plasma levels compared to the S/L or L/L genotype.	Pollock, *et al.* (2000) (298) Zanardi, *et al.* (2000) (299) Murphy, *et al.* (2004) (300) Kato, *et al.* (2005) (273) Perna, *et al.* (2005) (301) Lotrich, *et al.* (2008) (302) Yoshimura, *et al.* (2009) (303)	Weak
Clinical	The S/S genotype was significantly associated with a	Murphy, *et al.* (2004) (300) Perna, *et al.* (2005) (301)	Weak

	lower final daily paroxetine dose compared to the S/L or L/L genotype.	Yoshimura, *et al.* (2009) (303)	
Clinical	Severe depression at baseline (HAMD ≥ 25 or MADRS ≥31), high frequency of low activity genotypes (not specified) in nonresponder compared with the responder patients receiving paroxetine (yes: HAMD, no: MADRS). High frequency of low activity alleles in nonresponder patients (HAMD, MADRS).	Camarena, *et al.* (2019) (291)	Weak
Clinical	The S/S + S/L genotype was associated with significantly greater risk of discontinuation compared to the L/L genotype in depressive patients receiving paroxetine.	Murphy, *et al.* (2004) (300)	Moderate
Clinical	The 5-HTTLPR was not associated with significant differences in treatment discontinuation in depressive patients receiving paroxetine.	Kato, *et al.* (2006) (277) Aoki, *et al.* (2014) (304)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in treatment discontinuation in panic disorder patients receiving paroxetine.	Aoki, *et al.* (2014) (304) Watanabe, *et al.* (2017) (305)	Weak
Clinical	The S/S genotype was significantly associated with	Murphy, *et al.* (2004) (300) Kato, *et al.* (2006) (277)	Weak

	more severe adverse events compared to the L/L genotype in patients receiving paroxetine.	Tanaka, *et al.* (2008) (306) Murata, *et al.* (2010) (307) Perroud, *et al.* (2011) (308) Murata, *et al.* (2013) (309)	
Clinical	The VNTR intron 2 was not associated with significant differences in paroxetine discontinuation syndrome.	Murata, *et al.* (2010) (307)	Weak
Clinical	In patients with depression receiving paroxetine: The L/L or S/L genotype were associated with a faster response compared to the S/S genotype (11027924).	Zanardi, *et al.* (2000) (299) Pollock, *et al.* (2000) (298) Murphy, *et al.* (2004) (300) Kato, *et al.* (2006) (277) Bozina, *et al.* (2008) (310) Yoshimura, *et al.* (2009) (303) Tomita, *et al.* (2014) (311)	Moderate
Clinical	Paroxetine plasma concentration was significantly negatively correlated with improvement in MADRS score at week 6 in patients with the S/S but not the S/L + L/L genotype.	Tomita, *et al.* (2014) (311)	Moderate
Clinical	Higher paroxetine plasma concentration was significantly correlated with increased improvement in HAMD scores at week 2 (early response) in patients with the S/S + S/L but not L/L genotype.	Lotrich, *et al.* (2008) (302)	Weak
Clinical	The S/S + S/L genotyped improved more slowly compared to the L/L genotype when acute paroxetine levels	Lotrich, *et al.* (2008) (302)	Weak

	were < 60 ng/mL, at higher concentrations, all genotypes responded similarly in patients with depression.		
Clinical	The 5-HTTLPR was not associated with significant differences in response (YBOCS) in patients with obsessive-compulsive disorder receiving paroxetine.	Denys, *et al.* (2007) (312)	Moderate
Clinical	The 5-HTTLPR was not associated with significant differences in response (CGI-I score at week 2, PAS score) in patients with panic disorder receiving paroxetine.	Ishiguro, *et al.* (2011) (313) Watanabe, *et al.* (2017) (305)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in remission (CGI-S) in patients with panic disorder receiving paroxetine.	Watanabe, *et al.* (2017) (305)	Weak
Clinical	In panic disorder patients with the S/S genotype a significant negative correlation between the reduction in PAS score and paroxetine plasma concentration was found but not with the S/L genotype.	Saeki, *et al.* (2009) (314) Ishiguro, *et al.* (2011) (313)	Weak
Clinical	The S/L and L/L genotype was significantly associated with better response (PASS) compared to the S/S genotype only in female patients with	Perna, *et al.* (2005) (301)	Moderate

	panic disorder receiving paroxetine. Absence of panic attacks was significantly more frequent among L/L compared to S/L and S/S and no panic attacks after paroxetine treatment were also significantly more associated with L allele.		
Clinical	The 5-HTTLPR + rs25531 was not associated with significant differences in response (HAMD) in patients with depression receiving paroxetine.	Ruhe, *et al.* (2009) (315) Kato, *et al.* (2015) (280)	Weak
Clinical	The S/S genotype was significantly associated with better response (HAMD) and greater remission (HAMD) to paroxetine than fluvoxamine treatment but no significant difference in response or remission in the S/L genotype.	Kato, *et al.* (2005) (273)	Weak
Clinical	The S/S genotype was significantly associated with better response (HAMD) and greater remission (HAMD) compared to the S/L + L/L genotype with second switch therapy but not associated with significant differences in response or remission with initial antidepressant or	Wilkie, *et al.* (2009) (316)	Weak

	paroxetine therapy in patients with unipolar depression.		
Clinical	The 12/12 genotype was significantly associated with lack of response or remission (HAMD) compared to non-12/12 genotypes with the initial antidepressant therapy and not associated with significant differences in response with the second switch therapy or paroxetine treatment in patients with unipolar depression.	Wilkie, *et al.* (2009) (316)	Weak
Clinical	The L/L + 9 or 10/9 or 10 haplotype and the S/S + 12/12 haplotype are more frequent in non-responder when each is compared to all other haplotypes in patients with depression receiving paroxetine.	Bozina, *et al.* (2008) (310)	Weak
Clinical	The non-LA/LA genotypes were significantly associated with increased bleeding time, while the bleeding time did not increase in LA/LA patients receiving paroxetine. Patients without the LA allele showed significant decrease in serotonin and increase in PFA-ADP, PFA-EPI and platelet PF4 after 6 and 12 weeks of	Abdelmalik, *et al.* (2008) (317)	Weak

	paroxetine treatment compared to carriers with one or two LA alleles. But no differences in platelet serotonin levels between non-LA/LA and LA/LA genotypes.		
Clinical	The 5-HTTLPR was not associated with significant differences in PFA-closure time, frequency of bruising and mild spontaneous bleeding events in subjects receiving paroxetine.	Hougardy, *et al.* (2008) (318)	Weak
Clinical	Higher diencephalon SERT occupancy was associated with larger proportional HAMD score decreases in LA/LA genotype or LA allele carrier in patients receiving paroxetine. Higher midbrain SERT occupancy in LA/LA carriers was associated with larger proportional HAMD score decreases.	Ruhe, *et al.* (2009) (315)	Weak
Clinical	The 9 or 10/9 or 10 (non-12 allele) genotype was significantly associated with lower HAMD scores from the fourth week of paroxetine treatment compared to 9 or 10/12 or 12/12 genotype but no significant differences between the genotype or allele	Bozina, *et al.* (2008) (310)	Weak

	frequencies and non-/responders (HAMD).		
Clinical	The 5-HTTLPR was not associated with significant differences in mean pretreatment SERT availability and mean SERT occupancies after 6 weeks of treatment in the midbrain or diencephalon in patients receiving paroxetine. The LA/LA genotype was associated with a higher percentage of subjects reaching midbrain occupancies of >= 80% compared to non-LA/LA genotypes.	Ruhe, *et al.* (2009) (315)	Weak
Sertraline			
Clinical	The 5-HTTLPR was not significantly associated with differences in sertraline plasma levels.	Ng, *et al.* (2006) (319)	Weak
Clinical	The S/S genotype was significantly associated with lower sertraline dose compared to the S/L + L/L genotype.	Ng, *et al.* (2006) (319) Reimherr, *et al.* (2010) (320)	Weak
Clinical	The VNTR intron 2 was not significantly associated with differences in sertraline dose.	Nishioka, *et al.* (2013) (321)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in treatment discontinuation in depressive patients receiving sertraline.	Reimherr, *et al.* (2010) (320)	Weak

Clinical	The S/S + S/L genotype was associated with higher dropout rate compared to the L/L genotype in posttraumatic stress disorder patients receiving sertraline.	Mushtaq, *et al.* (2012) (322)	Weak
Clinical	The L allele was significantly associated with reduced adverse effect burden compared to the S allele in patients/subjects receiving sertraline.	Ng, *et al.* (2006) (319) Reimherr, *et al.* (2010) (320) Brunoni, *et al.* (2013) (323) Saiz-Rodriguez, *et al.* (2018) (173) Oz, *et al.* (2020) (252)	Weak
Clinical	The 5-HTTLPR + rs25531 was not associated with significant differences in total number of side effects in patients receiving sertraline.	Poweleit, *et al.* (2019) (176)	Weak
Clinical	The VNTR intron 2 was not associated with significant differences in side effects (suffering at least one ADR) in patients receiving sertraline.	Saiz-Rodriguez, *et al.* (2018) (173)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in response (BDI, HAMD, MADRS, CGI-I, MPS) in patients with depression receiving sertraline.	Durham, *et al.* (2004) (324) Ng, *et al.* (2006) (319) Dogan, *et al.* (2008) (325) Reimherr, *et al.* (2010) (320) Umene-Nakano, *et al.* (2010) (326) Brunoni, *et al.* (2013) (323) Nishioka, *et al.* (2013) (321) Gulfishan, *et al*. (2022)(327)	Weak

Clinical	The 5-HTTLPR was not associated with significant differences in remission (MPS) in patients with depression receiving sertraline.	Reimherr, *et al.* (2010) (320)	Weak
Clinical	The S/S genotype was significantly associated with better response (MPS, HAMD) and greater remission (MPS) compared to the S/L + L/L genotype in patients receiving combined sertraline and atomoxetine but not in patients with sertraline/placebo treatment.	Reimherr, *et al.* (2010) (320)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in mADCS-CGIC or CSDD scores or remission of depression based on a combination of mADCS-CGIC or CSDD scores in patients with Alzheimer Disease receiving sertraline.	Peters, *et al.* (2011) (328)	Weak
Clinical	The L/L genotype was significantly associated with decreased HADS anxiety, Mini-MAC hopelessness-helplessness and anxious preoccupation scores and increased fighting spirit score of Mini-MAC compared to the	Schillani, *et al.* (2008) (329)	Weak

	S/S + S/L genotype in cancer patients receiving sertraline.		
Clinical	The 5-HTTLPR was not associated with being a predictor of 10-week change in LSAS in patients with social anxiety disorder receiving sertraline.	Stein, *et al.* (2014) (330)	Weak
Clinical	The S/L + L/L genotype and the L/L genotype showed significant association with better response (PDSS) compared to the S/S genotype and the S/S +S/L genotype, respectively, in patients with panic disorder receiving sertraline.	Zou, *et al.* (2020) (331)	Moderate
Clinical	The L/L genotype was significantly associated with better and faster response (CAPS, IEP, CGI) compared to S/S and S/L genotype in patients with posttraumatic stress disorder receiving sertraline. No differences between S/S and S/L genotypes.	Mushtaq, *et al.* (2012) (322)	Moderate
Clinical	Predicted expression levels for SLC6A4 were not significantly associated with time to response or proportion of responders in patients with	Poweleit, *et al.* (2019) (176)	Moderate

	anxiety and depressive disorders receiving sertraline.		
Clinical	The 12/12 genotype was significantly associated with less response (yes: HAMD; no: HAMD, CGI-I) compared to the 10/12 genotype in patients with depression receiving sertraline.	Dogan, *et al.* (2008) (325) Nishioka, *et al.* (2013) (321)	Weak
Clinical	The VNTR intron 2 was not associated with significant differences in response (PDSS) in patients with panic disorder receiving sertraline.	Zou, *et al.* (2020) (331)	Weak
Clinical	The rs140701 variant was not associated with significant differences in response (PDSS) in patients with panic disorder receiving sertraline.	Zou, *et al.* (2020) (331)	Weak
Clinical	The rs3813034 variant was not associated with significant differences in response (PDSS) in patients with panic disorder receiving sertraline.	Zou, *et al.* (2020) (331)	Weak
Clinical	Patients with lower predicted levels of expression were treated with sertraline longer than those with higher predicted levels of expression.	Poweleit, *et al.* (2019) (176)	Weak
Clinical	The 5-HTTLPR did not moderate findings on mood and personality measurements	Simmons, *et al.* (2011) (332)	Weak

	in healthy subjects receiving sertraline.		
Venlafaxine			
Clinical	The combined plasma level of venlafaxine + O-desmethyl venlafaxine was elevated compared to standard range in a subject with S/L genotype.	Leibsetseder, *et al.* (2019) (333)	Weak
Clinical	In high VEN + ODV serum concentration (201–400 ng/mL), good response (CGI-I 1 or 2) was lacking in patients with the LA/LA genotype but was observed in more than half of the individuals with non-LA/LA genotypes but no significant association in patients with low (≤ 200 ng/mL)- and supra (> 400 ng/mL)- serum concentrations.	Proft, *et al.* (2014) (334)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in side effects (TSES) in patients receiving venlafaxine.	Lee, *et al.* (2010) (335)	Weak
Clinical	The VNTR intron 2 was not associated with significant differences in side effects (TSES) in patients receiving venlafaxine.	Lee, *et al.* (2010) (335)	Weak
Clinical	The S/L + L/L genotype was significantly associated with better response (yes: BDI,	Min, *et al.* (2009) (336) Lee, *et al.* (2010) (335) Ng, *et al.* (2013) (222)	Weak

	MADRS, HAMA; no: BAI, HAMD, CGI-I, CGI-S) compared to the S/S genotype in patients with depression receiving venlafaxine.		
Clinical (STAR*D)	The 5-HTTLPR was not associated with significant differences in remission (QIDS-C16, HAMD) in patients with depression receiving venlafaxine.	Min, *et al.* (2009) (336) Lee, *et al.* (2010) (335) Ahmed, *et al.* (2019) (184)	Weak
Clinical	The S/L genotype was associated with better response (YBOCS) (yes: non-/responder, no: decrease in score) compared to S/S or L/L genotype in patients with obsessive-compulsive disorder receiving venlafaxine.	Denys, *et al.* (2007) (312)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in response (HAMD) in patients with major/bipolar depressive disorder receiving venlafaxine.	Kirschheiner, er al. (2007) (337)	Weak
Clinical	The 5-HTTLPR + rs25531 was not associated with significant differences in response or remission (MADRS) or time to remission in patients with depression receiving venlafaxine.	Marshe, *et al.* (2017) (338)	Moderate

Clinical	The LA/LA genotype was associated with better response (HAMA, CGI-I) and greater remission (HAMA; CGI-I) compared to non-LA/LA genotypes in patients with generalized anxiety disorder receiving venlafaxine.	Lohoff, *et al.* (2013) (339)	Moderate
Clinical	The LA/LA genotype was significantly associated with less response (CGI-I) compared to non-LA/LA genotypes in patients with major/bipolar depressive disorder receiving venlafaxine.	Proft, *et al.* (2014) (334)	Weak
Clinical	The VNTR intron 2 was not associated with significant differences in response (MADRS, HAMD, CGI-I, CGI-S) in patients with depression receiving venlafaxine.	Min, *et al.* (2009) (336) Lee, *et al.* (2010) (335) Ng, *et al.* (2013) (222) Marshe, *et al.* (2017) (338)	Weak
Clinical	The VNTR intron 2 was not associated with significant differences in remission (QIDS-C16, HAMD, MADRS) or time to remission (MADRS) in patients with depression receiving venlafaxine.	Min, *et al.* (2009) (336) Lee, *et al.* (2010) (335) Marshe, *et al.* (2017) (338) Ahmed, *et al.* (2019) (184)	Weak
Clinical	The rs6354 variant was not associated with significant differences in remission	Wu, *et al.* (2021) (340)	Weak

	(HAMD) in patients receiving venlafaxine.		
Clinical	The rs1487971 variant was not associated with significant differences in remission (HAMD) in patients receiving venlafaxine.	Wu, *et al.* (2021) (340)	Weak
SSRIs/SNRIs (combined analyses)			
Clinical	The S/S (S/LG, LG/LG) or S/L genotype was significantly associated with increased risk of general adverse events compared to the L/L genotype in patients receiving an SSRI.	Kato, *et al.* (2006) (277) Hedenmalm, *et al.* (2006) (341) Smith, *et al.* (2007) (342) Bishop, *et al.* (2009) (343) Staeker, *et al.* (2014) (344) Ramesh, *et al.* (2022)(345)	Weak
Clinical	Females receiving SSRI with the L/L genotype were nearly eight times more likely to be categorized as having sexual dysfunction when taking oral contraceptive, while no relationship was observed in the group not taking oral contraceptive.	Bishop, *et al.* (2009) (343)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in antidepressant-induced mania in patients with bipolar disorder receiving SSRI + SNRI.	Frye, *et al.* (2015) (346)	Weak
Clinical	The 5-HTTLPR + rs25531 was not associated with significant	Frye, *et al.* (2015) (346)	Weak

	differences in antidepressant-induced mania in patients with bipolar disorder receiving SSRI + SNRI.		
Clinical	The S/S or S/L genotype was significantly associated with higher risk of side effects compared to the L/L genotype in patients receiving antidepressants.	Putzhammer, *et al.* (2005) (347) Popp, *et al.* (2006) (297) Wilkie, *et al.* (2009) (316) Strohmaier, *et al.* (2011) (348) Staeker, *et al.* (2014) (344)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in antidepressant-induced mania in patients with bipolar disorder.	Baumer, *et al.* (2006) (349)	Weak
Clinical (GENDEP)	Younger (<=42) patients with S/S genotype receiving antidepressants reported less sexual dysfunction (Antidepressant Side-Effect Checklist item 12) compared to older patients with the S/S genotype.	Strohmaier, *et al.* (2011) (348)	Weak
Clinical	The 12/12 genotype was significantly associated with more moderate to severe side effects compared to the 9/12 + 10/12 + 9/10 + 10/10 genotype in patients receiving SSRI.	Popp, *et al.* (2006) (297) Smits, *et al.* (2007) (342) Bishop, *et al.* (2009) (343) Wilkie, *et al.* (2009) (316) Staeker, *et al.* (2014) (344) Ramesh, *et al.* (2022)(345)	Weak
Clinical	The VNTR intron 2 was not associated with significant differences in antidepressant-	Frye, *et al.* (2015) (346)	Weak

	induced mania in patients receiving SSRI + SNRI.		
Clinical	The 5-HTTLPR-rs25531-VNTR intron 2 haplotype was not associated with significant differences in moderate or marked adverse effects compared to the 5-HTTLPR+rs25531 or VNTR intron 2 individually in patients receiving antidepressants.	Staeker, *et al.* (2014) (344)	Weak
Clinical	The L-A-10 haplotype was associated with reduced risk of antidepressant-induced mania in patients receiving SSRI + SNRI.	Frye, *et al.* (2015) (346)	Weak
Clinical	The S/S or S/L + 10/10 haplotype was significantly associated with higher risk of side effects compared to non-S/S or S/L + 10/10 haplotypes (L/L + 10/10 and S/S or S/L + 10/12 or 12/12 and L/L + 10/12 or 12/12) in patients treated with predominantly HTT-blocking antidepressants.	Popp, *et al.* (2006) (297)	Weak
Clinical	In patients with depression receiving SSRI: The S/S + S/L or S/S only genotype was significantly associated with better response compared with the L/L genotype.	Kim, *et al.* (2000) (350) Yu, *et al.* (2002) (283) Serretti, *et al.* (2004) (351) Kato, *et al.* (2006) (277) Smits, *et al.* (2008) (352) Min, *et al.* (2009) (336)	Weak

		Illi, *et al.* (2011) (353) Myung, *et al.* (2013) (354) Seripa, *et al.* (2015) (355) Ramesh, *et al.* (2022)(345)	
Clinical	The L/L genotype was significantly associated with greater remission (MADRS, HAMD) rate compared to the S/S or S/L genotype in patients with depression receiving SSRI.	Min, *et al.* (2009) (336) Illi, *et al.* (2011) (353)	Moderate
Clinical	The S/S + S/L genotype was significantly associated with nonresponse compared to the L/L genotype in patients 44 years or younger receiving SSRI but not in patients > 44 years.	Smits, *et al.* (2008) (352)	Weak
Clinical	The S/S + S/L genotype was significantly associated with nonresponse compared to the L/L genotype in female patients receiving SSRI.	Smits, *et al.* (2008) (352)	Weak
Clinical	The S/S genotype was significantly associated with less response (HAMD) compared to the S/L + L/L genotype in patients with major/bipolar depressive disorder receiving SSRI.	Serretti, *et al.* (2004) (356) Kirschheiner, *et al.* (2007) (337)	Moderate
Clinical	The 5-HTTLPR was not associated with significant	Yevtushenko, *et al.* (2010) (357)	Weak

	differences in response (HADS, CGI, panic attack frequency/month, Hospital Anxiety) in patients with panic disorder receiving SSRI.		
Clinical	The S/S genotype was significantly associated with selective and slower improvement of depressive "core" and somatic anxiety symptoms but in other symptomatologic clusters such as insomnia and motor retardation compared to the S/L + L/L genotype in patients with mood disorder receiving SSRI.	Serretti, *et al.* (2007) (358)	Moderate
Clinical	The S/S + S/L was significantly associated with less response (yes: >50% decrease in the frequency of binge–purging; no: YBC-EDS) compared to the L/L genotype in patients with bulimia nervosa receiving SSRI.	Erzegovesi, *et al.* (2004) (359) Monteleone, *et al.* (2005) (360)	Weak
Clinical	The L/L genotype was significantly associated with greater remission (complete absence of binge– purging) compared to S/S + S/L genotype in patients with	Monteleone, *et al.* (2005) (360)	Weak

	bulimia nervosa receiving SSRI.		
Clinical	The S allele was associated with poorer response (yes: LSAS; no: CGI-C) compared to the L allele in patients with generalized social anxiety disorder receiving SSRI.	Stein, *et al.* (2006) (361)	Weak
Clinical	The 5-HTTLPR + rs25531 was not associated with significant differences in response or remission (HAMD) in patients with depression receiving SSRI.	Dreimuller, *et al.* (2012) (362)	Weak
Clinical	Carriers of the LA allele with low serum concentrations were significantly associated with lower remission (HAMD) compared to high SSRI concentrations but no significant differences in remission was found in S/LG allele carriers or in response (HAMD) comparing high and low serum concentrations.	Dreimuller, *et al.* (2012) (362)	Weak
Weak	The S allele (S or LG) was associated with less response (yes: LSAS; no: CGI-C) compared to the LA allele in patients with generalized social anxiety disorder receiving SSRI.	Stein, *et al.* (2006) (361)	Clinical

Clinical	The genotypes without an LA allele were significantly associated with less response (CGI-I, CGI-S, PD-S D-Scale) compared to genotypes with LA alleles in patients with psychiatric diseases receiving SSRI.	Staeker, *et al.* (2014) (344)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in response (MADRS) in patients with depression receiving SSRI + SNRI.	Takahashi, *et al.* (2017) (363)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in response (YBOCS) in patients with obsessive-compulsive disorder receiving SSRI + SNRI.	Denys, *et al.* (2007) (312)	Weak
Clinical	The LA/LA genotype was significantly associated with less response (HAMD) in patients with depression receiving SSRI + SNRI.	Kao, *et al.* (2018) (364)	Moderate
Clinical	The 5-HTTLPR was not associated with significant differences in response (HAMD, CGI item 2) in patients with depression receiving antidepressants.	Popp, *et al.* (2006) (297) Kirschheiner, *et al.* (2007) (337)	Weak

Clinical	The S/S genotype was significantly associated with increased remission (BRMS) rate under antidepressant-lithium augmentation compared to S/L or L/L genotype.	Stamm, *et al.* (2008) (365)	Weak
Clinical	The 5-HTTLPR was not associated with significant differences in response (symptom severity rated with a simple three-point system) in patients with obsessive-compulsive disorder receiving antidepressants.	Billett, *et al.* (1997) (287)	Weak
Clinical	The S/S genotype was significantly associated with a lower frequency in responders compared to S/L + L/L genotype in female patients (but not male) receiving antidepressants.	Gressier, *et al.* (2009) (366)	Weak
Clinical	The 5-HTTLPR + rs25531 was not associated with significant differences in response (CGI, PD-S D-Scale scores) in patients with psychiatric diseases receiving antidepressants.	Staeker, *et al.* (2014) (344)	Weak
Clinical	The 5-HTTLPR + rs25531 was not associated with significant differences in response or remission (HAMD) in patients	Domschke, *et al.* (2014) (367)	Weak

	with depression receiving antidepressants.		
Clinical	In patients with depression receiving SSRI: The 12/12 genotype was significantly associated with better response (HAMD) compared to non-12/12 genotypes.	Kim, *et al.* (2000) (350) Smits, *et al.* (2008) (352) Min, *et al.* (2009) (336) Ramesh, *et al.* (2022)(345)	Moderate
Clinical	The 12/12 genotype was significantly associated with greater remission (HAMD) rate compared to the 10/10 +10/12 genotype in patients with depression receiving SSRI.	Min, *et al.* (2009) (336)	Weak
Clinical	The VNTR intron 2 was not associated with significant differences in response (CGI, PD-S D-Scale) in patients with psychiatric diseases receiving SSRI.	Staeker, *et al.* (2014) (344)	Weak
Clinical	The 12/12 and 10/12 genotype was significantly associated with less response compared to the 10/10 genotype in patients with depression receiving SSRI + SNRI.	Takahashi, *et al.* (2017) (363) Kao, *et al.* (2018) (364)	Weak
Clinical	The VNTR intron 2 was not associated with significant differences in response (CGI, PD-S D-Scale) in patients with	Staeker, *et al.* (2014) (344)	Weak

	psychiatric diseases receiving antidepressants.		
Clinical	The L/L + 12/12 haplotype was significantly associated with the highest therapeutic effect (HAMD) in patients receiving SSRI.	Min, *et al.* (2009) (336)	Weak
Clinical	The S/S + 12/12 carrier had high drug response rate in patients receiving SSRI.	Kim, *et al.* (2000) (350)	Weak
Clinical	The rs140701 variant was not associated with significant differences in response (HAMD) in patients with late-life depression receiving SSRI.	Seripa, *et al.* (2015) (355)	Weak
Clinical	The rs3813034 variant was not associated with significant differences in response (HAMD) in patients with depression receiving SSRI.	Seripa, *et al.* (2015) (355)	Weak
Clinical	The rs3813034 variant was significantly associated with the HAMD score change at 6 weeks in patients with depression receiving SSRI + SNRI; (IVS9 A- 90G (rs140701), G2356T (rs1042173), G2563T (rs3813034), and A3641C (rs7224199) were in strong LD).	Nonen, *et al.* (2016) (368)	Weak
Clinical	The rs56316081, rs199835170, rs140699, rs60195519,	Nonen, *et al.* (2016) (368)	Weak

	rs141337922, rs140701, rs6353, rs199990228, rs6352, rs13306796, rs1042173, rs185569563, rs56143548, rs7224199 variants were not associated with significant differences in response (HAMD) in patients with depression receiving SSRI +SNRI.		
Clinical	The magnitude of P1NP decrease was significantly higher in participants receiving antidepressants with the LA allele. No effect on bone resorption as measured by β-CTX change.	Garfield, *et al.* (2014) (369) Rawson, *et al.* (2017) (370)	Weak
Ex-vivo	Platelet 5-HTT kinetics: The L/L genotype was significantly associated with lower median Vmax compared to the S/S genotype but no significant differences in Km values.	Myung, *et al.* (2013) (354)	Weak
Clinical	The LA/LA genotype was significantly associated with increased 5-HTT mRNA level in patients with depression receiving SSRI + SNRI.	Kao, *et al.* (2018) (364)	Weak
Clinical	The S/S + S/LG + LG/LG genotype was significantly associated with longer hospitalization compared the	Staeker, *et al.* (2014) (344)	Weak

	LA/LA + LA/LG genotype in patients receiving SSRI.		
Clinical	The S allele was associated with lower Z-scores at the hip and spine in patients younger than 50 years but not in older patients with psychiatric diagnoses receiving antidepressants.	Lapid, *et al.* (2017) (371)	Weak
Clinical	The 12 allele was significantly associated with increased 5-HTT mRNA level in patients with depression receiving SSRI + SNRI.	Kao, *et al.* (2018) (364)	Moderate
Clinical	The VNTR intron 2 was not associated with significant differences in hospitalization time in patients receiving antidepressants.	Staeker, *et al.* (2014) (344)	Weak

ABC-CV-IRR: Aberrant Behavior Checklist--Community Version-irritability scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BRMS: Bech-Rafaelsen Mania Scale; CAPS: Clinician-Administered PTSD Scale; CDRS-R: Children's Depression Rating Scale-Revised; CGI-I: Clinical Global Impression – Improvement scale; CGI-S: Clinical Global Impression-Severity scale; ADR: Adverse drug reaction; CSDD: Cornell Scale for Depression in Dementia; HADS: Hospital Anxiety and Depression Scale; HAMD: Hamilton Rating Scale for Depression; IES-R: Impact of Event Scale-Revised; LSAS: Liebowitz Social Anxiety Scale; MADRS: Montgomery and Asberg Depression Rating Scale; mADCS-CGIC: Modified AD Cooperative Study-Clinical Global Impression of Change; mini-MAC: Mini-Mental Adjustment to Cancer; MPS: Malingering Probability Scale; PD-S D-scale: Paranoid Depression Scale, anxious-depressive symptoms, PDSS: Panic Disorder Severity Scale; PFA-ADP: Platelet Function Assay-ADP; PFA-EPI: Platelet Function Assay-Epinephrine; PSWQ: Penn State Worry Questionnaire; QIDS, QIDS-SR, QIDS-C, QIDS-C16: Quick Inventory of Depressive Symptomatology (QIDS) C=clinician rated, SR=self-rated, C19= clinician rated 16 items; RBS-R-CRS: Ritualistic/ Sameness Behavior Subscale Scores; SCARED: Screen for Child Anxiety Related Disorders; SERT: serotonin transporter; TSES: Toronto Side Effects Scale; YBOCS: Yale-Brown Obsessive Compulsive Scale; YBC-EDS: Yale-Brown-Cornell Eating Disorders Scale; YBOCS: Yale-Brown Obsessive Compulsive Scale

TABLE S4. EVIDENCE LINKING *HTR2A* GENOTYPE TO ANTIDEPRESSANT PHENOTYPE

Type of Experimental Model	Major Findings	References	Level of Evidence
In-vitro	The rs6311-rs6313 CT-GA genotype was associated with allelic expression imbalance in the extended 5' untranslated regions. Samples with the rs6311-rs6313 TT-AA genotype expressed 2.5-fold less of the upstream 5'UTR relative to samples with the CC-GG genotype.	Smith, *et al.* (2013) (372)	Moderate
In-vitro	The rs76665058 AG genotype was associated with allelic expression imbalance in the extended 3' untranslated regions. Samples with the rs76665058 G allele expressed 1.6- to 2.7-fold more mRNA than the A allele. The rs76665058 G allele was associated with 2.9-fold more expression of the E2– splice isoform mRNA compared to the AA genotype.	Smith, *et al.* (2013) (372)	Weak
Es-/citalopram			
Clinical	rs6311-rs6313 was not associated with side effects in patients receiving es-/citalopram.	Smith, *et al.* (2013) (372) Garfield, *et al.* (2014) (247) Amitai, *et al.* (2016) (373) Demirbugen, *et al.* (2018) (374) Oz, *et al.* (2020) (252)	Weak

Clinical	The rs7323441 variant was not associated with significant differences in side effects (including gastrointestinal) in patients receiving citalopram.	Smith, *et al.* (2013) (372)	Weak
Clinical	rs6311- rs6313 was not associated with significant differences in symptom improvement, response, or remission in patients receiving es-/citalopram.	Choi, *et al.* (2005) (375) McMahon, *et al.* (2006) (376) Peters, *et al.* (2009) (377) Arias, *et al.* (2013) Smith, *et al.* (2013) (372) Basu, *et al.* (2015) (251) Su, *et al.* (2016) (378) Kang, *et al.* (2016) (263) Brunoni, *et al.* (2020) (379)	High
Clinical	The rs6306 variant was not associated with significant differences in response and remission in patients receiving citalopram.	Peters, *et al.* (2009) (377)	High
Clinical	The rs6314 variant was not associated with significant differences in response (QIDS-SR) or remission (QIDS- SR) in patients receiving citalopram.	Peters, *et al.* (2009) (377)	Moderate
Clinical	The rs1928040 variant was not associated with significant differences in response (QIDS-C), remission, (QIDS-C) or change in QIDS-C scores in patients receiving citalopram.	(STAR*D) McMahon, *et al.* (2006) (376)	Moderate
Clinical	The rs3125 variant was not associated with significant	Peters, *et al.* (2009) (377)	Moderate

	differences in response (QIDS-SR) or remission (QIDS- SR) in patients receiving citalopram.		
Clinical	The rs7997012 AA genotype was significantly associated with increased response and remission in patients receiving citalopram but not in patients receiving escitalopram.	McMahon, *et al.* (2006) (376) Paddock, *et al.* (2007) (380) Peters, *et al.* (2009) (377) Uher, *et al.* (2009) (381) Su, *et al.* (2016) (378) Brunoni, *et al.* (2020) (379)	Weak
Clinical	The rs7323441 variant was not associated with significant differences in change in QIDS scores in patients receiving citalopram.	Smith, *et al.* (2013) (372)	Moderate
Clinical	The rs9316233 (minor allele C) and rs2224721 (minor allele T) variants significantly predicted response to escitalopram.	Uher, *et al.* (2009) (381)	Moderate
Clinical	The rs7997012 variant was not associated with significant differences in remission (HAMA) or change in HAMA scores in patients receiving escitalopram.	Su, *et al.* (2016) (378)	Weak
Clinical	The rs7997012 variant was not associated with significant	Najjar, *et al.* (2015) (248)	Weak

	differences in RBS-R-CRS and ABC-CV-IRR score over time in patients with autism receiving escitalopram.		
Clinical	The rs7997012 variant was not associated with significant differences in escitalopram dose over time in patients with autism.	Najjar, *et al.* (2015) (248)	Weak
Clinical	The rs6311-rs6313 TT-AA + CT-GA genotypes were significantly associated with reduced attention as measured by the digit span in patients receiving escitalopram compared to placebo.	Lenze, *et al.* (2013) (269)	Weak
Clinical	Greater response to escitalopram over time was significantly associated with having at least one long allele of *SLC6A4* 5-HTTLPR, being an intermediate CYP2C19 metabolizer, and having a CC-GG genotype for rs6311-rs6313.	Strawn, *et al.* (2020) (104)	Weak
Clinical	rs6311- rs6313 was not associated with significant differences in remission (HAMA) or HAMA scores over time in patients receiving escitalopram.	Su, *et al.* (2016) (378)	Moderate
Clinical	The rs6314 variant was not associated with significant differences in response on neuropathic pain in patients receiving escitalopram	Brasch-Anderson, *et al.* (2011) (382)	Weak
Duloxetine			

Clinical	The rs7997012 variant was not associated with significant differences in change in HAMD scores in patients receiving duloxetine.	Perlis, *et al.* (2009) (383)	Weak
Clinical	The rs7997012 variant was not associated with significant differences in changes in sitting diastolic blood pressure in patients receiving duloxetine.	Fijal, *et al.* (2013) (384)	Weak
Clinical	The rs6314 variant was not associated with significant differences in changes in sitting diastolic blood pressure in patients receiving duloxetine.	Fijal, *et al.* (2013) (384)	Weak
Clinical	rs6311-rs6313 was not associated with significant differences in changes in sitting diastolic blood pressure in patients receiving duloxetine.	Fijal, *et al.* (2013) (384)	Weak
Clinical	The rs1928040 variant was not associated with significant differences in change in HAMD scores in patients receiving duloxetine.	Perlis, *et al.* (2009) (383)	Weak
Clinical	The rs1923884 variant was not associated with significant differences in change in HAMD scores in patients receiving duloxetine.	Perlis, *et al.* (2009) (383)	Weak
Clinical	The rs9534505 variant was not associated with significant differences in change in HAMD	Perlis, *et al.* (2009) (383)	Weak

	scores in patients receiving duloxetine.		
Clinical	The rs2760351 variant was not associated with significant differences in change in HAMD scores in patients receiving duloxetine.	Perlis, *et al.* (2009) (383)	Weak
Fluoxetine			
Clinical	The rs7997012 GG genotype was significantly associated with better improvement based on CGI-S score changes and remission as compared to the AG and AA genotype changes in patients receiving fluoxetine.	Gasso, *et al.* (2018) (385)	Weak
Clinical	The rs7997012 GG genotype was not significantly associated with differences in recovery or improvement based on CDI or GAF/CGAS score changes in patients receiving fluoxetine.	Gasso, *et al.* (2018) (385)	Weak
Clinical	The rs7997012 variant was not associated with significant differences in categorical response (CGI-I <=2) or time to response in patients receiving fluoxetine.	Troy, et al. (2020) (148)	Weak
Clinical	The rs7997012 variant was not associated with significant differences in readmission in patients receiving fluoxetine. However, the rs7997012 GG genotype showed a trend of fewer	Gasso, *et al.* (2018) (385)	Weak

	readmissions compared to the AG + AA genotypes.		
Clinical	The rs7997012 variant was not associated with significant differences in the number of suicide attempts in patients receiving fluoxetine.	Gasso, *et al.* (2018) (385)	Weak
Clinical	rs6311- rs6313 was not associated with significant differences in response, remission, or recovery in patients receiving fluoxetine.	Peters, *et al.* (2004) (284) Hong, *et al.* (2006) (285) Gasso, *et al.* (2018) (385)	Moderate
Clinical	rs6311- rs6313 CC-GG genotype was significantly associated with faster response (GCI-I <=2) compared to the CT-AG + TT-AA genotypes in patients receiving fluoxetine.	Troy, et al. (2020) (148)	Weak
Clinical	The rs6305 variant was not associated with significant differences in response (CGI-I), specific response vs nonspecific response or specific response vs nonspecific response and nonresponse in patients receiving fluoxetine.	Peters, *et al.* (2004) (284)	Weak
Clinical	The rs6314 variant was significantly associated with specific response vs nonspecific response in patients receiving fluoxetine (risk allele and direction not specified) but not with differences in response	Peters, *et al.* (2004) (284)	Weak

	(CGI-I) or specific response vs nonspecific response and nonresponse.		
Clinical	The rs3125 variant was significantly associated with specific response vs nonspecific response in patients receiving fluoxetine (risk allele and direction not specified) but not with differences in response (CGI-I) or specific response vs nonspecific response and nonresponse.	Peters, *et al.* (2004) (284)	Moderate
Clinical	The rs17288723 variant was not associated with significant differences in remission or recovery in patients receiving fluoxetine.	Gasso, *et al.* (2018) (385)	Weak
Clinical	The rs7333412 variant was not associated with significant differences in remission (non-/remitter) or recovery (non-/recovered) in patients receiving fluoxetine.	Gasso, *et al.* (2018) (385)	Weak
Clinical	The rs1923882 variant was not associated with differences in response, remission, or recovery in patients receiving fluoxetine.	Peters, *et al.* (2004) (284) Gasso, *et al.* (2018) (385)	Weak
Clinical	The rs7322347 variant was not associated with significant differences in remission or recovery in patients receiving fluoxetine.	Gasso, *et al.* (2018) (385)	Weak

Fluvoxamine			
Clinical	rs6311-rs6313 was not associated with side effects during fluvoxamine treatment.	Yoshida, *et al.* (2003) (386) Kato, *et al.* (2006) (277) Suzuki, *et al.* (2006) (127)	Weak
Clinical	rs6311- rs6313 was not associated with significant differences in response (YBOCS) in patients with obsessive-compulsive disorder receiving fluvoxamine.	Sina, *et al.* (2018) (387)	Weak
Clinical	The rs6311-rs6313 CC-GG genotype was significantly associated with better improvement (percent HAMD score reduction) compared to CT-GA + TT-AA genotypes	Kato, *et al.* (2006) (277)	Weak
Clinical	rs6311-rs6313 was not significantly associated with differences in response in patients with major depressive disorder receiving fluvoxamine.	Sato, *et al.* (2002) (388) Kato, *et al.* (2006) (277)	Moderate
Clinical	The rs6311-rs6313 CC-GG genotype was significantly associated with lower fluvoxamine plasma levels compared to the CT-GA + TT-AA genotypes.	Sato, *et al.* (2002) (388) Yoshida, *et al.* (2003) (386) Kato, *et al.* (2006) (277)	Weak
Milnacipran			
Clinical	rs6311-rs6313 was not associated with significant differences of	Higuchi, *et al.* (2009) (296)	Weak

	nausea or sweating in patients receiving milnacipran.		
Clinical	rs6311-rs6313 was not associated with significant differences in response (MADRS), remission (MADRS), or the time-course of MADRS scores in patients receiving milnacipran.	Yoshida, *et al.* (2004) (295)	Weak
Clinical	rs6311-rs6313 was not associated with significant differences in milnacipran plasma concentration.	Yoshida, *et al.* (2004) (295)	Weak
Paroxetine			
Clinical	The rs6311-rs6313 CC-GG genotype was significantly associated with greater severity of side effects and treatment discontinuation compared to the CT-GA + TT-AA genotypes in patients receiving paroxetine.	Murphy, *et al.* (2003) (168) Kato, *et al.* (2006) (277) Tanaka, *et al.* (2008) (306) Wilkie, *et al.* (2009) (316)	Weak
Clinical	rs6311-rs6313 was not associated with significant differences in discontinuation syndrome after paroxetine treatment.	Murata, *et al.* (2010) (307)	Weak
Clinical	The rs6314 variant was not associated with significant differences in side effects in patients receiving paroxetine after a failed treatment with an antidepressant.	Wilkie, *et al.* (2009) (316)	Weak
Clinical	The rs6311-rs6313 CC-GG genotype was associated with response (YBOCS). The rs6311-	Denys, *et al.* (2007) (312)	Weak

	rs6313 CC-GG genotype was significantly associated with a greater decrease on the YBOCS compared to CT-GA + TT-AA genotypes in patients receiving paroxetine.		
Clinical	rs6311- rs6313 was not associated with significant differences in response, remission, or symptom improvement in patients receiving paroxetine.	Kato, *et al.* (2006) (277) Wilkie, *et al.* (2009) (316)	Moderate
Clinical	rs6311-rs6313 was not associated with significant differences in paroxetine plasma levels.	Murphy, *et al.* (2003) (168) Kato, *et al.* (2006) (277)	Moderate
Clinical	The rs6314 GA genotype was significantly associated with being a responder (HAMD) and remitter (HAMD) in patients receiving paroxetine after failed antidepressant treatments.	Wilkie, *et al.* (2009) (316)	Missing
Sertraline			
Clinical	The rs7997012 variant was not associated with significant differences in the total number of side effects in patients receiving sertraline.	Poweleit, *et al.* (2019) (176)	Weak
Clinical	rs6311-rs6313 was not associated with side effects in patients receiving sertraline.	Demirbugen, *et al.* (2018) (374) Saiz-Rodriguez, *et al.* (2018) (173) Poweleit, *et al.* (2019) (176) Oz, *et al.* (2020) (252)	Weak

Clinical	The rs7997012 variant was not associated with maximum sertraline dose or time to the average maximum sertraline dose.	Poweleit, *et al.* (2019) (176)	Weak
Clinical	The rs7997012 variant was not associated with time to response in patients receiving sertraline.	Poweleit, *et al.* (2019) (176)	Weak
Clinical	rs6311-rs6313 was not associated with significant differences in mADCS-CGIC or CSDD score or remission (mADCS-CGIC, CSDD) in patients receiving sertraline.	Peters, *et al.* (2011) (328)	Weak
Clinical	rs6311-rs6313 was not associated with significant differences in response (PDSS) in patients receiving sertraline.	Zou, *et al.* (2020) (331)	Moderate
Clinical	rs6311-rs6313 was not associated with significant differences in change in LSAS score in patients receiving sertraline.	Stein, *et al.* (2014) (330)	Moderate
Clinical	The rs6311-rs6313 TT-AA + CT-GA genotypes were significantly associated with higher maximum sertraline dose and higher sertraline dose at response compared to the CC-GG genotype.	Poweleit, *et al.* (2019) (176)	Weak
Clinical	rs6311-rs6313 was significantly associated with time to the average maximum sertraline dose, with patients with the TT-AA genotype requiring fewer days	Poweleit, *et al.* (2019) (176)	Weak

	and with the CC-GG genotype more days.		
Clinical	rs6311-rs6313 was not associated with significant differences in time to response in patients receiving sertraline.	Poweleit, *et al.* (2019) (176)	Weak
Clinical	The rs3742278 variant was not associated with significant differences in change in LSAS score in patients receiving sertraline.	Stein, *et al.* (2014) (330)	Weak
Venlafaxine			
Clinical	The rs7997012 GG + GA genotypes were significantly associated with greater HAMA score reduction, greater response (HAMA), and improvement (CGI) and treatment outcome over time based on HAMA score compared to the AA genotype in patients receiving venlafaxine.	Lohoff, *et al.* (2013) (389)	Weak
Clinical	The rs7997012 GG + GA genotypes were not significantly associated with differences in remission (HAMA) in patients receiving venlafaxine. Patients with the rs7997012 GG + GA genotypes had significantly lower in HAMD scores compared to the AA genotype at 6 months.	Lohoff, *et al.* (2013) (389)	Weak
Clinical	rs6311- rs6313 was not associated with significant differences in response, remission, time-to-	Marshe, *et al.* (2017) (338) Yuan, *et al.* (2018) (390)	Moderate

	remission, or symptom improvement in patients receiving venlafaxine.		
Clinical	rs6311-rs6313 was not associated with significant differences in response (YBOCS) or changes in YBOCS score in patients receiving venlafaxine.	Denys, *et al.* (2007) (312)	Weak
Clinical	rs9567746 was not associated with significant differences in remission (MADRS), time to remission, response across time points, percentage change in MADRS score in patients receiving venlafaxine.	Marshe, *et al.* (2017) (338)	Weak
Clinical	rs2274639 was not associated with significant differences in remission (MADRS), time to remission, response across time points, percentage change in MADRS score in patients receiving venlafaxine.	Marshe, *et al.* (2017) (338)	Moderate
SSRIs, SNRIs, and/or any antidepressant (studies analyzing SSRI, SNRIs, or all antidepressants as a class)			
Clinical	The rs7997012 AA genotype was significantly associated with more side effects compared to the GA + GG genotypes in patients receiving SSRIs, SNRIs, or TCAs without antipsychotics.	Staeker, *et al.* (2014) (344)	Weak
Clinical	The rs7997012 AA genotype was significantly associated with more side effects compared to the GA	Staeker, *et al.* (2014) (344)	Weak

	+ GG genotypes in patients SSRIs.		
Cinical	rs6311-rs6313 was not associated with significant differences in risk of fetal congenital heart abnormality when prenatal exposed to SSRI or SNRI.	Daud, *et al.* (2017) (391)	Weak
Clinical	The rs6311-rs6313 TT-AA genotype was significantly more prevalent in the sexual dysfunction group in male patients receiving SSRI or SNRI.	Liang, *et al.* (2012) (392)	Weak
Clinical	The rs6311-rs6313 CC-GG genotype was significantly associated with decreased odds for dizziness and increased odds for poor concentration, while the rs6311-rs6313 CT-GA genotype was significantly associated with increased odds for excessive sweating, diarrhea, constipation, and blurred vision in patients receiving SSRIs.	Badamasi, *et al.* (2021) (393)	Weak
Clinical	The rs6311-rs6313 CC-GG genotype was significantly associated with increased likelihood of sexual dysfunction compared to the CT-GA + TT-AA genotypes in patients receiving SSRIs.	Bishop, *et al.* (2006) (394) Masiran, *et al.* (2013) (395) Masiran, *et al.* (2014) (396) Shultz, et al. (2021) (397)	Weak
Clinical	rs6314 was not associated with significant differences in risk of fetal congenital heart abnormality	Daud, *et al.* (2017) (391)	Weak

	when prenatal exposed to SSRIs or SNRIs.		
Clinical	rs1928040 was not associated with significant differences in risk of fetal congenital heart abnormality when prenatal exposed to SSRIs or SNRIs.	Daud, *et al.* (2017) (391)	Weak
Clinical	rs7997012 was not associated with significant differences in response, remission, or symptom improvement in patients receiving antidepressants.	Illi, *et al.* (2009) (398) Horstmann, *et al.* (2010) (399) Kishi, *et al.* (2010) (400) Viikki, *et al.* (2011) (401) Staeker, *et al.* (2014) (344)	Moderate
Clinical	Better response after citalopram, fluoxetine, paroxetine or ECT treatment was more clearly detected in male patients who had both GA genotype at rs7997012 and TT-AA genotype for rs6311-rs6313.	Viikki, *et al.* (2011) (401)	Weak
Clinical	rs6311- rs6313 was not associated with significant differences in response, remission, or symptom improvement in patients receiving antidepressants.	Viikki, *et al.* (2011) (401) Qesseveur, *et al.* (2016) (402)	Weak
Clinical	rs6311- rs6313 was not associated with significant differences in response (YBOCS, Sheehan Disability Scale) in patients receiving antidepressants.	Corregiari, *et al.* (2012) (403)	Weak
Clinical	rs6311- rs6313 was associated with significant differences in response or remission in patients receiving SSRIs.	Cusin, *et al.* (2002) (404) Illi, *et al.* (2009) (398) Kishi, *et al.* (2010) (400) Li, *et al.* (2012) (405)	Weak

		Noordam, *et al.* (2015) (406) Dong, *et al.* (2016) (407) Badamasi, *et al.* (2021) (393) Sun, *et al.* (2021) (408)	
Clinical	The rs6311-rs6313-rs1928040 C-G-A haplotype was significantly less prevalent and the C-G-G haplotype was significantly more prevalent with response (SIGH-D) in patients receiving fluvoxamine, sertraline, or paroxetine.	Kishi, *et al.* (2010) (400)	Moderate
Clinical	rs1928040 was not associated with significant differences in response or remission in patients receiving fluvoxamine, sertraline, or paroxetine.	Kishi, *et al.* (2010) (400)	Weak
Clinical	rs6306 was not associated with significant differences in response (HAMD) or time-course of response but patients with the AA genotype had significant higher HAMD scores at baseline and after 6 weeks of fluvoxamine or paroxetine treatment as compared to GG and GA genotypes.	Cusin, *et al.* (2002) (404)	Moderate
Clinical	The rs6305 GG genotype was significantly more frequent among the non-responders vs responders (YBOCS) in patients receiving fluoxetine, fluvoxamine, citalopram,	Corregiari, *et al.* (2012) (403)	Moderate

	sertraline, paroxetine, or clomipramine.		
Clinical	rs6305 was not associated with significant differences in response (HAMD) in patients receiving citalopram, paroxetine, or sertraline.	Li, *et al.* (2012) (405)	Moderate
Clinical	rs6314 was not associated with significant differences in response (HAMD), remission (HAMD), HAMD score, or percentage of HAMD improvement from baseline in patients receiving antidepressants (mainly SSRI and SNRI).	Qesseveur, *et al.* (2016) (402)	Moderate
Clinical	The rs17288723 CC genotype was significantly associated with change in HAMD score over time and remission but not with differences in response (HAMD) in patients receiving antidepressants.	Horstmann, *et al.* (2010) (399)	Moderate
Clinical	The rs7333412 GG genotype was significantly associated with higher HAMD scores, lower percentage of HAMD improvement from baseline, and lower response compared to AA + AG genotypes but not with differences in remission (HAMD) in patients receiving antidepressants (mainly SSRI and SNRI).	Qesseveur, *et al.* (2016) (402)	Moderate

Clincal	rs7333412 was associated with response (%ΔHAMD, binary) and remission (HAMD score, binary) in patients receiving paroxetine, citalopram, escitalopram, and fluoxetine.	Kao, *et al.* (2020) (409)	Weak
Clinical	rs1923882 was associated with remission (HAMD score, binary) but not response (%ΔHAMD, binary) in patients receiving paroxetine, citalopram, escitalopram, and fluoxetine.	Kao, *et al.* (2020) (409)	Weak
Clinical	The rs3803189 GT + GG genotypes were significantly associated with greater likelihood of response (HAMD) compared to the TT genotype in patients receiving escitalopram, fluvoxamine, fluoxetine, or sertraline.	Sun, *et al.* (2021) (408)	Weak
Clinical	rs3803189 was associated with response (%ΔHAMD, binary) and remission (HAMD score, binary) in patients receiving paroxetine, citalopram, escitalopram, and fluoxetine.	Kao, *et al.* (2020) (409)	Weak
Clinical	rs7322347 was associated with remission (HAMD score, binary) but not response (%ΔHAMD, binary) in patients receiving paroxetine, citalopram, escitalopram, and fluoxetine.	Kao, *et al.* (2020) (409)	Weak

Clinical	rs17289304 was not associated with significant differences in response (HAMD) or remission (HAMD) in patients receiving fluoxetine, paroxetine, citalopram, or sertraline.	Dong, *et al.* (2016) (407)	Weak

[a]See Level of Evidence section for definitions. ABC-CV-IRR: Aberrant Behavior Checklist--Community Version-irritability scale; CGI: Clinical Global Impression – Improvement scale; CSDD: Cornell Scale for Depression in Dementia; ECT: Electroconvulsive therapy; CGI-I: Clinical Global Impressions-Improvement, CDI: Children's Depression Inventory, GAF: Global Assessment of Functioning, CGAS: Children's Global Assessment Scale, HAMD: Hamilton Rating Scale for Depression; LSAS: Liebowitz Social Anxiety Scale; MADRS: Montgomery and Asberg Depression Rating Scale; mADCS-CGIC: Modified AD Cooperative Study-Clinical Global Impression of Change; PDSS: Panic Disorder Severity Scale; QIDS, QIDS-SR, QIDS-C: Quick Inventory of Depressive Symptomatology (QIDS) C=clinician rated, SR=self-rated; RBS-R-CRS: Ritualistic/ Sameness Behavior Subscale Scores; SIGH-D: Structured Interview Guide for the Hamilton Depression Rating Scale; YBOCS: Yale-Brown Obsessive Compulsive Scale

TABLE S5. METABOLISM OF ANTIDEPRESSANTS INCLUDED IN THIS GUIDELINE

Drug	Enzyme(s) involved in major metabolic pathway	Active compound/metabolite	Less active/inactive metabolite	PharmGKB pathway
Citalopram/ Escitalopram	CYPC19	Citalopram/Escitalopram	N-desmethylcitalopram/N-desmethylescitalopram	https://www.pharmgkb.org/pathway/PA164713429
Duloxetine	CYP1A2	Duloxetine	4-hydroxyduloxetine	https://www.pharmgkb.org/pathway/PA166255221
Fluoxetine	CYP2D6	Fluoxetine/S-norfluoxetine		https://www.pharmgkb.org/pathway/PA161749012
	CYP2D6/CYP2C9		R-norfluoxetine	
Fluvoxamine	CYP2D6	Fluvoxamine	Fluvoxamine acid	https://www.pharmgkb.org/chemical/PA449690
Levomilnacipran	CYP3A4	Levomilnacipran	Desethyl levomilnacipran, p-hydroxy-levomilnacipran	
Milnacipran	glucuronidation	Milnacipran	l-milnacipran carbamoyl-O-glucuronide	
Paroxetine	CYP2D6	Paroxetine	Paroxetine catechol	https://www.pharmgkb.org/pathway/PA166121347
Sertraline	CYP2C19	Sertraline	N-desmethylsertraline	https://www.pharmgkb.org/pathway/PA166181117
	CYP2B6	Sertraline	N-desmethylsertraline	
Venlafaxine	CYP2D6	Venlafaxine/O-desmethylvenlafaxine	N-desmethylvenlafaxine	https://www.pharmgkb.org/pathway/PA166014758
Desvenlafaxine	CYP2C19, CYP3A4	Desvenlafaxine	N,O-didesmethyl venlafaxine	https://www.pharmgkb.org/pathway/PA166014758
Vilazodone	CYP3A4	Vilazodone	Oxidative metabolites	
Vortioxetine	CYP2D6	Vortioxetine	Vortioxetine Benzoic acid	https://www.pharmgkb.org/pathway/PA166255301

TABLE S6. DOSING RECOMMENDATION FOR FLUOXETINE BASED ON CYP2D6 PHENOTYPE

Phenotype	Implication	Therapeutic Recommendation	Classification of Recommendation	Considerations
CYP2D6 Ultrarapid metabolizer	Increased metabolism of fluoxetine and decreased fluoxetine:norfluoxetine ratio as compared to normal metabolizers. There is a lack of evidence supporting the clinical impact of decreased fluoxetine:norfluoxetine ratio. The extent to which ultrarapid metabolizers phenoconvert to normal, intermediate, or poor metabolizers due to	No action recommended based on genotype for fluoxetine because of minimal evidence regarding the impact on efficacy or side effects.	No recommendation	

	fluoxetine and norfluoxetine inhibition of CYP2D6 is unclear.			
CYP2D6 Normal metabolizer	Normal metabolism. The extent to which normal metabolizers phenoconvert to intermediate or poor metabolizers due to fluoxetine and norfluoxetine inhibition of CYP2D6 is unclear.	Initiate therapy with recommended starting dose.	Strong	
CYP2D6 Intermediate metabolizer	Decreased metabolism of fluoxetine and increased fluoxetine:norfluoxetine ratio but similar total active	No action recommended based on genotype for fluoxetine because of minimal evidence	No recommendation	

	enantiomer concentrations compared to normal metabolizers. There is a lack of evidence supporting the clinical impact of increased fluoxetine:norfluoxetine ratio. The extent to which intermediate metabolizers phenoconvert to poor metabolizer due to fluoxetine and norfluoxetine inhibition of CYP2D6 is unclear.	regarding the impact on efficacy or side effects.		

CYP2D6 Poor metabolizer	Decreased metabolism of fluoxetine to active metabolites and greatly increased fluoxetine:norfluoxetine ratio but similar total active enantiomer concentrations compared to normal metabolizers. There is a lack of evidence supporting the clinical impact of increased fluoxetine:norfluoxetine ratio.	No action recommended based on genotype for fluoxetine because of minimal evidence regarding the impact on efficacy or side effects.	No recommendation	

TABLE S7. DOSING RECOMMENDATIONS FOR CITALOPRAM AND ESCITALOPRAM BASED ON *HTR2A* GENOTYPE

Genotype	Implications	Recommendations	Classification of recommendation[a]	Considerations
rs6311G; rs6313C	Mixed evidence for the effect of genetic variability on citalopram/escitalopram response, remission or side effects.	No action recommended based on genotype for citalopram/escitalopram because of insufficient evidence supporting clinical use.	No recommendation	Some meta-analyses show a small but statistically significant antidepressant class association with response, remission or side effects but there remains a lack of clarity regarding how to translate this into clinical action.
rs7997012G	Mixed evidence for the effect of genetic variability on citalopram/escitalopram response or remission.	No action recommended based on genotype for citalopram/escitalopram because of insufficient evidence supporting clinical use.	No recommendation	Some meta-analyses show a statistically significant small to medium antidepressant class association with response or remission but there remains a lack of clarity regarding how to translate this into clinical action.
Other variants	No effect or insufficient evidence for escitalopram/citalopram response, remission or side effects.	No action recommended based on genotype for citalopram/escitalopram because of insufficient evidence supporting clinical use.	No recommendation	

TABLE S8. DOSING RECOMMENDATIONS FOR FLUOXETINE, FLUVOXAMINE, PAROXETINE, SERTRALINE, DULOXETINE, VENLAFAXINE, DESVENLAFAXINE, VILAZODONE, VORTIOXETINE, LEVOMILNACIPRAN AND MILNACIPRAN BASED ON *HTR2A* GENOTYPE

Genotype	Implications	Recommendations	Classification of recommendation[a]	Considerations
rs6311G; rs6313C	Weak to no evidence for the effect of genetic variability on response, remission or side effects.	No action recommended based on genotype because of insufficient evidence supporting clinical use.	No recommendation	Some meta-analyses show a statistically significant small antidepressant class association with response or remission but there remains a lack of clarity regarding how to translate this into clinical action.
rs7997012G	Weak to no evidence for the effect of genetic variability on response or remission.	No action recommended based on genotype because of insufficient evidence supporting clinical use.	No recommendation	Some meta-analyses show a statistically significant small to medium antidepressant class association with response or remission but there remains a lack of clarity regarding how to translate this into clinical action.
Other variants	No effect or insufficient evidence for response, remission or side effects.	No action recommended based on genotype because of insufficient evidence supporting clinical use.	No recommendation	

TABLE S9. DOSING RECOMMENDATIONS FOR *SLC6A4* AND CITALOPRAM, ESCITALOPRAM, FLUOXETINE, FLUVOXAMINE, PAROXETINE, SERTRALINE, DULOXETINE, VENLAFAXINE, DESVENLAFAXINE, VILAZODONE, VORTIOXETINE, LEVOMILNACIPRAN AND MILNACIPRAN

Genotype	Implications	Recommendations	Classification of recommendation[a]	Considerations
5HTTLPR L	Mixed evidence for the effect of genetic variability on SSRI response, remission, or side effects.	No action recommended based on genotype for SSRIs because of insufficient evidence supporting clinical use.	No recommendation	Some meta-analyses show a small-to-medium and statistically significant SSRI antidepressant class association with increased response, increased remission, or decreased side effects in persons of European descent. These findings do not appear to be generalizable across other population groups. The impact of these associations with SSRI dose are unclear. There are insufficient data to confirm the presence or absence of an SLC6A4 genotype association with non-SSRI response, remission, or side effects. There remains a lack of clarity regarding how to translate this into clinical action.
Intron 2 VNTR 12 repeat	Mixed evidence for the effect of genetic variability on SSRI response or remission.	No action recommended based on genotype for SSRI because of insufficient evidence supporting clinical use.	No recommendation	

Other variants	No effect or insufficient evidence for SSRI response, remission, or side effects.	No action recommended based on genotype for SSRIs because of insufficient evidence supporting clinical use.	No recommendation	

TABLE S10. META-ANALYSES OF EVIDENCE LINKING GENETIC VARIATION TO ANTIDEPRESSANT PHENOTYPES

Major Findings	References
CYPs	
Meta-analysis included 147 subjects from 3 studies (20 healthy-single dose and 127 patients - 3 studies above). CYP2B6 PMs had increased mean **sertraline** blood levels compared to NMs.	Parikh, *et al.* (2022) (175)
Meta-analysis included 1262 subjects from 4 studies. CYP2C19 PMs had significantly increased exposure to **escitalopram** compared to NMs.	Milosavljević, *et al.* (2020) (410)
Meta-analysis included 146 subjects from 6 studies. CYP2D6 IMs had significantly increased exposure to **fluvoxamine** compared to NMs.	Milosavljević, *et al.* (2020) (410)
Meta-analysis included 41 subjects from 3 studies (IM vs NM) and 73 subjects from 2 studies (PM vs NM). CYP2D6 IMs and CYP2D6 PMs had significantly increased exposure to **paroxetine** compared to NMs.	Milosavljević, *et al.* (2020) (410)
Meta-analysis included 917 subjects from 3 studies (IM vs NM) and 577 subjects from 2 studies (PM vs NM). CYP2C19 IMs and CYP2C19 PMs had significantly increased exposure to **sertraline** compared to NMs.	Milosavljević, *et al.* (2020) (410)
Meta-analysis included 8 studies with a total 716 patients (less per each compared parameter). CYP2D6 PMs, CYP2D6 IMs, and IMs + PMs had significant **venlafaxine** exposure increases compared to CYP2D6 NMs.	Milosavljević, *et al.* (2020) (410)
Meta-analysis included a total 14 studies with a total 1035 patients and healthy subjects (less per each compared parameter). CYP2D6 PMs (AS0) or IMs (AS0.5-1) had a significantly higher Cmax of **venlafaxine** than NMs (AS2). PMs also had higher Cmax than IMs + NMs, while NMs had a lower Cmax than IMs + PMs. CYP2D6 IMs had a significantly higher AUC of venlafaxine than NMs, while PMs had only had a higher AUC compared to IMs + NMs not NMs. PMs had higher stable venlafaxine serum concentration than IMs + NMs, while no significant difference was observed between PMs and NMs and NMs compared to IMs + PMs. No significant difference in T1/2 of venlafaxine was found for PMs vs NMs, IMs vs NMs, and PMs vs IMs + NMs comparison. CYP2D6 PMs or IMs had a significant lower Cmax of O-desmethylvenlafaxine than NMs. CYP2D6 PMs had a significant lower O-desmethylvenlafaxine stable serum concentration than NMs or IMs + NMs. CYP2D6 PMs vs non-PMs were not associated with HDRS17 or YBOCS response. CYP2D6 PMs showed a significant difference	Lin, *et al.* (2019) (411)

for reduction of HDRS17 compared to non-PMs (one study). There was no association of the overall rate of adverse events comparing CYP2D6 PMs with NMs + IMs.	
Meta-analysis of GENDEP, STAR*D, PGRN-AMPS, GenPod cohort included analyses of 2558 patients for efficacy and 2037 patients for side effects analysis. CYP2C19 PMs (*2/*2) had higher symptom improvement and remission rates compared to NMs (non-rs4244285 and rs12248560 carrier) while taking **(es)citalopram**. No difference was seen in total side effect burden, however in the initial weeks of treatment PMs had a higher risk for **(es)citalopram** side effects such gastrointestinal, neurological or sexual side effects. **(Es)Citalopram** dose was not different between the CYP2C19 phenotypes.	Fabbri, *et al.* (2018) (412)
Meta-analysis included a total 847 patients from psychiatric patient trials and 140 healthy subjects from pharmacokinetic studies. CYP2C19 PMs (*2 or *3/*2 or *3) had increased exposure to **(es)citalopram** by 95 %, IMs (*1/*2 or *3) by 30 %, IMs (*17/*2 or *3) by 25 % compared to NMs (*1/*1). Subjects with CYP2C19*17/*17 had decreased exposure by 36 % and CYP2C19*17/*1 by 14 % compared to NM (*1/*1).	Chang, *et al.* (2014) (413)
Meta-analysis with quantifiable **vortioxetine** plasma concentrations from 887 healthy subjects with either single or multiple doses. CYP2D6 inferred phenotype on oral clearance was identified as statistically significant covariate–parameter relationships. CYP2D6 PMs (AS0) had about a 50% lower CL/F compared to NMs (AS1.5-2).	Areberg, *et al.* (2014) (414)
Meta-analysis with quantifiable **vortioxetine** plasma concentrations from 887 healthy subjects with either single or multiple doses. CYP2C19 NMs had on average 1.4 times the CL/F of CYP2C19 PMs.	Areberg, *et al.* (2014) (414)
HTR2A	
Meta-analysis including 7 studies with a total 801 patients with major depressive disorder receiving antidepressants. In this analysis, rs6313 G allele was considered as rs6311 C allele. The rs6311-rs6313 CC-GG genotype was significantly associated with higher risk of side effects (OR 1.91, CI: 1.32–2.78, P = 0.0006).	Kato, *et al.* (2010) (415)
Meta-analysis including 6 studies with a total 590 patients with major depressive disorder receiving SSRIs (fluvoxamine, paroxetine, and various SSRIs). In this analysis, rs6313 G allele was considered as rs6311 C allele. The rs6311-rs6313 CC-GG genotype was significantly associated with higher risk of side effects (OR 2.33, CI: 1.53–3.56, P < 0.0001). Four studies specified gastrointestinal symptom induced by SSRIs and the OR of gastrointestinal side effect with 311 subjects was significant (OR 2.30, CI: 1.26–4.21, P = 0.007) in the same direction of the total side effects.	Kato, *et al.* (2010) (415)

Meta-analysis including 7 studies for treatment outcome with a total 1012 patients with major depressive disorder receiving antidepressants. The outcome measures included HAMD remission score change for HTR2A 102T/C (6 weeks), MADRS response score change for HTR2A -1438A/G (6weeks), MADRS response score change for HTR2A -1438A/G (6 weeks), HAMD response remission score change for HTR2A -1438A/G (4 weeks), HAMD response for HTR2A 102T/C (4 weeks), HAMD response remission score change for HTR2A -1438A/G (6 weeks), HAMD response remission for HTR2A 102T/C (6 or more weeks). In this analysis, rs6313 G allele was considered as rs6311 C allele. No significant association between rs6311-rs6313 and treatment outcome was found (OR 1.06 CI: 0.78–1.44, P = 0.69).	Kato, *et al.* (2010) (415)
Meta-analysis including 4 studies for treatment outcome with a total 429 patients with major depressive disorder receiving SSRIs (fluvoxamine, fluoxetine, citalopram, paroxetine). The outcome measures included MADRS response score change for HTR2A -1438A/G (6 weeks), HAMD response remission score change for HTR2A -1438A/G (4 weeks), HAMD response for HTR2A 102T/C (4 weeks), and HAMD response remission score change for HTR2A -1438A/G (6 weeks). In this analysis, rs6313 G allele was considered as rs6311 C allele. The rs6311-rs6313 CC-GG genotype was marginal significantly associated with a favorable response compared to CT-AG or TT-AA genotypes (OR 1.69 CI: 1.03–2.75, P = 0.04). The included studies were in Asian population.	Kato, *et al.* (2010) (415)
Meta-analysis including 6 studies and the STAR*D data with a total of 2295 subjects with major depressive disorder receiving antidepressants. No significant association between the rs6311 variant (CC vs CT + TT) and antidepressant response in the whole sample. In studies including Asians populations, the pooling CC and CT versus TT showed a weak association with response (OR 1.66, 95%CI: 1.06–2.60, p = 0.03). Sensitivity analysis for rs6311 demonstrated that the pooled OR was no more significant after the exclusion of each of two studies one at a time in the Asian subgroup.	Niitsu, *et al.* (2013) (416)
Meta-analysis including 3 studies and the STAR*D data with a total of 2082 subjects with major depressive disorder receiving antidepressants. No significant association between the rs6311 variant (CC vs CT + TT) and remission was found.	Niitsu, *et al.* (2013) (416)
Meta-analysis including 7 studies and the STAR*D data with a total of 3140 subjects with major depressive disorder receiving antidepressants. No significant association between the rs6313 variant (GG + GA vs AA) and antidepressant response was found.	Niitsu, *et al.* (2013) (416)

Meta-analysis including 4 studies and the STAR*D data with a total of 2562 subjects with major depressive disorder receiving antidepressants. No significant association between the rs6313 variant (GG vs GA + AA) and remission was found.	Niitsu, *et al.* (2013) (416)
Meta-analysis including 3 studies and the STAR*D data with a total of 2195 subjects with major depressive disorder receiving antidepressants. No significant association between the rs7997012 variant (GG vs GA + AA) and antidepressant response was found.	Niitsu, *et al.* (2013) (416)
Meta-analysis including 5 studies and the STAR*D data with a total of 2704 subjects with major depressive disorder receiving antidepressants. No significant association between the rs7997012 variant (GG vs GA + AA) and remission was found in the whole sample. In non-SSRIs/mixed ADs subgroup, an association with remission was found in the pooling GG and GA versus AA (OR 3.19, 95%CI: 1.57–6.46, p = 0.001), and in the pooling GG versus AA (OR 3.40, 95%CI: 1.69–6.85, p = 0.0006). Sensitivity analysis demonstrated that for rs7997012 in the genotype pooling GG and GA versus AA was no more significant after the exclusion of one study. However, the pooled OR in the GG versus AA comparison for rs7997012 continued to be significant after exclusion of each single study.	Niitsu, *et al.* (2013) (416)
Meta-analysis including 16 studies with a total of 1962 subjects with depression receiving SSRIs or SNRIs. A significant relationship was found between rs6311 variant and higher treatment response within the entire sample in the dominant genetic model (CC + CT vs TT: OR: 1.40, 95% CI: 1.12–1.76; P = 0.003).	Wan, *et al.* (2021) (417)
A statistically significant relationship was found between higher treatment response and rs6311 variant within the following stratified subgroups: MDD, Asian, > 4 weeks, and SSRIs.	Wan, *et al.* (2021) (417)
Meta-analysis including 6 studies with a total of 982 subjects with depression receiving SSRIs. A significant relationship was found between rs6311 variant and higher remission within the follow-up ≤4 weeks subgroup in the recessive genetic model (CC vs TT + CT: OR: 3.08, 95% CI: 1.07–8.89; P = 0.04) and homozygote genetic model (CC vs TT: OR: 21.16, 95% CI: 1.12–401.46; P = 0.04).	Wan, *et al.* (2021) (417)
Meta-analysis including 11 studies with a total of 1372 subjects with depression receiving SSRIs or SNRIs. A significant relationship was found between rs6311 variant and increased risks of side-effects within the Caucasian subgroup in the recessive genetic model (CC vs TT + CT: OR: 1.81, 95% CI: 1.01–3.24; P = 0.05) and homozygote genetic model (CC vs TT: OR: 2.07, 95% CI: 1.17–7.52; P = 0.02).	Wan, *et al.* (2021) (417)
Meta-analysis including 12 studies with a total of 2713 subjects with depression receiving antidepressants. A significant relationship was found between rs6313 variant and higher	Wan, *et al.* (2021) (417)

treatment response within the following subgroups in the recessive genetic model (AA + AG vs GG): SSRIs (OR: 1.31, 95% CI: 1.02–1.68; P = 0.04); >4 weeks (OR: 1.28, 95% CI: 1.00–1.62; P = 0.05).	
Meta-analysis including 7 studies with a total of 1886 subjects with depression receiving antidepressants. A significant relationship was found between rs6313 variant and lower remission in the following subgroups in the recessive genetic model (AA + AG vs GG): Caucasian (OR: 0.72, 95% CI: 0.53–0.98; P = 0.04); mixed depression (OR: 0.60, 95% CI: 0.40–0.88; P = 0.009); mixed ADs (OR: 0.70, 95% 0.51–0.96; P = 0.03).	Wan, *et al.* (2021) (417)
Meta-analysis including 7 studies with a total of 804 subjects with depression receiving antidepressants. A significant relationship was found between rs6313 variant and reduced risks of side effects in the entire sample in the recessive genetic model (AA vs GG: OR: 0.54, 95% CI: 0.29–0.99; P = 0.05) and homozygote genetic model (AA + AG vs GG: OR: 0.57, 95% CI: 0.4–0.83; P = 0.003).	Wan, *et al.* (2021) (417)
Meta-analysis including 4 studies with a total of 678 subjects with depression receiving antidepressants. No significant relationship was found between rs7997012 variant and response, however the variant had a tendency to affect the response within the mixed ADs subgroup in the homozygote model (GG vs AA OR: 2.29, 95% CI: 0.99–5.30; P = 0.05).	Wan, *et al.* (2021) (417)
Meta-analysis including 8 studies with a total of 1434 subjects with depression receiving antidepressants. A significant relationship was found between rs7997012 variant and higher remission in all three genetic models (GG vs AA + GA: OR: 1.30, 95% CI: 1.01–1.66; P = 0.04; GA + GG vs AA: OR: 2.20, 95% CI: 1.53–3.16; P < 0.0001; GG vs AA: OR: 2.73, 95% CI: 1.78–4.17; P < 0.00001). The statistically significant relationship between remission and the variant was also identified in the following subgroups: Caucasian, MDD, mixed depression, and mixed antidepressants.	Wan, *et al.* (2021) (417)
In one study with 229 subjects, no significant relationship was found between rs7997012 variant and side effects in subjects with depression receiving sertraline.	Wan, *et al.* (2021) (417)
In a pairwise meta-analysis, the HTR2A variants were not associated with the efficacy of antidepressants in major depression (rs7997012: GG + GA vs AA: OR = 1.75; 95% CI = 0.97–3.17; rs6313: GG + AG vs AA: OR = 1.23; 95% CI = 0.92–1.64; rs6311: CC + CT vs TT: OR = 1.20; 95% CI = 0.851.70). No significant association was identified from the subgroup analyses by ethnicity (Asian or Caucasian). There was no pairwise meta-analysis of the rs6314 with only two studies.	Du, *et al.* (2020) (418)

SCL6A4	
Pooled OR of nine studies of side-effects rate induced by antidepressants including 2642 subjects was significant with a reduced risk of side effects for the 5-HTTLPR L allele (0.64, CI: 0.49–0.82, P = 0.0005). SSRIs only: Pooled OR of eight studies with 2323 subjects (0.58, CI: 0.45–0.77, P = 0.0001).	Kato, *et al.* (2010) (415)
In the Caucasians using SSRIs only (12 studies), carriers of the 5-HTTLPR L/L or L/S genotype were more likely to be responders compared to S/S carriers (L/L+L/S vs. S/S: OR=1.71, 95%CI 1.30-2.24, p=0.001; L/L vs. S/S: OR=1.94, 95%CI 1.42-2.66, p<0.001). No effects on response or remission were found in the Asians or mixed/other groups.	Ren, *et al.* (2020) (419)
No significant associations were found between the 5-HTTLPR + rs25531 triallelic polymorphism and response (10 studies) or remission (5 studies) rates for all antidepressants.	Ren, *et al.* (2020) (419)
Seven studies comprising 535 participants showed 5-HTTLPR L carriers had greater odds of antidepressant response when compared to carriers of the S/S genotype (L/L+L/S vs. S/S: OR = 1.97, 95% CI = 1.27–3.05, p = 0.002). European only: L/L+L/S vs. S/S: OR = 1.890, 95% CI = 1.19–2.98, p = 0.006. SSRIs only: L/L+L/S vs. S/S: OR = 1.899, 95% CI = 0.721–5.006, p = 0.194. Without rs25531: L/L+L/S vs. S/S: OR 1.879, 95%CI 1.157–3.050, p = 0.011 showed similar results found in the full analysis.	Stein, *et al.* (2021) (420)
11 studies comprising 2737 individuals showed no significant associations between the three 5-HTTLPR genetic models and antidepressant tolerability. SSRI only: L allele carriers reported fewer ADRs relative to S/S carriers (L/L vs. S/S: OR = 0.59, 95% CI = 0.42–0.82, p = 0.002; L/L+L/S vs. S/S: OR = 0.64, 95% CI = 0.49–0.84, p = 0.001). European using SSRI: L carriers reported fewer ADRs to S carriers (L vs. S: OR = 0.79, 95% CI = 0.64–0.99, p = 0.045; LL/LS vs. SS: OR = 0.58, 95% CI = 0.43–0.78, p < 0.001)	Stein, *et al.* (2021) (420)
Meta-analysis including 15 studies with a total of 3367 subjects of predominantly European ancestry receiving antidepressants (10 studies with 2504 individuals for SSRI antidepressants; 5 studies with 863 individuals for “other” antidepressants). No evidence was found that the 5-HTTLPR S allele compared to the L allele was associated with increased odds of discontinuation from antidepressant treatment overall (OR 1.00, 95% CI 0.81–1.22, p=0.96) or in the SSRI group (OR 1.09, 95% CI 0.83–1.42, p=0.53) or other antidepressant group (OR 0.86, 95% CI 0.68–1.09, p=0.22). No evidence of an association between 5-HTTLPR genotype and SSRI discontinuation was found comparing S/S vs S/L + L/L; S/S + S/L vs L/L; S/S vs L/L.	Crawford, *et al.* (2013) (421)

Meta-analysis including 4 studies with a total of 371 subjects of predominantly East Asian ancestry receiving antidepressants (3 studies with 236 individuals for SSRI antidepressants; 1 study with 135 individuals for "other" antidepressants). The 5-HTTLPR S allele (S vs L) was associated with reduced odds of discontinuation from SSRI treatment (OR 0.28, 95% CI 0.12–0.64, p=0.002). Comparing the S/S vs L/L genotype did not alter results substantially.	Crawford, *et al.* (2013) (421)
Meta-analysis including 8 studies with a total of 1546 subjects with major depressive disorder receiving antidepressants. No significant association between VNTR intron 2 and response was found considering all studies and comparing subjects homozygous for the 12 repeats variation vs carriers of 9 or 10 repeats. The analysis was stratified by ethnicity (Caucasian, Asian, and other/mixed), and antidepressant class (SSRIs and mixed/other antidepressants). The analysis in Asian subjects treated with SSRIs showed a significant association for subjects homozygous for the 12 repeats variation with better response (OR = 4.24, 95%CI: 1.32–13.63, p = 0.02) but high heterogeneity across studies remained.	Niitsu, *et al.* (2013) (416)
Meta-analysis including 19 studies with a total of 3675 Caucasian subjects receiving antidepressants (16 studies with 2785 individuals for SSRI antidepressants; 6 studies with 890 individuals for "other" antidepressants). A significant association was found between 5-HTTLPR L allele (vs S/S) and response rate for SSRIs (OR = 1.58, C.I. 95% 1.16–2.16, p = 0.004) but not for all antidepressant classes combined or only non-SSRI antidepressants. A higher probability of remission during SSRI treatment (OR = 1.53, C.I. 95% 1.14–2.04, p = 0.004) was found for the L allele vs S/S genotype. No association with response or remission was found when comparing the S allele vs the L/L genotype.	Porcelli, *et al.* (2012) (422)
Meta-analysis including 11 studies with a total of 1429 Asian subjects receiving antidepressants (7 studies with 716 individuals for SSRI antidepressants; 5 studies with 713 individuals for "other" antidepressants). The only evidence of association between 5-HTTLPR and antidepressant efficacy was found pooling the L/L genotype vs the S allele. The L/L genotype showed higher remission probability (OR = 2.10, C.I. 95% 1.15–3.84, p = 0.02) considering mixed antidepressants. No significant association was found between L/L genotype (vs S allele) and reponse rate for SSRI, other/mixed antidepressants, or all antidepressants.	Porcelli, *et al.* (2012) (422)
Meta-analysis including 15 studies with 1435 subjects with mood disorder receiving SSRIs. A significant association was found for the 5-HTTLPR genotype with remission rate (S/L + L/L vs S/S, P < 0.0001), with response rate (L/L vs S/L + S/S, P=0.0002), and with response rate within 4 week (S/L + L/L vs S/S, P=0.003; L/L vs S/L + S/S, P < 0.00001).	Serretti, *et al.* (2007) (423)

Meta-analysis including 3 studies with 548 subjects diagnosed with a major depressive episode and receiving SSRIs. A significant association was found for the 5-HTTLPR L/L genotype with better treatment response.	Serretti, *et al.* (2006) (424)

REFERENCES

1. CPIC. CPIC® Guideline for Selective Serotonin Reuptake Inhibitors and CYP2D6 and CYP2C19 [Available from: https://cpicpgx.org/guidelines/cpic-guideline-for-ssri-and-snri-antidepressants/.
2. Robarge JD, Li L, Desta Z, Nguyen A, Flockhart DA. The star-allele nomenclature: retooling for translational genomics. Clinical pharmacology and therapeutics. 2007;82(3):244-8.
3. Desta Z, El-Boraie A, Gong L, Somogyi AA, Lauschke VM, Dandara C, et al. PharmVar GeneFocus: CYP2B6. Clinical pharmacology and therapeutics. 2021;110(1):82-97.
4. Botton MR, Whirl-Carrillo M, Del Tredici AL, Sangkuhl K, Cavallari LH, Agundez JAG, et al. PharmVar GeneFocus: CYP2C19. Clinical pharmacology and therapeutics. 2021;109(2):352-66.
5. Nofziger C, Turner AJ, Sangkuhl K, Whirl-Carrillo M, Agundez JAG, Black JL, et al. PharmVar GeneFocus: CYP2D6. Clinical pharmacology and therapeutics. 2020;107(1):154-70.
6. Gaedigk A, Simon SD, Pearce RE, Bradford LD, Kennedy MJ, Leeder JS. The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype. Clinical pharmacology and therapeutics. 2008;83(2):234-42.
7. Caudle KE, Sangkuhl K, Whirl-Carrillo M, Swen JJ, Haidar CE, Klein TE, et al. Standardizing CYP2D6 Genotype to Phenotype Translation: Consensus Recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group. Clin Transl Sci. 2020;13(1):116-24.
8. Dahl ML, Johansson I, Bertilsson L, Ingelman-Sundberg M, Sjoqvist F. Ultrarapid hydroxylation of debrisoquine in a Swedish population. Analysis of the molecular genetic basis. The Journal of pharmacology and experimental therapeutics. 1995;274(1):516-20.
9. Ramamoorthy A, Skaar TC. Gene copy number variations: it is important to determine which allele is affected. Pharmacogenomics. 2011;12(3):299-301.
10. Jarvis JP, Peter AP, Shaman JA. Consequences of CYP2D6 Copy-Number Variation for Pharmacogenomics in Psychiatry. Front Psychiatry. 2019;10:432.
11. Gaedigk A, Jaime LK, Bertino JS, Jr., Berard A, Pratt VM, Bradfordand LD, et al. Identification of Novel CYP2D7-2D6 Hybrids: Non-Functional and Functional Variants. Front Pharmacol. 2010;1:121.
12. Gaedigk A. Complexities of CYP2D6 gene analysis and interpretation. International review of psychiatry. 2013;25(5):534-53.
13. Sim SC, Daly AK, Gaedigk A. CYP2D6 update: revised nomenclature for CYP2D7/2D6 hybrid genes. Pharmacogenet Genomics. 2012;22(9):692-4.
14. Gaedigk A, Fuhr U, Johnson C, Berard LA, Bradford D, Leeder JS. CYP2D7-2D6 hybrid tandems: identification of novel CYP2D6 duplication arrangements and implications for phenotype prediction. Pharmacogenomics. 2010;11(1):43-53.
15. Wang D, Papp AC, Sun X. Functional characterization of CYP2D6 enhancer polymorphisms. Human molecular genetics. 2014.
16. Wang D, Poi MJ, Sun X, Gaedigk A, Leeder JS, Sadee W. Common CYP2D6 polymorphisms affecting alternative splicing and transcription: long-range haplotypes with two regulatory variants modulate CYP2D6 activity. Human molecular genetics. 2014;23(1):268-78.
17. Sanchez-Spitman AB, Moes DA, Gelderblom H, Dezentje VO, Swen JJ, Guchelaar HJ. The effect of rs5758550 on CYP2D6*2 phenotype and formation of endoxifen in breast cancer patients using tamoxifen. Pharmacogenomics. 2017;18(12):1125-32.
18. Boone EC, Wang WY, Gaedigk R, Cherner M, Berard A, Leeder JS, et al. Long-Distance Phasing of a Tentative "Enhancer" Single-Nucleotide Polymorphism With CYP2D6 Star Allele Definitions. Front Pharmacol. 2020;11:486.

19. Sibbing D, Gebhard D, Koch W, Braun S, Stegherr J, Morath T, et al. Isolated and interactive impact of common CYP2C19 genetic variants on the antiplatelet effect of chronic clopidogrel therapy. J Thromb Haemost. 2010;8(8):1685-93.
20. PharmGKB. PGx Gene-specific Information Tables [Available from: https://www.pharmgkb.org/page/pgxGeneRef.
21. Braten LS, Haslemo T, Jukic MM, Ivanov M, Ingelman-Sundberg M, Molden E, et al. A Novel CYP2C-Haplotype Associated With Ultrarapid Metabolism of Escitalopram. Clinical pharmacology and therapeutics. 2021;110(3):786-93.
22. Braten LS, Ingelman-Sundberg M, Jukic MM, Molden E, Kringen MK. Impact of the novel CYP2C:TG haplotype and CYP2B6 variants on sertraline exposure in a large patient population. Clin Transl Sci. 2022.
23. Kee PS, Maggo SDS, Kennedy MA, Barclay ML, Miller AL, Lehnert K, et al. Omeprazole Treatment Failure in Gastroesophageal Reflux Disease and Genetic Variation at the CYP2C Locus. Front Genet. 2022;13:869160.
24. Kalman LV, Agundez J, Appell ML, Black JL, Bell GC, Boukouvala S, et al. Pharmacogenetic allele nomenclature: International workgroup recommendations for test result reporting. Clinical pharmacology and therapeutics. 2016;99(2):172-85.
25. Tayeh MK, Gaedigk A, Goetz MP, Klein TE, Lyon E, McMillin GA, et al. Clinical pharmacogenomic testing and reporting: A technical standard of the American College of Medical Genetics and Genomics (ACMG). Genetics in medicine : official journal of the American College of Medical Genetics. 2022;24(4):759-68.
26. CPIC. CPIC® Guideline for Clopidogrel and CYP2C19 2021 [Available from: https://cpicpgx.org/guidelines/guideline-for-clopidogrel-and-cyp2c19/.
27. PharmGKB. Gene-specific Information Tables for CYP2C19 2021 [Available from: https://www.pharmgkb.org/page/cyp2c19RefMaterials.
28. Pratt VM, Del Tredici AL, Hachad H, Ji Y, Kalman LV, Scott SA, et al. Recommendations for Clinical CYP2C19 Genotyping Allele Selection: A Report of the Association for Molecular Pathology. J Mol Diagn. 2018;20(3):269-76.
29. Pratt VM, Cavallari LH, Del Tredici AL, Gaedigk A, Hachad H, Ji Y, 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(9):1047-64.
30. Sim SC, Nordin L, Andersson TM, Virding S, Olsson M, Pedersen NL, et al. Association between CYP2C19 polymorphism and depressive symptoms. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics. 2010;153B(6):1160-6.
31. Persson A, Sim SC, Virding S, Onishchenko N, Schulte G, Ingelman-Sundberg M. Decreased hippocampal volume and increased anxiety in a transgenic mouse model expressing the human CYP2C19 gene. Molecular psychiatry. 2014;19(6):733-41.
32. Bijl MJ, Luijendijk HJ, van den Berg JF, Visser LE, van Schaik RH, Hofman A, et al. Association between the CYP2D6*4 polymorphism and depression or anxiety in the elderly. Pharmacogenomics. 2009;10(4):541-7.
33. Gonzalez I, Penas-Lledo EM, Perez B, Dorado P, Alvarez M, A LL. Relation between CYP2D6 phenotype and genotype and personality in healthy volunteers. Pharmacogenomics. 2008;9(7):833-40.
34. Suzuki E, Kitao Y, Ono Y, Iijima Y, Inada T. Cytochrome P450 2D6 polymorphism and character traits. Psychiatric genetics. 2003;13(2):111-3.

35. Roberts RL, Luty SE, Mulder RT, Joyce PR, Kennedy MA. Association between cytochrome P450 2D6 genotype and harm avoidance. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics. 2004;127B(1):90-3.
36. Penas-Lledo EM, Dorado P, Aguera Z, Gratacos M, Estivill X, Fernandez-Aranda F, et al. CYP2D6 polymorphism in patients with eating disorders. The pharmacogenomics journal. 2012;12(2):173-5.
37. Penas-Lledo EM, Llerena A. CYP2D6 variation, behaviour and psychopathology: implications for pharmacogenomics-guided clinical trials. British journal of clinical pharmacology. 2014;77(4):673-83.
38. Penas LEM, Dorado P, Pacheco R, Gonzalez I, A LL. Relation between CYP2D6 genotype, personality, neurocognition and overall psychopathology in healthy volunteers. Pharmacogenomics. 2009;10(7):1111-20.
39. Llerena A, Edman G, Cobaleda J, Benitez J, Schalling D, Bertilsson L. Relationship between personality and debrisoquine hydroxylation capacity. Suggestion of an endogenous neuroactive substrate or product of the cytochrome P4502D6. Acta psychiatrica Scandinavica. 1993;87(1):23-8.
40. Penas-Lledo E, Guillaume S, Naranjo ME, Delgado A, Jaussent I, Blasco-Fontecilla H, et al. A combined high CYP2D6-CYP2C19 metabolic capacity is associated with the severity of suicide attempt as measured by objective circumstances. The pharmacogenomics journal. 2014.
41. Blasco-Fontecilla H, Penas-Lledo E, Vaquero-Lorenzo C, Dorado P, Saiz-Ruiz J, Llerena A, et al. CYP2D6 Polymorphism and Mental and Personality Disorders in Suicide Attempters. Journal of personality disorders. 2013.
42. Penas-Lledo EM, Blasco-Fontecilla H, Dorado P, Vaquero-Lorenzo C, Baca-Garcia E, Llerena A. CYP2D6 and the severity of suicide attempts. Pharmacogenomics. 2012;13(2):179-84.
43. Penas-Lledo EM, Dorado P, Aguera Z, Gratacos M, Estivill X, Fernandez-Aranda F, et al. High risk of lifetime history of suicide attempts among CYP2D6 ultrarapid metabolizers with eating disorders. Molecular psychiatry. 2011;16(7):691-2.
44. Zackrisson AL, Lindblom B, Ahlner J. High frequency of occurrence of CYP2D6 gene duplication/multiduplication indicating ultrarapid metabolism among suicide cases. Clinical pharmacology and therapeutics. 2010;88(3):354-9.
45. Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, Breen G, et al. A mega-analysis of genome-wide association studies for major depressive disorder. Molecular psychiatry. 2013;18(4):497-511.
46. Wang H, Song K, Chen Z, Yu Y. Poor metabolizers at the cytochrome P450 2C19 loci is at increased risk of developing cancer in Asian populations. PloS one. 2013;8(8):e73126.
47. Zhou LP, Luan H, Dong XH, Jin GJ, Man DL, Shang H. Genetic variants of CYP2D6 gene and cancer risk: a HuGE systematic review and meta-analysis. Asian Pacific journal of cancer prevention : APJCP. 2012;13(7):3165-72.
48. Yan P, Gao B, Wang S, Wang S, Li J, Song M. Association of 5-HTR2A -1438A/G polymorphism with anorexia nervosa and bulimia nervosa: A meta-analysis. Neurosci Lett. 2021;755:135918.
49. Mattina GF, Samaan Z, Hall GB, Steiner M. The association of HTR2A polymorphisms with obsessive-compulsive disorder and its subtypes: A meta-analysis. J Affect Disord. 2020;275:278-89.
50. Cheng P, Zhang J, Wu Y, Liu W, Zhu J, Chen Z, et al. 5-HTTLPR polymorphism and depression risk in Parkinson's disease: an updated meta-analysis. Acta Neurol Belg. 2021;121(4):933-40.
51. Zhang LJ, Zeng XT, Zhao MJ, He DF, Liu JY, Liu MY. The important effect of 5-HTTLPR polymorphism on the risk of depression in patients with coronary heart disease: a meta-analysis. BMC Cardiovasc Disord. 2020;20(1):141.
52. Jia Z, Wang L, Yu B, Li Q, Dong X. Association between polymorphisms in the serotonin transporter gene-linked polymorphic region and risk for irritable bowel syndrome in China: evidence based on a meta-analysis. J Int Med Res. 2019;47(7):2810-8.

53. Jiao YR, Wang W, Lei PC, Jia HP, Dong J, Gou YQ, et al. 5-HTT, BMPR2, EDN1, ENG, KCNA5 gene polymorphisms and susceptibility to pulmonary arterial hypertension: A meta-analysis. Gene. 2019;680:34-42.
54. Rao S, Han X, Shi M, Siu CO, Waye MMY, Liu G, et al. Associations of the serotonin transporter promoter polymorphism (5-HTTLPR) with bipolar disorder and treatment response: A systematic review and meta-analysis. Progress in neuro-psychopharmacology & biological psychiatry. 2019;89:214-26.
55. Fanelli G, Serretti A. The influence of the serotonin transporter gene 5-HTTLPR polymorphism on suicidal behaviors: a meta-analysis. Progress in neuro-psychopharmacology & biological psychiatry. 2019;88:375-87.
56. Oo KZ, Aung YK, Jenkins MA, Win AK. Associations of 5HTTLPR polymorphism with major depressive disorder and alcohol dependence: A systematic review and meta-analysis. Aust N Z J Psychiatry. 2016;50(9):842-57.
57. Wang JY, Jia CX, Lian Y, Sun SH, Lyu M, Wu A. Association of the HTR2A 102T/C polymorphism with attempted suicide: a meta-analysis. Psychiatric genetics. 2015;25(4):168-77.
58. Lan F, Cao C, Liu J, Li W. Obstructive sleep apnea syndrome susceptible genes in the Chinese population: a meta-analysis of 21 case-control studies. Sleep Breath. 2015;19(4):1441-8.
59. Ramanathan S, Glatt SJ. Serotonergic system genes in psychosis of Alzheimer dementia: meta-analysis. Am J Geriatr Psychiatry. 2009;17(10):839-46.
60. Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. Molecular psychiatry. 2022.
61. Meijerman I, Sanderson LM, Smits PH, Beijnen JH, Schellens JH. Pharmacogenetic screening of the gene deletion and duplications of CYP2D6. Drug metabolism reviews. 2007;39(1):45-60.
62. Kim EY, Lee SS, Jung HJ, Jung HE, Yeo CW, Shon JH, et al. Robust CYP2D6 genotype assay including copy number variation using multiplex single-base extension for Asian populations. Clinica chimica acta; international journal of clinical chemistry. 2010;411(23-24):2043-8.
63. Hicks JK, Swen JJ, Gaedigk A. Challenges in CYP2D6 phenotype assignment from genotype data: a critical assessment and call for standardization. Current drug metabolism. 2014;15(2):218-32.
64. Nofziger C, Paulmichl M. Accurately genotyping CYP2D6: not for the faint of heart. Pharmacogenomics. 2018;19(13):999-1002.
65. Scott SA, Sangkuhl K, Gardner EE, Stein CM, Hulot JS, Johnson JA, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. Clinical pharmacology and therapeutics. 2011;90(2):328-32.
66. Scott SA, Martis S, Peter I, Kasai Y, Kornreich R, Desnick RJ. Identification of CYP2C19*4B: pharmacogenetic implications for drug metabolism including clopidogrel responsiveness. The pharmacogenomics journal. 2012;12(4):297-305.
67. Skierka JM, Black JL, 3rd. Analysis of compound heterozygous CYP2C19 genotypes to determine cis and trans configurations. Pharmacogenomics. 2014;15(9):1197-205.
68. Scott SA, Tan Q, Baber U, Yang Y, Martis S, Bander J, et al. An allele-specific PCR system for rapid detection and discrimination of the CYP2C19 *4A, *4B, and *17 alleles: implications for clopidogrel response testing. J Mol Diagn. 2013;15(6):783-9.
69. Twesigomwe D, Drogemoller BI, Wright GEB, Siddiqui A, da Rocha J, Lombard Z, et al. StellarPGx: A Nextflow Pipeline for Calling Star Alleles in Cytochrome P450 Genes. Clinical pharmacology and therapeutics. 2021;110(3):741-9.
70. Sangkuhl K, Whirl-Carrillo M, Whaley RM, Woon M, Lavertu A, Altman RB, et al. Pharmacogenomics Clinical Annotation Tool (PharmCAT). Clinical pharmacology and therapeutics. 2020;107(1):203-10.
71. Botton MR, Lu X, Zhao G, Repnikova E, Seki Y, Gaedigk A, et al. Structural variation at the CYP2C locus: Characterization of deletion and duplication alleles. Hum Mutat. 2019;40(11):e37-e51.

72. Lam YW, Gaedigk A, Ereshefsky L, Alfaro CL, Simpson J. CYP2D6 inhibition by selective serotonin reuptake inhibitors: analysis of achievable steady-state plasma concentrations and the effect of ultrarapid metabolism at CYP2D6. Pharmacotherapy. 2002;22(8):1001-6.
73. Gex-Fabry M, Eap CB, Oneda B, Gervasoni N, Aubry JM, Bondolfi G, et al. CYP2D6 and ABCB1 genetic variability: influence on paroxetine plasma level and therapeutic response. Therapeutic drug monitoring. 2008;30(4):474-82.
74. Guzey C, Spigset O. Low serum concentrations of paroxetine in CYP2D6 ultrarapid metabolizers. Journal of clinical psychopharmacology. 2006;26(2):211-2.
75. Cicali EJ, Elchynski AL, Cook KJ, Houder JT, Thomas CD, Smith DM, et al. How to Integrate CYP2D6 Phenoconversion Into Clinical Pharmacogenetics: A Tutorial. Clinical pharmacology and therapeutics. 2021;110(3):677-87.
76. Borges S, Desta Z, Jin Y, Faouzi A, Robarge JD, Philips S, et al. Composite functional genetic and comedication CYP2D6 activity score in predicting tamoxifen drug exposure among breast cancer patients. J Clin Pharmacol. 2010;50(4):450-8.
77. Smith DM, Weitzel KW, Elsey AR, Langaee T, Gong Y, Wake DT, et al. CYP2D6-guided opioid therapy improves pain control in CYP2D6 intermediate and poor metabolizers: a pragmatic clinical trial. Genetics in medicine : official journal of the American College of Medical Genetics. 2019;21(8):1842-50.
78. Wadelius M, Darj E, Frenne G, Rane A. Induction of CYP2D6 in pregnancy. Clinical pharmacology and therapeutics. 1997;62(4):400-7.
79. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents 2018 [Available from: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.
80. Shuldiner AR, Relling MV, Peterson JF, Hicks JK, Freimuth RR, Sadee W, et al. The Pharmacogenomics Research Network Translational Pharmacogenetics Program: overcoming challenges of real-world implementation. Clinical pharmacology and therapeutics. 2013;94(2):207-10.
81. Wilke RA, Xu H, Denny JC, Roden DM, Krauss RM, McCarty CA, et al. The emerging role of electronic medical records in pharmacogenomics. Clinical pharmacology and therapeutics. 2011;89(3):379-86.
82. Peterson JF, Bowton E, Field JR, Beller M, Mitchell J, Schildcrout J, et al. Electronic health record design and implementation for pharmacogenomics: a local perspective. Genetics in medicine : official journal of the American College of Medical Genetics. 2013;15(10):833-41.
83. Gottesman O, Kuivaniemi H, Tromp G, Faucett WA, Li R, Manolio TA, et al. The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future. Genetics in medicine : official journal of the American College of Medical Genetics. 2013;15(10):761-71.
84. Kullo IJ, Jarvik GP, Manolio TA, Williams MS, Roden DM. Leveraging the electronic health record to implement genomic medicine. Genetics in medicine : official journal of the American College of Medical Genetics. 2013;15(4):270-1.
85. Hicks JK, Crews KR, Hoffman JM, Kornegay NM, Wilkinson MR, Lorier R, et al. A clinician-driven automated system for integration of pharmacogenetic interpretations into an electronic medical record. Clinical pharmacology and therapeutics. 2012;92(5):563-6.
86. Lloret-Linares C, Bosilkovska M, Daali Y, Gex-Fabry M, Heron K, Bancila V, et al. Phenotypic Assessment of Drug Metabolic Pathways and P-Glycoprotein in Patients Treated With Antidepressants in an Ambulatory Setting. J Clin Psychiatry. 2018;79(2).
87. Grasmader K, Verwohlt PL, Rietschel M, Dragicevic A, Muller M, Hiemke C, et al. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. European journal of clinical pharmacology. 2004;60(5):329-36.

88. Rudberg I, Mohebi B, Hermann M, Refsum H, Molden E. Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients. Clinical pharmacology and therapeutics. 2008;83(2):322-7.
89. Tsai MH, Lin KM, Hsiao MC, Shen WW, Lu ML, Tang HS, et al. Genetic polymorphisms of cytochrome P450 enzymes influence metabolism of the antidepressant escitalopram and treatment response. Pharmacogenomics. 2010;11(4):537-46.
90. de Vos A, van der Weide J, Loovers HM. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. The pharmacogenomics journal. 2011;11(5):359-67.
91. Huezo-Diaz P, Perroud N, Spencer EP, Smith R, Sim S, Virding S, et al. CYP2C19 genotype predicts steady state escitalopram concentration in GENDEP. J Psychopharmacol. 2012;26(3):398-407.
92. Noehr-Jensen L, Zwisler ST, Larsen F, Sindrup SH, Damkier P, Nielsen F, et al. Impact of CYP2C19 phenotypes on escitalopram metabolism and an evaluation of pupillometry as a serotonergic biomarker. European journal of clinical pharmacology. 2009;65(9):887-94.
93. Herrlin K, Yasui-Furukori N, Tybring G, Widen J, Gustafsson LL, Bertilsson L. Metabolism of citalopram enantiomers in CYP2C19/CYP2D6 phenotyped panels of healthy Swedes. British journal of clinical pharmacology. 2003;56(4):415-21.
94. Yin OQ, Wing YK, Cheung Y, Wang ZJ, Lam SL, Chiu HF, et al. Phenotype-genotype relationship and clinical effects of citalopram in Chinese patients. Journal of clinical psychopharmacology. 2006;26(4):367-72.
95. Yu BN, Chen GL, He N, Ouyang DS, Chen XP, Liu ZQ, et al. Pharmacokinetics of citalopram in relation to genetic polymorphism of CYP2C19. Drug metabolism and disposition: the biological fate of chemicals. 2003;31(10):1255-9.
96. Fudio S, Borobia AM, Pinana E, Ramirez E, Tabares B, Guerra P, et al. Evaluation of the influence of sex and CYP2C19 and CYP2D6 polymorphisms in the disposition of citalopram. European journal of pharmacology. 2010;626(2-3):200-4.
97. Huang X, Li C, Li C, Li Z, Li X, Liao J, et al. CYP2C19 Genotyping May Provide a Better Treatment Strategy when Administering Escitalopram in Chinese Population. Front Pharmacol. 2021;12:730461.
98. Zastrozhin MS, Skryabin VY, Petukhov AE, Torrado MV, Pankratenko EP, Zastrozhina AK, et al. Effects of CYP2C19 genetic polymorphism on the steady-state concentration of citalopram in patients with major depressive disorder. The pharmacogenomics journal. 2021;21(4):435-9.
99. Shelton RC, Parikh SV, Law RA, Rothschild AJ, Thase ME, Dunlop BW, et al. Combinatorial Pharmacogenomic Algorithm is Predictive of Citalopram and Escitalopram Metabolism in Patients with Major Depressive Disorder. Psychiatry Res. 2020;290:113017.
100. Chen B, Xu Y, Jiang T, Feng R, Sun J, Zhang W, et al. Estimation of CYP2D6*10 genotypes on citalopram disposition in Chinese subjects by population pharmacokinetic assay. Journal of clinical pharmacy and therapeutics. 2013;38(6):504-11.
101. Uckun Z, Baskak B, Ozel-Kizil ET, Ozdemir H, Devrimci Ozguven H, Suzen HS. The impact of CYP2C19 polymorphisms on citalopram metabolism in patients with major depressive disorder. Journal of clinical pharmacy and therapeutics. 2015;40(6):672-9.
102. Tsuchimine S, Ochi S, Tajiri M, Suzuki Y, Sugawara N, Inoue Y, et al. Effects of Cytochrome P450 (CYP) 2C19 Genotypes on Steady-State Plasma Concentrations of Escitalopram and its Desmethyl Metabolite in Japanese Patients With Depression. Therapeutic drug monitoring. 2018;40(3):356-61.
103. Jukic MM, 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. The American journal of psychiatry. 2018;175(5):463-70.

104. Strawn JR, Mills JA, Schroeder H, Mossman SA, Varney ST, Ramsey LB, et al. Escitalopram in Adolescents With Generalized Anxiety Disorder: A Double-Blind, Randomized, Placebo-Controlled Study. J Clin Psychiatry. 2020;81(5).
105. Hodgson K, Tansey K, Dernovsek MZ, Hauser J, Henigsberg N, Maier W, et al. Genetic differences in cytochrome P450 enzymes and antidepressant treatment response. J Psychopharmacol. 2014;28(2):133-41.
106. Ohlsson Rosenborg S, Mwinyi J, Andersson M, Baldwin RM, Pedersen RS, Sim SC, et al. Kinetics of omeprazole and escitalopram in relation to the CYP2C19*17 allele in healthy subjects. European journal of clinical pharmacology. 2008;64(12):1175-9.
107. Bernini de Brito R, Ghedini PC. CYP2C19 polymorphisms and outcomes of Escitalopram treatment in Brazilians with major depression. Heliyon. 2020;6(5):e04015.
108. Bishop JR, Najjar F, Rubin LH, Guter SJ, Owley T, Mosconi MW, et al. Escitalopram pharmacogenetics: CYP2C19 relationships with dosing and clinical outcomes in autism spectrum disorder. Pharmacogenet Genomics. 2015;25(11):548-54.
109. Peters EJ, Slager SL, Kraft JB, Jenkins GD, Reinalda MS, McGrath PJ, et al. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PloS one. 2008;3(4):e1872.
110. Mrazek DA, Biernacka JM, O'Kane DJ, Black JL, Cunningham JM, Drews MS, et al. CYP2C19 variation and citalopram response. Pharmacogenet Genomics. 2011;21(1):1-9.
111. Hodgson K, Uher R, Crawford AA, Lewis G, O'Donovan MC, Keers R, et al. Genetic predictors of antidepressant side effects: a grouped candidate gene approach in the Genome-Based Therapeutic Drugs for Depression (GENDEP) study. J Psychopharmacol. 2014;28(2):142-50.
112. He Q, Yuan Z, Liu Y, Zhang J, Yan H, Shen L, et al. Correlation between cytochrome P450 2C19 genetic polymorphism and treatment response to escitalopram in panic disorder. Pharmacogenet Genomics. 2017;27(8):279-84.
113. He Q, Mei Y, Liu Y, Yuan Z, Zhang J, Yan H, et al. Effects of Cytochrome P450 2C19 Genetic Polymorphisms on Responses to Escitalopram and Levels of Brain-Derived Neurotrophic Factor in Patients With Panic Disorder. Journal of clinical psychopharmacology. 2019;39(2):117-23.
114. Aldrich SL, Poweleit EA, Prows CA, Martin LJ, Strawn JR, Ramsey LB. Influence of CYP2C19 Metabolizer Status on Escitalopram/Citalopram Tolerability and Response in Youth With Anxiety and Depressive Disorders. Front Pharmacol. 2019;10:99.
115. Campos AI, Byrne EM, Mitchell BL, Wray NR, Lind PA, Licinio J, et al. Impact of CYP2C19 metaboliser status on SSRI response: a retrospective study of 9500 participants of the Australian Genetics of Depression Study. The pharmacogenomics journal. 2022;22(2):130-5.
116. Kumar Y, Kung S, Shinozaki G. CYP2C19 variation, not citalopram dose nor serum level, is associated with QTc prolongation. J Psychopharmacol. 2014;28(12):1143-8.
117. Petry N, Lupu R, Gohar A, Larson EA, Peterson C, Williams V, et al. CYP2C19 genotype, physician prescribing pattern, and risk for long QT on serotonin selective reuptake inhibitors. Pharmacogenomics. 2019;20(5):343-51.
118. Asakura S, Hayano T, Hagino A, Koyama T. Long-term administration of escitalopram in patients with social anxiety disorder in Japan. Neuropsychiatr Dis Treat. 2016;12:1817-25.
119. Hodgson K, Tansey KE, Uher R, Dernovsek MZ, Mors O, Hauser J, et al. Exploring the role of drug-metabolising enzymes in antidepressant side effects. Psychopharmacology (Berl). 2015;232(14):2609-17.
120. Rossow KM, Aka IT, Maxwell-Horn AC, Roden DM, Van Driest SL. Pharmacogenetics to Predict Adverse Events Associated With Antidepressants. Pediatrics. 2020;146(6).
121. Rahikainen AL, Vauhkonen P, Pett H, Palo JU, Haukka J, Ojanpera I, et al. Completed suicides of citalopram users-the role of CYP genotypes and adverse drug interactions. Int J Legal Med. 2019;133(2):353-63.

122. Bahar MA, Lanting P, Bos JHJ, Sijmons RH, Hak E, Wilffert B. Impact of Drug-Gene-Interaction, Drug-Drug-Interaction, and Drug-Drug-Gene-Interaction on (es)Citalopram Therapy: The PharmLines Initiative. J Pers Med. 2020;10(4).
123. Hu XX, Yuan LJ, Fang P, Mao YH, Zhan YY, Li XY, et al. Effect of CYP2D6 genetic polymorphism on the metabolism of citalopram in vitro. Drug metabolism and pharmacokinetics. 2016;31(2):133-8.
124. Han KM, Chang HS, Choi IK, Ham BJ, Lee MS. CYP2D6 P34S Polymorphism and Outcomes of Escitalopram Treatment in Koreans with Major Depression. Psychiatry investigation. 2013;10(3):286-93.
125. Zastrozhin MS, Grishina EA, Denisenko NP, Skryabin VY, Markov DD, Savchenko LM, et al. Effects of CYP2D6 genetic polymorphisms on the efficacy and safety of fluvoxamine in patients with depressive disorder and comorbid alcohol use disorder. Pharmacogenomics and personalized medicine. 2018;11:113-9.
126. Zastrozhin M, Skryabin V, Smirnov V, Zastrozhina A, Grishina E, Ryzhikova K, et al. Effect of Genetic Polymorphism of the CYP2D6 Gene on the Efficacy and Safety of Fluvoxamine in Major Depressive Disorder. Am J Ther. 2021;29(1):e26-e33.
127. 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 : official publication of the American College of Neuropsychopharmacology. 2006;31(4):825-31.
128. Suzuki Y, Sugai T, Fukui N, Watanabe J, Ono S, Inoue Y, et al. CYP2D6 genotype and smoking influence fluvoxamine steady-state concentration in Japanese psychiatric patients: lessons for genotype-phenotype association study design in translational pharmacogenetics. J Psychopharmacol. 2011;25(7):908-14.
129. Carrillo JA, Dahl ML, Svensson JO, Alm C, Rodriguez I, Bertilsson L. Disposition of fluvoxamine in humans is determined by the polymorphic CYP2D6 and also by the CYP1A2 activity. Clinical pharmacology and therapeutics. 1996;60(2):183-90.
130. Spigset O, Granberg K, Hagg S, Norstrom A, Dahlqvist R. Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms. European journal of clinical pharmacology. 1997;52(2):129-33.
131. Spigset O, Axelsson S, Norstrom A, Hagg S, Dahlqvist R. The major fluvoxamine metabolite in urine is formed by CYP2D6. European journal of clinical pharmacology. 2001;57(9):653-8.
132. Watanabe J, Suzuki Y, Fukui N, Sugai T, Ono S, Inoue Y, et al. Dose-dependent effect of the CYP2D6 genotype on the steady-state fluvoxamine concentration. Therapeutic drug monitoring. 2008;30(6):705-8.
133. Ohara K, Tanabu S, Ishibashi K, Ikemoto K, Yoshida K, Shibuya H. CYP2D6*10 alleles do not determine plasma fluvoxamine concentration/dose ratio in Japanese subjects. European journal of clinical pharmacology. 2003;58(10):659-61.
134. Gerstenberg G, Aoshima T, Fukasawa T, Yoshida K, Takahashi H, Higuchi H, et al. Effects of the CYP 2D6 genotype and cigarette smoking on the steady-state plasma concentrations of fluvoxamine and its major metabolite fluvoxamino acid in Japanese depressed patients. Therapeutic drug monitoring. 2003;25(4):463-8.
135. Zastrozhin MS, Skryabin V, Smirnov V, Zastrozhina AK, Kaverina EV, Klepikov DA, et al. Impact of the Omics-Based Biomarkers on the Fluvoxamine's Steady-State Concentration, Efficacy and Safety in Patients with Affective Disorders Comorbid with Alcohol Use Disorder. Psychopharmacol Bull. 2021;51(1):69-80.
136. Eap CB, Bondolfi G, Zullino D, Savary-Cosendai L, Powell-Golay K, Kosel M, et al. Concentrations of the enantiomers of fluoxetine and norfluoxetine after multiple doses of fluoxetine in cytochrome P4502D6 poor and extensive metabolizers. Journal of clinical psychopharmacology. 2001;21(3):330-4.

137. Charlier C, Broly F, Lhermitte M, Pinto E, Ansseau M, Plomteux G. Polymorphisms in the CYP 2D6 gene: association with plasma concentrations of fluoxetine and paroxetine. Therapeutic drug monitoring. 2003;25(6):738-42.
138. Hamelin BA, Turgeon J, Vallee F, Belanger PM, Paquet F, LeBel M. The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin. Clinical pharmacology and therapeutics. 1996;60(5):512-21.
139. Fjordside L, Jeppesen U, Eap CB, Powell K, Baumann P, Brosen K. The stereoselective metabolism of fluoxetine in poor and extensive metabolizers of sparteine. Pharmacogenetics. 1999;9(1):55-60.
140. A LL, Dorado P, Berecz R, Gonzalez AP, Penas LEM. Effect of CYP2D6 and CYP2C9 genotypes on fluoxetine and norfluoxetine plasma concentrations during steady-state conditions. European journal of clinical pharmacology. 2004;59(12):869-73.
141. Magalhaes P, Alves G, Fortuna A, Llerena A, Falcao A, Clinical Collaborators of the Gn GPKPDADS. Pharmacogenetics and therapeutic drug monitoring of fluoxetine in a real-world setting: A PK/PD analysis of the influence of (non-)genetic factors. Exp Clin Psychopharmacol. 2020;28(5):589-600.
142. Hinrichs JW, Loovers HM, Scholten B, van der Weide J. Semi-quantitative CYP2D6 gene doses in relation to metabolic ratios of psychotropics. European journal of clinical pharmacology. 2008;64(10):979-86.
143. Gasso P, Rodriguez N, Mas S, Pagerols M, Blazquez A, Plana MT, et al. Effect of CYP2D6, CYP2C9 and ABCB1 genotypes on fluoxetine plasma concentrations and clinical improvement in children and adolescent patients. The pharmacogenomics journal. 2014;14(5):457-62.
144. Sagahon-Azua J, Medellin-Garibay SE, Chavez-Castillo CE, Gonzalez-Salinas CG, Milan-Segovia RDC, Romano-Moreno S. Factors associated with fluoxetine and norfluoxetine plasma concentrations and clinical response in Mexican patients with mental disorders. Pharmacol Res Perspect. 2021;9(5):e00864.
145. Zastrozhin MS, Skryabin VY, Petukhov AE, Pankratenko EP, Grishina EA, Ryzhikova KA, et al. Impact of CYP2D6 Polymorphism on Equilibrium Concentration of Fluoxetine in Patients Diagnosed With Major Depressive Disorder and Comorbid Alcohol Use Disorders. J Psychiatr Pract. 2021;27(5):372-9.
146. Sallee FR, DeVane CL, Ferrell RE. Fluoxetine-related death in a child with cytochrome P-450 2D6 genetic deficiency. Journal of child and adolescent psychopharmacology. 2000;10(1):27-34.
147. Roberts RL, Mulder RT, Joyce PR, Luty SE, Kennedy MA. No evidence of increased adverse drug reactions in cytochrome P450 CYP2D6 poor metabolizers treated with fluoxetine or nortriptyline. Human psychopharmacology. 2004;19(1):17-23.
148. Troy TF, Poweleit EA, Strawn JR, Martin LJ, Ramsey LB. The Influence of Pharmacodynamic Genes on Fluoxetine Response in Pediatric Anxiety and Depressive Disorders. Journal of child and adolescent psychopharmacology. 2020;30(4):276-7.
149. Fang P, He JY, Han AX, Lan T, Dai DP, Cai JP, et al. Effects of CYP2C19 Variants on Fluoxetine Metabolism in vitro. Pharmacology. 2017;100(1-2):91-7.
150. Sindrup SH, Brosen K, Gram LF, Hallas J, Skjelbo E, Allen A, et al. The relationship between paroxetine and the sparteine oxidation polymorphism. Clinical pharmacology and therapeutics. 1992;51(3):278-87.
151. Alfaro CL, Lam YW, Simpson J, Ereshefsky L. CYP2D6 status of extensive metabolizers after multiple-dose fluoxetine, fluvoxamine, paroxetine, or sertraline. Journal of clinical psychopharmacology. 1999;19(2):155-63.
152. Solai LK, Pollock BG, Mulsant BH, Frye RF, Miller MD, Sweet RA, et al. Effect of nortriptyline and paroxetine on CYP2D6 activity in depressed elderly patients. Journal of clinical psychopharmacology. 2002;22(5):481-6.

153. Zourkova A, Hadasova E. Paroxetine-induced conversion of cytochrome P450 2D6 phenotype and occurence of adverse effects. General physiology and biophysics. 2003;22(1):103-13.
154. Laine K, Tybring G, Hartter S, Andersson K, Svensson JO, Widen J, et al. Inhibition of cytochrome P4502D6 activity with paroxetine normalizes the ultrarapid metabolizer phenotype as measured by nortriptyline pharmacokinetics and the debrisoquin test. Clinical pharmacology and therapeutics. 2001;70(4):327-35.
155. Storelli F, Matthey A, Lenglet S, Thomas A, Desmeules J, Daali Y. Impact of CYP2D6 Functional Allelic Variations on Phenoconversion and Drug-Drug Interactions. Clinical pharmacology and therapeutics. 2018;104(1):148-57.
156. Chen R, Wang H, Shi J, Shen K, Hu P. Cytochrome P450 2D6 genotype affects the pharmacokinetics of controlled-release paroxetine in healthy Chinese subjects: comparison of traditional phenotype and activity score systems. European journal of clinical pharmacology. 2015;71(7):835-41.
157. Nishimura M, Ueda M, Saruwatari J, Nakashima H, Ogusu N, Aoki A, et al. Influence of the cytochrome P450 2D6 *10/*10 genotype on the pharmacokinetics of paroxetine in Japanese patients with major depressive disorder: a population pharmacokinetic analysis. Pharmacogenet Genomics. 2016;26(9):403-13.
158. Chen R, Shen K, Hu P. Polymorphism in CYP2D6 affects the pharmacokinetics and dose escalation of paroxetine controlled-release tablet in healthy Chinese subjects. Int J Clin Pharmacol Ther. 2017;55(11):853-60.
159. Sawamura K, Suzuki Y, Someya T. Effects of dosage and CYP2D6-mutated allele on plasma concentration of paroxetine. European journal of clinical pharmacology. 2004;60(8):553-7.
160. Feng Y, Pollock BG, Ferrell RE, Kimak MA, Reynolds CF, 3rd, Bies RR. Paroxetine: population pharmacokinetic analysis in late-life depression using sparse concentration sampling. British journal of clinical pharmacology. 2006;61(5):558-69.
161. Findling RL, Nucci G, Piergies AA, Gomeni R, Bartolic EI, Fong R, et al. Multiple dose pharmacokinetics of paroxetine in children and adolescents with major depressive disorder or obsessive-compulsive disorder. Neuropsychopharmacology. 2006;31(6):1274-85.
162. Van Nieuwerburgh FC, Denys DA, Westenberg HG, Deforce DL. Response to serotonin reuptake inhibitors in OCD is not influenced by common CYP2D6 polymorphisms. International journal of psychiatry in clinical practice. 2009;13(1):345-8.
163. Saruwatari J, Nakashima H, Tsuchimine S, Nishimura M, Ogusu N, Yasui-Furukori N. Possible impact of the CYP2D6*10 polymorphism on the nonlinear pharmacokinetic parameter estimates of paroxetine in Japanese patients with major depressive disorders. Pharmacogenomics and personalized medicine. 2014;7:121-7.
164. Austin-Zimmerman I, Wronska M, Wang B, Irizar H, Thygesen JH, Bhat A, et al. The Influence of CYP2D6 and CYP2C19 Genetic Variation on Diabetes Mellitus Risk in People Taking Antidepressants and Antipsychotics. Genes (Basel). 2021;12(11).
165. Zourkova A, Ceskova E, Hadasova E, Ravcukova B. Links among paroxetine-induced sexual dysfunctions, gender, and CYP2D6 activity. Journal of sex & marital therapy. 2007;33(4):343-55.
166. Sato A, Okura Y, Minagawa S, Ohno Y, Fujita S, Kondo D, et al. Life-threatening serotonin syndrome in a patient with chronic heart failure and CYP2D6*1/*5. Mayo Clinic proceedings. 2004;79(11):1444-8.
167. Stedman CA, Begg EJ, Kennedy MA, Roberts R, Wilkinson TJ. Cytochrome P450 2D6 genotype does not predict SSRI (fluoxetine or paroxetine) induced hyponatraemia. Human psychopharmacology. 2002;17(4):187-90.
168. Murphy GM, Jr., Kremer C, Rodrigues HE, Schatzberg AF. Pharmacogenetics of antidepressant medication intolerance. The American journal of psychiatry. 2003;160(10):1830-5.

169. Sugai T, Suzuki Y, Sawamura K, Fukui N, Inoue Y, Someya T. The effect of 5-hydroxytryptamine 3A and 3B receptor genes on nausea induced by paroxetine. The pharmacogenomics journal. 2006;6(5):351-6.
170. Yuce-Artun N, Baskak B, Ozel-Kizil ET, Ozdemir H, Uckun Z, Devrimci-Ozguven H, et al. Influence of CYP2B6 and CYP2C19 polymorphisms on sertraline metabolism in major depression patients. Int J Clin Pharm. 2016;38(2):388-94.
171. Rudberg I, Hermann M, Refsum H, Molden E. Serum concentrations of sertraline and N-desmethyl sertraline in relation to CYP2C19 genotype in psychiatric patients. European journal of clinical pharmacology. 2008;64(12):1181-8.
172. Wang JH, Liu ZQ, Wang W, Chen XP, Shu Y, He N, et al. Pharmacokinetics of sertraline in relation to genetic polymorphism of CYP2C19. Clinical pharmacology and therapeutics. 2001;70(1):42-7.
173. Saiz-Rodriguez M, Belmonte C, Roman M, Ochoa D, Koller D, Talegon M, et al. Effect of Polymorphisms on the Pharmacokinetics, Pharmacodynamics and Safety of Sertraline in Healthy Volunteers. Basic & clinical pharmacology & toxicology. 2018;122(5):501-11.
174. Braten LS, Haslemo T, Jukic MM, Ingelman-Sundberg M, Molden E, Kringen MK. Impact of CYP2C19 genotype on sertraline exposure in 1200 Scandinavian patients. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2020;45(3):570-6.
175. Parikh SV, Law RA, Hain DT, Rothschild AJ, Thase ME, Dunlop BW, et al. Combinatorial pharmacogenomic algorithm is predictive of sertraline metabolism in patients with major depressive disorder. Psychiatry Res. 2022;308:114354.
176. Poweleit EA, Aldrich SL, Martin LJ, Hahn D, Strawn JR, Ramsey LB. Pharmacogenetics of Sertraline Tolerability and Response in Pediatric Anxiety and Depressive Disorders. Journal of child and adolescent psychopharmacology. 2019;29(5):348-61.
177. Brown JT, Gregornik DB, Jorgenson A, Watson D, Roiko SA, Bishop JR. Sertraline dosing trends in children and adolescents stratified by CYP2C19 genotype. Pharmacogenomics. 2022;23(4):247-53.
178. Preskorn S, Patroneva A, Silman H, Jiang Q, Isler JA, Burczynski ME, et al. Comparison of the pharmacokinetics of venlafaxine extended release and desvenlafaxine in extensive and poor cytochrome P450 2D6 metabolizers. Journal of clinical psychopharmacology. 2009;29(1):39-43.
179. Nichols AI, Focht K, Jiang Q, Preskorn SH, Kane CP. Pharmacokinetics of venlafaxine extended release 75 mg and desvenlafaxine 50 mg in healthy CYP2D6 extensive and poor metabolizers: a randomized, open-label, two-period, parallel-group, crossover study. Clin Drug Investig. 2011;31(3):155-67.
180. Kuzin M, Scharrer I, Nolan D, Baumgartner M, Paulzen M, Schoretsanitis G, et al. The role of the poor metabolizer genotype CYP2D6 and CYP1A2 phenotype in the pharmacokinetics of duloxetine and venlafaxine-A case report. Basic & clinical pharmacology & toxicology. 2020;127(4):354-7.
181. Zastrozhin, Petukhov, Pankratenko, Grishina, Ryzhikova, Skryabin, et al. Impact of Polymorphism of CYP2D6 on Equilibrium Concentration of Duloxetine in Patients Suffering from Major Depressive Disorder. Psychopharmacol Bull. 2020;50(3):47-57.
182. Hoffmann M, Russmann S, Niedrig DF. Severe CNS depression with duloxetine, ciprofloxacin and CYP2D6 deficiency-role and recognition of drug-drug-gene interactions. European journal of clinical pharmacology. 2022;78(4):703-5.
183. Kamei S, Kaneto H, Tanabe A, Irie S, Hirata Y, Shimoda M, et al. Rapid onset of syndrome of inappropriate antidiuretic hormone secretion induced by duloxetine in an elderly type 2 diabetic patient with painful diabetic neuropathy. J Diabetes Investig. 2015;6(3):343-5.
184. Ahmed AT, Biernacka JM, Jenkins G, Rush AJ, Shinozaki G, Veldic 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;246:62-8.

185. Puozzo C, Lens S, Reh C, Michaelis K, Rosillon D, Deroubaix X, et al. Lack of interaction of milnacipran with the cytochrome p450 isoenzymes frequently involved in the metabolism of antidepressants. Clinical pharmacokinetics. 2005;44(9):977-88.
186. Zhan YY, Liang BQ, Wang H, Wang ZH, Weng QH, Dai DP, et al. Effect of CYP2D6 variants on venlafaxine metabolism in vitro. Xenobiotica. 2016;46(5):424-9.
187. Otton SV, Ball SE, Cheung SW, Inaba T, Rudolph RL, Sellers EM. Venlafaxine oxidation in vitro is catalysed by CYP2D6. British journal of clinical pharmacology. 1996;41(2):149-56.
188. Fukuda T, Nishida Y, Zhou Q, Yamamoto I, Kondo S, Azuma J. The impact of the CYP2D6 and CYP2C19 genotypes on venlafaxine pharmacokinetics in a Japanese population. European journal of clinical pharmacology. 2000;56(2):175-80.
189. Veefkind AH, Haffmans PM, Hoencamp E. Venlafaxine serum levels and CYP2D6 genotype. Therapeutic drug monitoring. 2000;22(2):202-8.
190. van der Weide J, van Baalen-Benedek EH, Kootstra-Ros JE. Metabolic ratios of psychotropics as indication of cytochrome P450 2D6/2C19 genotype. Therapeutic drug monitoring. 2005;27(4):478-83.
191. Shams ME, Arneth B, Hiemke C, Dragicevic A, Muller MJ, Kaiser R, et al. CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. Journal of clinical pharmacy and therapeutics. 2006;31(5):493-502.
192. Hermann M, Hendset M, Fosaas K, Hjerpset M, Refsum H. Serum concentrations of venlafaxine and its metabolites O-desmethylvenlafaxine and N-desmethylvenlafaxine in heterozygous carriers of the CYP2D6*3, *4 or *5 allele. European journal of clinical pharmacology. 2008;64(5):483-7.
193. Arneth B, Shams M, Hiemke C, Hartter S. Rapid and reliable genotyping procedure for detection of alleles with mutations, deletion, or/and duplication of the CYP2D6 gene. Clin Biochem. 2009;42(12):1282-90.
194. Kandasamy M, Srinivas P, Subramaniam K, Ravi S, John J, Shekar R, et al. Differential outcomes from metabolic ratios in the identification of CYP2D6 phenotypes--focus on venlafaxine and O-desmethylvenlafaxine. European journal of clinical pharmacology. 2010;66(9):879-87.
195. Launiainen T, Rasanen I, Vuori E, Ojanpera I. Fatal venlafaxine poisonings are associated with a high prevalence of drug interactions. Int J Legal Med. 2011;125(3):349-58.
196. McAlpine DE, Biernacka JM, Mrazek DA, O'Kane DJ, Stevens SR, Langman LJ, et al. Effect of cytochrome P450 enzyme polymorphisms on pharmacokinetics of venlafaxine. Therapeutic drug monitoring. 2011;33(1):14-20.
197. Kingback M, Karlsson L, Zackrisson AL, Carlsson B, Josefsson M, Bengtsson F, et al. Influence of CYP2D6 genotype on the disposition of the enantiomers of venlafaxine and its major metabolites in postmortem femoral blood. Forensic Sci Int. 2012;214(1-3):124-34.
198. Jiang F, Kim HD, Na HS, Lee SY, Seo DW, Choi JY, et al. The influences of CYP2D6 genotypes and drug interactions on the pharmacokinetics of venlafaxine: exploring predictive biomarkers for treatment outcomes. Psychopharmacology (Berl). 2015;232(11):1899-909.
199. Karlsson L, Zackrisson AL, Josefsson M, Carlsson B, Green H, Kugelberg FC. Influence of CYP2D6 and CYP2C19 genotypes on venlafaxine metabolic ratios and stereoselective metabolism in forensic autopsy cases. The pharmacogenomics journal. 2015;15(2):165-71.
200. Mannheimer B, Haslemo T, Lindh JD, Eliasson E, Molden E. Risperidone and Venlafaxine Metabolic Ratios Strongly Predict a CYP2D6 Poor Metabolizing Genotype. Therapeutic drug monitoring. 2016;38(1):127-34.
201. Montane Jaime LK, Paul J, Lalla A, Legall G, Gaedigk A. Impact of CYP2D6 on venlafaxine metabolism in Trinidadian patients with major depressive disorder. Pharmacogenomics. 2018;19(3):197-212.

202. Komahashi-Sasaki H, Yasui-Furukori N, Sasaki T, Shinozaki M, Hayashi Y, Kato K, et al. Effects of CYP2D6 Genotypes on Venlafaxine Metabolism in Japanese Psychiatric Patients With Depression. Therapeutic drug monitoring. 2021;43(5):681-7.
203. Sasaki T, Yasui-Furukori N, Komahashi-Sasaki H, Shinozaki M, Hayashi Y, Kato K, et al. CYP2D6*10 polymorphism and the enantioselective O-desmethylation of S-(+)- and R-(-)-venlafaxine in Japanese psychiatric patients. Basic & clinical pharmacology & toxicology. 2021;128(5):677-85.
204. van der Lee M, Allard WG, Vossen R, Baak-Pablo RF, Menafra R, Deiman B, et al. Toward predicting CYP2D6-mediated variable drug response from CYP2D6 gene sequencing data. Sci Transl Med. 2021;13(603).
205. Jukic MM, Smith RL, Molden E, Ingelman-Sundberg M. Evaluation of the CYP2D6 Haplotype Activity Scores Based on Metabolic Ratios of 4,700 Patients Treated With Three Different CYP2D6 Substrates. Clinical pharmacology and therapeutics. 2021;110(3):750-8.
206. Ganesh SV, Beunk L, Nikolik B, van der Weide J, Bet PM. Therapeutic Drug Monitoring of Psychotropics as a Diagnostic Tool for CYP2D6 Poor Metabolizer Phenotype. Therapeutic drug monitoring. 2021;43(5):672-80.
207. Hole K, Arnestad M, Molden E, Haslemo T. Dose-Dependent Inhibition of CYP2D6 by Bupropion in Patients With Depression. Journal of clinical psychopharmacology. 2021;41(3):281-5.
208. Eap CB, Lessard E, Baumann P, Brawand-Amey M, Yessine MA, O'Hara G, et al. Role of CYP2D6 in the stereoselective disposition of venlafaxine in humans. Pharmacogenetics. 2003;13(1):39-47.
209. Lessard E, Yessine MA, Hamelin BA, O'Hara G, LeBlanc J, Turgeon J. Influence of CYP2D6 activity on the disposition and cardiovascular toxicity of the antidepressant agent venlafaxine in humans. Pharmacogenetics. 1999;9(4):435-43.
210. Lobello KW, Preskorn SH, Guico-Pabia CJ, Jiang Q, Paul J, Nichols AI, et al. Cytochrome P450 2D6 phenotype predicts antidepressant efficacy of venlafaxine: a secondary analysis of 4 studies in major depressive disorder. J Clin Psychiatry. 2010;71(11):1482-7.
211. Whyte EM, Romkes M, Mulsant BH, Kirshne MA, Begley AE, Reynolds CF, 3rd, et al. CYP2D6 genotype and venlafaxine-XR concentrations in depressed elderly. Int J Geriatr Psychiatry. 2006;21(6):542-9.
212. Fukuda T, Yamamoto I, Nishida Y, Zhou Q, Ohno M, Takada K, et al. Effect of the CYP2D6*10 genotype on venlafaxine pharmacokinetics in healthy adult volunteers. British journal of clinical pharmacology. 1999;47(4):450-3.
213. Ciusani E, Zullino DF, Eap CB, Brawand-Amey M, Brocard M, Baumann P. Combination therapy with venlafaxine and carbamazepine in depressive patients not responding to venlafaxine: pharmacokinetic and clinical aspects. J Psychopharmacol. 2004;18(4):559-66.
214. Haller-Gloor F, Eap CB, Turgeon J, Baumann P. High-dose venlafaxine treatment in a depressed patient with a genetic CYP2D6 deficiency. International journal of psychiatry in clinical practice. 2004;8(3):191-5.
215. Wijnen PA, Limantoro I, Drent M, Bekers O, Kuijpers PM, Koek GH. Depressive effect of an antidepressant: therapeutic failure of venlafaxine in a case lacking CYP2D6 activity. Ann Clin Biochem. 2009;46(Pt 6):527-30.
216. Gressier F, Ellul P, Dutech C, Ait Tayeb AEK, Monfort J, Corruble E, et al. Serotonin toxicity in a CYP2D6 poor metabolizer, initially diagnosed as a drug-resistant major depression. The American journal of psychiatry. 2014;171(8):890.
217. Berm E, Kok R, Hak E, Wilffert B. Relation between CYP2D6 Genotype, Phenotype and Therapeutic Drug Concentrations among Nortriptyline and Venlafaxine Users in Old Age Psychiatry. Pharmacopsychiatry. 2016;49(5):186-90.

218. Kringen MK, Braten LS, Haslemo T, Molden E. The Influence of Combined CYP2D6 and CYP2C19 Genotypes on Venlafaxine and O-Desmethylvenlafaxine Concentrations in a Large Patient Cohort. Journal of clinical psychopharmacology. 2020;40(2):137-44.
219. McAlpine DE, O'Kane DJ, Black JL, Mrazek DA. Cytochrome P450 2D6 genotype variation and venlafaxine dosage. Mayo Clinic proceedings. 2007;82(9):1065-8.
220. Taranu A, Colle R, Gressier F, El Asmar K, Becquemont L, Corruble E, et al. Should a routine genotyping of CYP2D6 and CYP2C19 genetic polymorphisms be recommended to predict venlafaxine efficacy in depressed patients treated in psychiatric settings? Pharmacogenomics. 2017;18(7):639-50.
221. van der Schans J, Hak E, Postma M, Breuning L, Brouwers J, Ditters K, et al. Effects of Pharmacogenetic Screening for CYP2D6 Among Elderly Starting Therapy With Nortriptyline or Venlafaxine: A Pragmatic Randomized Controlled Trial (CYSCE Trial). Journal of clinical psychopharmacology. 2019;39(6):583-90.
222. Ng C, Sarris J, Singh A, Bousman C, Byron K, Peh LH, et al. Pharmacogenetic polymorphisms and response to escitalopram and venlafaxine over 8 weeks in major depression. Human psychopharmacology. 2013;28(5):516-22.
223. Brandl EJ, Tiwari AK, Zhou X, Deluce J, Kennedy JL, Muller DJ, et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. The pharmacogenomics journal. 2014;14(2):176-81.
224. Rolla R, Gramaglia C, Dalo V, Ressico F, Prosperini P, Vidali M, et al. An observational study of Venlafaxine and CYP2D6 in clinical practice. Clin Lab. 2014;60(2):225-31.
225. Chua EW, Foulds J, Miller AL, Kennedy MA. Novel CYP2D6 and CYP2C19 variants identified in a patient with adverse reactions towards venlafaxine monotherapy and dual therapy with nortriptyline and fluoxetine. Pharmacogenet Genomics. 2013;23(9):494-7.
226. Jornil J, Nielsen TS, Rosendal I, Ahlner J, Zackrisson AL, Boel LW, et al. A poor metabolizer of both CYP2C19 and CYP2D6 identified by mechanistic pharmacokinetic simulation in a fatal drug poisoning case involving venlafaxine. Forensic Sci Int. 2013;226(1-3):e26-31.
227. Garcia S, Schuh M, Cheema A, Atwal H, Atwal PS. Palpitations and Asthenia Associated with Venlafaxine in a CYP2D6 Poor Metabolizer and CYP2C19 Intermediate Metabolizer. Case Rep Genet. 2017;2017:6236714.
228. Singh H, DuBois B, Al-Jammali Z, Barrett T. Pharmacogenomics in the clinic: genetic polymorphism contributing to venlafaxine-associated heart failure. Pharmacogenomics. 2019;20(17):1175-8.
229. Volon B, Willemart T, Haufroid V, Hantson P. Recurrence of Serotonin Toxicity and Influence of Cytochrome 2D6 Polymorphism. Prim Care Companion CNS Disord. 2019;21(6).
230. Frederiksen T, Smith RL, Jukic MM, Molden E. Association Between CYP2D6 Metabolizer Status and Vortioxetine Exposure and Treatment Switching: A Retrospective, Naturalistic Cohort Study Using Therapeutic Drug Monitoring Data From 640 Patients. Journal of clinical psychopharmacology. 2022;42(4):396-9.
231. Ng CH, Bousman C, Smith DJ, Dowling N, Byron K, King J, et al. A Prospective Study of Serotonin and Norepinephrine Transporter Genes and the Response to Desvenlafaxine Over 8 Weeks in Major Depressive Disorder. Pharmacopsychiatry. 2016;49(5):210-2.
232. Perlis RH, Fijal B, Dharia S, Heinloth AN, Houston JP. Failure to replicate genetic associations with antidepressant treatment response in duloxetine-treated patients. Biol Psychiatry. 2010;67(11):1110-3.
233. Rahikainen AL, Majaharju S, Haukka J, Palo JU, Sajantila A. Serotonergic 5HTTLPR/rs25531 s-allele homozygosity associates with violent suicides in male citalopram users. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics. 2017;174(7):691-700.

234. Kronenberg S, Apter A, Brent D, Schirman S, Melhem N, Pick N, et al. Serotonin transporter polymorphism (5-HTTLPR) and citalopram effectiveness and side effects in children with depression and/or anxiety disorders. Journal of child and adolescent psychopharmacology. 2007;17(6):741-50.
235. Rotberg B, Kronenberg S, Carmel M, Frisch A, Brent D, Zalsman G, et al. Additive effects of 5-HTTLPR (serotonin transporter) and tryptophan hydroxylase 2 G-703T gene polymorphisms on the clinical response to citalopram among children and adolescents with depression and anxiety disorders. Journal of child and adolescent psychopharmacology. 2013;23(2):117-22.
236. Capozzo MA, Schillani G, Aguglia E, De Vanna M, Grassi L, Conte MA, et al. Serotonin transporter 5-HTTLPR polymorphism and response to citalopram in terminally ill cancer patients: report of twenty-one cases. Tumori. 2009;95(4):479-83.
237. Lanctot KL, Rapoport MJ, Chan F, Rajaram RD, Strauss J, Sicard T, et al. Genetic predictors of response to treatment with citalopram in depression secondary to traumatic brain injury. Brain Inj. 2010;24(7-8):959-69.
238. Mrazek DA, Rush AJ, Biernacka JM, O'Kane DJ, Cunningham JM, Wieben ED, et al. SLC6A4 variation and citalopram response. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics. 2009;150B(3):341-51.
239. Shiroma PR, Drews MS, Geske JR, Mrazek DA. SLC6A4 polymorphisms and age of onset in late-life depression on treatment outcomes with citalopram: a Sequenced Treatment Alternatives to Relieve Depression (STAR*D) report. Am J Geriatr Psychiatry. 2014;22(11):1140-8.
240. Kraft JB, Peters EJ, Slager SL, Jenkins GD, Reinalda MS, McGrath PJ, et al. Analysis of association between the serotonin transporter and antidepressant response in a large clinical sample. Biol Psychiatry. 2007;61(6):734-42.
241. Smith GS, Lotrich FE, Malhotra AK, Lee AT, Ma Y, Kramer E, et al. Effects of serotonin transporter promoter polymorphisms on serotonin function. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2004;29(12):2226-34.
242. Arias B, Catalan R, Gasto C, Gutierrez B, Fananas L. 5-HTTLPR polymorphism of the serotonin transporter gene predicts non-remission in major depression patients treated with citalopram in a 12-weeks follow up study. Journal of clinical psychopharmacology. 2003;23(6):563-7.
243. Eichhammer P, Langguth B, Wiegand R, Kharraz A, Frick U, Hajak G. Allelic variation in the serotonin transporter promoter affects neuromodulatory effects of a selective serotonin transporter reuptake inhibitor (SSRI). Psychopharmacology (Berl). 2003;166(3):294-7.
244. Kellner M, Demiralay C, Muhtz C, Husemann J, Kolsch W, Hiemke C, et al. No effect of six weeks of treatment with escitalopram on mood in healthy volunteers--irrespective of genotype for the promoter of the serotonin transporter. Psychiatry Res. 2008;161(3):339-43.
245. Huezo-Diaz P, Uher R, Smith R, Rietschel M, Henigsberg N, Marusic A, et al. Moderation of antidepressant response by the serotonin transporter gene. Br J Psychiatry. 2009;195(1):30-8.
246. Hinkelmann K, Dragoi L, Gompf J, Muhtz C, Demiralay C, Yassouridis A, et al. Decreased recognition of negative affect after selective serotonin reuptake inhibition is dependent on genotype. Psychiatry Res. 2010;177(3):354-7.
247. Garfield LD, Dixon D, Nowotny P, Lotrich FE, Pollock BG, Kristjansson SD, et al. Common selective serotonin reuptake inhibitor side effects in older adults associated with genetic polymorphisms in the serotonin transporter and receptors: data from a randomized controlled trial. Am J Geriatr Psychiatry. 2014;22(10):971-9.
248. Najjar F, Owley T, Mosconi MW, Jacob S, Hur K, Guter SJ, et al. Pharmacogenetic Study of Serotonin Transporter and 5HT2A Genotypes in Autism. Journal of child and adolescent psychopharmacology. 2015;25(6):467-74.

249. Hu XZ, Rush AJ, Charney D, Wilson AF, Sorant AJ, Papanicolaou GJ, et al. Association between a functional serotonin transporter promoter polymorphism and citalopram treatment in adult outpatients with major depression. Arch Gen Psychiatry. 2007;64(7):783-92.
250. Maron E, Tammiste A, Kallassalu K, Eller T, Vasar V, Nutt DJ, et al. Serotonin transporter promoter region polymorphisms do not influence treatment response to escitalopram in patients with major depression. Eur Neuropsychopharmacol. 2009;19(6):451-6.
251. Basu A, Chadda RK, Sood M, Kaur H, Kukreti R. Association of serotonin transporter (SLC6A4) and receptor (5HTR1A, 5HTR2A) polymorphisms with response to treatment with escitalopram in patients with major depressive disorder: A preliminary study. Indian J Med Res. 2015;142(1):40-5.
252. Oz MD, Baskak B, Uckun Z, Artun NY, Ozdemir H, Ozel TK, et al. 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. The pharmacogenomics journal. 2020;20(3):443-50.
253. Perroud N, Aitchison KJ, Uher R, Smith R, Huezo-Diaz P, Marusic A, et al. Genetic predictors of increase in suicidal ideation during antidepressant treatment in the GENDEP project. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2009;34(12):2517-28.
254. Margoob MA, Mushtaq D, Murtza I, Mushtaq H, Ali A. Serotonin transporter gene polymorphism and treatment response to serotonin reuptake inhibitor (escitalopram) in depression: An open pilot study. Indian J Psychiatry. 2008;50(1):47-50.
255. Lavretsky H, Siddarth P, Kumar A, Reynolds CF, 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(1):55-9.
256. Lewis G, Mulligan J, Wiles N, Cowen P, Craddock N, Ikeda M, et al. Polymorphism of the 5-HT transporter and response to antidepressants: randomised controlled trial. Br J Psychiatry. 2011;198(6):464-71.
257. Won ES, Chang HS, Lee HY, Ham BJ, Lee MS. Association between serotonin transporter-linked polymorphic region and escitalopram antidepressant treatment response in Korean patients with major depressive disorder. Neuropsychobiology. 2012;66(4):221-9.
258. Sahraian S, Babashams M, Reza-Soltani P, Najmabadi H, Kahrizi K, Gorgani SH. Serotonin Transporter Polymorphism (5-HTTLPR) and Citalopram Effectiveness in Iranian Patients with Major Depressive Disorder. Iran J Psychiatry. 2013;8(2):86-91.
259. Tatham EL, Hall GB, Clark D, Foster J, Ramasubbu R. The 5-HTTLPR and BDNF polymorphisms moderate the association between uncinate fasciculus connectivity and antidepressants treatment response in major depression. Eur Arch Psychiatry Clin Neurosci. 2017;267(2):135-47.
260. Mandal T, Bairy LK, Sharma P. Association between functional polymorphisms in serotonin transporter gene (SLC6A4) and escitalopram treatment response in depressive patients in a South Indian population. European journal of clinical pharmacology. 2020;76(6):807-14.
261. Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Glatt CE, Latoussakis V, Kelly RE, Jr., et al. Serotonin transporter polymorphisms, microstructural white matter abnormalities and remission of geriatric depression. J Affect Disord. 2009;119(1-3):132-41.
262. Poland RE, Lesser IM, Wan YJ, Gertsik L, Yao J, Raffel LJ, et al. Response to citalopram is not associated with SLC6A4 genotype in African-Americans and Caucasians with major depression. Life Sci. 2013;92(20-21):967-70.
263. Kang HJ, Bae KY, Kim SW, Shin IS, Hong YJ, Ahn Y, et al. Associations between Serotonergic Genes and Escitalopram Treatment Responses in Patients with Depressive Disorder and Acute Coronary Syndrome: The EsDEPACS Study. Psychiatry investigation. 2016;13(1):157-60.

264. Keers R, Uher R, Huezo-Diaz P, Smith R, Jaffee S, Rietschel M, et al. Interaction between serotonin transporter gene variants and life events predicts response to antidepressants in the GENDEP project. The pharmacogenomics journal. 2011;11(2):138-45.
265. Muhonen LH, Lahti J, Alho H, Lonnqvist J, Haukka J, Saarikoski ST. Serotonin transporter polymorphism as a predictor for escitalopram treatment of major depressive disorder comorbid with alcohol dependence. Psychiatry Res. 2011;186(1):53-7.
266. Schillani G, Capozzo MA, Era D, De Vanna M, Grassi L, Conte MA, et al. Pharmacogenetics of escitalopram and mental adaptation to cancer in palliative care: report of 18 cases. Tumori. 2011;97(3):358-61.
267. Lenze EJ, Goate AM, Nowotny P, Dixon D, Shi P, Bies RR, et al. Relation of serotonin transporter genetic variation to efficacy of escitalopram for generalized anxiety disorder in older adults. Journal of clinical psychopharmacology. 2010;30(6):672-7.
268. Owley T, Brune CW, Salt J, Walton L, Guter S, Ayuyao N, et al. A pharmacogenetic study of escitalopram in autism spectrum disorders. Autism Res. 2010;3(1):1-7.
269. Lenze EJ, Dixon D, Nowotny P, Lotrich FE, Dore PM, Pollock BG, et al. Escitalopram reduces attentional performance in anxious older adults with high-expression genetic variants at serotonin 2A and 1B receptors. Int J Neuropsychopharmacol. 2013;16(2):279-88.
270. Smeraldi E, Zanardi R, Benedetti F, Di Bella D, Perez J, Catalano M. Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. Molecular psychiatry. 1998;3(6):508-11.
271. Di Bella D, Erzegovesi S, Cavallini MC, Bellodi L. Obsessive-Compulsive Disorder, 5-HTTLPR polymorphism and treatment response. The pharmacogenomics journal. 2002;2(3):176-81.
272. Yoshida K, Ito K, Sato K, Takahashi H, Kamata M, Higuchi H, et al. Influence of the serotonin transporter gene-linked polymorphic region on the antidepressant response to fluvoxamine in Japanese depressed patients. Progress in neuro-psychopharmacology & biological psychiatry. 2002;26(2):383-6.
273. Kato M, Ikenaga Y, Wakeno M, Okugawa G, Nobuhara K, Fukuda T, et al. Controlled clinical comparison of paroxetine and fluvoxamine considering the serotonin transporter promoter polymorphism. International clinical psychopharmacology. 2005;20(3):151-6.
274. Ito K, Yoshida K, Sato K, Takahashi H, Kamata M, Higuchi H, et al. A variable number of tandem repeats in the serotonin transporter gene does not affect the antidepressant response to fluvoxamine. Psychiatry Res. 2002;111(2-3):235-9.
275. Sugie Y, Sugie H, Fukuda T, Ito M, Sasada Y, Nakabayashi M, et al. Clinical efficacy of fluvoxamine and functional polymorphism in a serotonin transporter gene on childhood autism. J Autism Dev Disord. 2005;35(3):377-85.
276. Mandelli L, Marino E, Pirovano A, Calati R, Zanardi R, Colombo C, et al. Interaction between SERTPR and stressful life events on response to antidepressant treatment. Eur Neuropsychopharmacol. 2009;19(1):64-7.
277. Kato M, Fukuda T, Wakeno M, Fukuda K, Okugawa G, Ikenaga Y, 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(4):186-95.
278. Takahashi H, Yoshida K, Ito K, Sato K, Kamata M, Higuchi H, et al. No association between the serotonergic polymorphisms and incidence of nausea induced by fluvoxamine treatment. Eur Neuropsychopharmacol. 2002;12(5):477-81.
279. Zanardi R, Serretti A, Rossini D, Franchini L, Cusin C, Lattuada E, et al. Factors affecting fluvoxamine antidepressant activity: influence of pindolol and 5-HTTLPR in delusional and nondelusional depression. Biol Psychiatry. 2001;50(5):323-30.

280. Kato M, Serretti A, Nonen S, Takekita Y, Wakeno M, Azuma J, et al. Genetic variants in combination with early partial improvement as a clinical utility predictor of treatment outcome in major depressive disorder: the result of two pooled RCTs. Transl Psychiatry. 2015;5:e513.
281. Kato M, Nonen S, Serretti A, Tetsuo S, Takekita Y, Azuma J, et al. 5-HTTLPR rs25531A > G differentially influence paroxetine and fluvoxamine antidepressant efficacy: a randomized, controlled trial. Journal of clinical psychopharmacology. 2013;33(1):131-2.
282. Perlis RH, Mischoulon D, Smoller JW, Wan YJ, Lamon-Fava S, Lin KM, et al. Serotonin transporter polymorphisms and adverse effects with fluoxetine treatment. Biol Psychiatry. 2003;54(9):879-83.
283. Yu YW, Tsai SJ, Chen TJ, Lin CH, Hong CJ. Association study of the serotonin transporter promoter polymorphism and symptomatology and antidepressant response in major depressive disorders. Molecular psychiatry. 2002;7(10):1115-9.
284. Peters EJ, Slager SL, McGrath PJ, Knowles JA, Hamilton SP. Investigation of serotonin-related genes in antidepressant response. Molecular psychiatry. 2004;9(9):879-89.
285. Hong CJ, Chen TJ, Yu YW, Tsai SJ. Response to fluoxetine and serotonin 1A receptor (C-1019G) polymorphism in Taiwan Chinese major depressive disorder. The pharmacogenomics journal. 2006;6(1):27-33.
286. Manoharan A, Shewade DG, Rajkumar RP, Adithan S. Serotonin transporter gene (SLC6A4) polymorphisms are associated with response to fluoxetine in south Indian major depressive disorder patients. European journal of clinical pharmacology. 2016;72(10):1215-20.
287. Billett EA, Richter MA, King N, Heils A, Lesch KP, Kennedy JL. Obsessive compulsive disorder, response to serotonin reuptake inhibitors and the serotonin transporter gene. Molecular psychiatry. 1997;2(5):403-6.
288. Silva H, Iturra P, Solari A, Villarroel J, Jerez S, Jimenez M, et al. Fluoxetine response in impulsive-aggressive behavior and serotonin transporter polymorphism in personality disorder. Psychiatric genetics. 2010;20(1):25-30.
289. Joyce PR, Mulder RT, Luty SE, McKenzie JM, Miller AL, Rogers GR, et al. Age-dependent antidepressant pharmacogenomics: polymorphisms of the serotonin transporter and G protein beta3 subunit as predictors of response to fluoxetine and nortriptyline. Int J Neuropsychopharmacol. 2003;6(4):339-46.
290. Gudayol-Ferre E, Herrera-Guzman I, Camarena B, Cortes-Penagos C, Herrera-Abarca JE, Martinez-Medina P, et al. The role of clinical variables, neuropsychological performance and SLC6A4 and COMT gene polymorphisms on the prediction of early response to fluoxetine in major depressive disorder. J Affect Disord. 2010;127(1-3):343-51.
291. Camarena B, Alvarez-Icaza D, Hernandez S, Aguilar A, Munch L, Martinez C, et al. Association Study Between Serotonin Transporter Gene and Fluoxetine Response in Mexican Patients With Major Depressive Disorder. Clin Neuropharmacol. 2019;42(1):9-13.
292. Gudayol-Ferre E, Herrera-Guzman I, Camarena B, Cortes-Penagos C, Herrera-Abarca JE, Martinez-Medina P, et al. Prediction of remission of depression with clinical variables, neuropsychological performance, and serotonergic/dopaminergic gene polymorphisms. Human psychopharmacology. 2012;27(6):577-86.
293. Kraft JB, Slager SL, McGrath PJ, Hamilton SP. Sequence analysis of the serotonin transporter and associations with antidepressant response. Biol Psychiatry. 2005;58(5):374-81.
294. Little KY, Zhang L, Cook E. Fluoxetine-induced alterations in human platelet serotonin transporter expression: serotonin transporter polymorphism effects. J Psychiatry Neurosci. 2006;31(5):333-9.
295. Yoshida K, Takahashi H, Higuchi H, Kamata M, Ito K, Sato K, et al. Prediction of antidepressant response to milnacipran by norepinephrine transporter gene polymorphisms. The American journal of psychiatry. 2004;161(9):1575-80.

296. Higuchi H, Takahashi H, Kamata M, Yoshida K. Influence of serotonergic/noradrenergic gene polymorphisms on nausea and sweating induced by milnacipran in the treatment of depression. Neuropsychiatr Dis Treat. 2009;5:393-8.
297. Popp J, Leucht S, Heres S, Steimer W. Serotonin transporter polymorphisms and side effects in antidepressant therapy--a pilot study. Pharmacogenomics. 2006;7(2):159-66.
298. Pollock BG, Ferrell RE, Mulsant BH, Mazumdar S, Miller M, Sweet RA, et al. Allelic variation in the serotonin transporter promoter affects onset of paroxetine treatment response in late-life depression. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2000;23(5):587-90.
299. Zanardi R, Benedetti F, Di Bella D, Catalano M, Smeraldi E. Efficacy of paroxetine in depression is influenced by a functional polymorphism within the promoter of the serotonin transporter gene. Journal of clinical psychopharmacology. 2000;20(1):105-7.
300. Murphy GM, Jr., Hollander SB, Rodrigues HE, Kremer C, Schatzberg AF. Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. Arch Gen Psychiatry. 2004;61(11):1163-9.
301. Perna G, Favaron E, Di Bella D, Bussi R, Bellodi L. Antipanic efficacy of paroxetine and polymorphism within the promoter of the serotonin transporter gene. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2005;30(12):2230-5.
302. Lotrich FE, Pollock BG, Kirshner M, Ferrell RF, Reynolds Iii CF. Serotonin transporter genotype interacts with paroxetine plasma levels to influence depression treatment response in geriatric patients. J Psychiatry Neurosci. 2008;33(2):123-30.
303. Yoshimura R, Umene-Nakano W, Suzuki A, Ueda N, Miyamoto K, Ikenouchi-Sugita A, et al. Rapid response to paroxetine is associated with plasma paroxetine levels at 4 but not 8 weeks of treatment, and is independent of serotonin transporter promoter polymorphism in Japanese depressed patients. Human psychopharmacology. 2009;24(6):489-94.
304. Aoki A, Ishiguro S, Watanabe T, Ueda M, Hayashi Y, Akiyama K, et al. Factors affecting discontinuation of initial treatment with paroxetine in panic disorder and major depressive disorder. Neuropsychiatr Dis Treat. 2014;10:1793-8.
305. Watanabe T, Ueda M, Ishiguro S, Hayashi Y, Aoki A, Shinozaki M, et al. Early Improvement and Marriage Are Determinants of the 12-Month Treatment Outcome of Paroxetine in Outpatients with Panic Disorder. Clin Psychopharmacol Neurosci. 2017;15(4):382-90.
306. Tanaka M, Kobayashi D, Murakami Y, Ozaki N, Suzuki T, Iwata N, et al. Genetic polymorphisms in the 5-hydroxytryptamine type 3B receptor gene and paroxetine-induced nausea. Int J Neuropsychopharmacol. 2008;11(2):261-7.
307. Murata Y, Kobayashi D, Imuta N, Haraguchi K, Ieiri I, Nishimura R, et al. Effects of the serotonin 1A, 2A, 2C, 3A, and 3B and serotonin transporter gene polymorphisms on the occurrence of paroxetine discontinuation syndrome. Journal of clinical psychopharmacology. 2010;30(1):11-7.
308. Perroud N, Bondolfi G, Uher R, Gex-Fabry M, Aubry JM, Bertschy G, et al. Clinical and genetic correlates of suicidal ideation during antidepressant treatment in a depressed outpatient sample. Pharmacogenomics. 2011;12(3):365-77.
309. Murata Y, Kamishioiri Y, Tanaka K, Sugimoto H, Sakamoto S, Kobayashi D, et al. Severe sleepiness and excess sleep duration induced by paroxetine treatment is a beneficial pharmacological effect, not an adverse reaction. J Affect Disord. 2013;150(3):1209-12.
310. Bozina N, Peles AM, Sagud M, Bilusic H, Jakovljevic M. Association study of paroxetine therapeutic response with SERT gene polymorphisms in patients with major depressive disorder. World J Biol Psychiatry. 2008;9(3):190-7.

311. Tomita T, Yasui-Furukori N, Nakagami T, Tsuchimine S, Ishioka M, Kaneda A, et al. The influence of 5-HTTLPR genotype on the association between the plasma concentration and therapeutic effect of paroxetine in patients with major depressive disorder. PloS one. 2014;9(5):e98099.
312. Denys D, Van Nieuwerburgh F, Deforce D, Westenberg HG. Prediction of response to paroxetine and venlafaxine by serotonin-related genes in obsessive-compulsive disorder in a randomized, double-blind trial. J Clin Psychiatry. 2007;68(5):747-53.
313. Ishiguro S, Watanabe T, Ueda M, Saeki Y, Hayashi Y, Akiyama K, et al. Determinants of pharmacodynamic trajectory of the therapeutic response to paroxetine in Japanese patients with panic disorder. European journal of clinical pharmacology. 2011;67(12):1213-21.
314. Saeki Y, Watanabe T, Ueda M, Saito A, Akiyama K, Inoue Y, et al. Genetic and pharmacokinetic factors affecting the initial pharmacotherapeutic effect of paroxetine in Japanese patients with panic disorder. European journal of clinical pharmacology. 2009;65(7):685-91.
315. Ruhe HG, Ooteman W, Booij J, Michel MC, Moeton M, Baas F, et al. Serotonin transporter gene promoter polymorphisms modify the association between paroxetine serotonin transporter occupancy and clinical response in major depressive disorder. Pharmacogenet Genomics. 2009;19(1):67-76.
316. Wilkie MJ, Smith G, Day RK, Matthews K, Smith D, Blackwood D, et al. Polymorphisms in the SLC6A4 and HTR2A genes influence treatment outcome following antidepressant therapy. The pharmacogenomics journal. 2009;9(1):61-70.
317. Abdelmalik N, Ruhe HG, Barwari K, van den Dool EJ, Meijers JC, Middeldorp S, et al. Effect of the selective serotonin reuptake inhibitor paroxetine on platelet function is modified by a SLC6A4 serotonin transporter polymorphism. J Thromb Haemost. 2008;6(12):2168-74.
318. Hougardy DM, Egberts TC, van der Graaf F, Brenninkmeijer VJ, Derijks LJ. Serotonin transporter polymorphism and bleeding time during SSRI therapy. British journal of clinical pharmacology. 2008;65(5):761-6.
319. Ng CH, Easteal S, Tan S, Schweitzer I, Ho BK, Aziz S. Serotonin transporter polymorphisms and clinical response to sertraline across ethnicities. Progress in neuro-psychopharmacology & biological psychiatry. 2006;30(5):953-7.
320. Reimherr F, Amsterdam J, Dunner D, Adler L, Zhang S, Williams D, et al. Genetic polymorphisms in the treatment of depression: speculations from an augmentation study using atomoxetine. Psychiatry Res. 2010;175(1-2):67-73.
321. Nishioka G, Yashima H, Kiuchi Y, Nakamura S, Oyamada H, Ishii M, et al. Prediction and structural equation model of sertraline treatment response in Japanese patients with major depressive disorder. Human psychopharmacology. 2013;28(6):576-85.
322. Mushtaq D, Ali A, Margoob MA, Murtaza I, Andrade C. Association between serotonin transporter gene promoter-region polymorphism and 4- and 12-week treatment response to sertraline in posttraumatic stress disorder. J Affect Disord. 2012;136(3):955-62.
323. Brunoni AR, Kemp AH, Shiozawa P, Cordeiro Q, Valiengo LC, Goulart AC, et al. Impact of 5-HTTLPR and BDNF polymorphisms on response to sertraline versus transcranial direct current stimulation: implications for the serotonergic system. Eur Neuropsychopharmacol. 2013;23(11):1530-40.
324. Durham LK, Webb SM, Milos PM, Clary CM, Seymour AB. The serotonin transporter polymorphism, 5HTTLPR, is associated with a faster response time to sertraline in an elderly population with major depressive disorder. Psychopharmacology (Berl). 2004;174(4):525-9.
325. Dogan O, Yuksel N, Ergun MA, Yilmaz A, Ilhan MN, Karslioglu HE, et al. Serotonin transporter gene polymorphisms and sertraline response in major depression patients. Genet Test. 2008;12(2):225-31.
326. Umene-Nakano W, Yoshimura R, Ueda N, Suzuki A, Ikenouchi-Sugita A, Hori H, et al. Predictive factors for responding to sertraline treatment: views from plasma catecholamine metabolites and serotonin transporter polymorphism. J Psychopharmacol. 2010;24(12):1764-71.

327. Gulfishan S, Halder S, Kar R, Srivastava S, Gupta R. Association of serotonin transporter gene polymorphism with efficacy of the antidepressant drugs sertraline and mirtazapine in newly diagnosed patients with major depressive disorders. Human psychopharmacology. 2022;37(4):e2833.
328. Peters ME, Vaidya V, Drye LT, Rosenberg PB, Martin BK, Porsteinsson AP, et al. Sertraline for the treatment of depression in Alzheimer disease: genetic influences. J Geriatr Psychiatry Neurol. 2011;24(4):222-8.
329. Schillani G, Capozzo MA, Aguglia E, De Vanna M, Grassi L, Conte MA, et al. 5-HTTLPR polymorphism of serotonin transporter and effects of sertraline in terminally ill cancer patients: report of eleven cases. Tumori. 2008;94(4):563-7.
330. Stein MB, Keshaviah A, Haddad SA, Van Ameringen M, Simon NM, Pollack MH, et al. Influence of RGS2 on sertraline treatment for social anxiety disorder. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2014;39(6):1340-6.
331. 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(1):388.
332. Simmons JG, Allen NB. Mood and personality effects in healthy participants after chronic administration of sertraline. J Affect Disord. 2011;134(1-3):377-85.
333. Leibetseder A, Wagner J, Tomasits J, Haring HP, Hutterer M, Trenkler J, et al. Spontaneous Intracerebral Hemorrhage Due to Delta Storage Pool Disease in a Patient on a Serotonin-Norepinephrine Reuptake Inhibitor. Front Neurol. 2019;10:1257.
334. Proft F, Kopf J, Olmes D, Hempel S, Schmidt B, Riederer P, et al. SLC6A2 and SLC6A4 variants interact with venlafaxine serum concentrations to influence therapy outcome. Pharmacopsychiatry. 2014;47(7):245-50.
335. Lee SH, Choi TK, Lee E, Seok JH, Lee SH, Lee HS, et al. Serotonin transporter gene polymorphism associated with short-term treatment response to venlafaxine. Neuropsychobiology. 2010;62(3):198-206.
336. Min W, Li T, Ma X, Li Z, Yu T, Gao D, et al. Monoamine transporter gene polymorphisms affect susceptibility to depression and predict antidepressant response. Psychopharmacology (Berl). 2009;205(3):409-17.
337. Kirchheiner J, Nickchen K, Sasse J, Bauer M, Roots I, Brockmoller J. A 40-basepair VNTR polymorphism in the dopamine transporter (DAT1) gene and the rapid response to antidepressant treatment. The pharmacogenomics journal. 2007;7(1):48-55.
338. Marshe VS, Maciukiewicz M, Rej S, Tiwari AK, Sibille E, Blumberger DM, et al. Norepinephrine Transporter Gene Variants and Remission From Depression With Venlafaxine Treatment in Older Adults. The American journal of psychiatry. 2017;174(5):468-75.
339. Lohoff FW, Narasimhan S, Rickels K. Interaction between polymorphisms in serotonin transporter (SLC6A4) and serotonin receptor 2A (HTR2A) genes predict treatment response to venlafaxine XR in generalized anxiety disorder. The pharmacogenomics journal. 2013;13(5):464-9.
340. Wu N, Liu L, Ren D, Yuan F, Bi Y, Guo Z, et al. No Association Between SLC6A4 Gene Polymorphisms With Treatment Remission to Venlafaxine in Han Chinese Depressive Patients. Clin Neuropharmacol. 2021;44(2):53-6.
341. Hedenmalm K, Guzey C, Dahl ML, Yue QY, Spigset O. Risk factors for extrapyramidal symptoms during treatment with selective serotonin reuptake inhibitors, including cytochrome P-450 enzyme, and serotonin and dopamine transporter and receptor polymorphisms. Journal of clinical psychopharmacology. 2006;26(2):192-7.
342. Smits K, Smits L, Peeters F, Schouten J, Janssen R, Smeets H, et al. Serotonin transporter polymorphisms and the occurrence of adverse events during treatment with selective serotonin reuptake inhibitors. International clinical psychopharmacology. 2007;22(3):137-43.

343. Bishop JR, Ellingrod VL, Akroush M, Moline J. The association of serotonin transporter genotypes and selective serotonin reuptake inhibitor (SSRI)-associated sexual side effects: possible relationship to oral contraceptives. Human psychopharmacology. 2009;24(3):207-15.
344. Staeker J, Leucht S, Laika B, Steimer W. Polymorphisms in serotonergic pathways influence the outcome of antidepressant therapy in psychiatric inpatients. Genet Test Mol Biomarkers. 2014;18(1):20-31.
345. Ramesh V, Venkatesan V, Ramasamy B. Role of serotonin transporter and receptor gene polymorphisms in treatment response to selective serotonin reuptake inhibitors in major depressive disorder. Human psychopharmacology. 2022;37(4):e2830.
346. Frye MA, McElroy SL, Prieto ML, Harper KL, Walker DL, Kung S, et al. Clinical risk factors and serotonin transporter gene variants associated with antidepressant-induced mania. J Clin Psychiatry. 2015;76(2):174-80.
347. Putzhammer A, Schoeler A, Rohrmeier T, Sand P, Hajak G, Eichhammer P. Evidence of a role for the 5-HTTLPR genotype in the modulation of motor response to antidepressant treatment. Psychopharmacology (Berl). 2005;178(2-3):303-8.
348. Strohmaier J, Wust S, Uher R, Henigsberg N, Mors O, Hauser J, et al. Sexual dysfunction during treatment with serotonergic and noradrenergic antidepressants: clinical description and the role of the 5-HTTLPR. World J Biol Psychiatry. 2011;12(7):528-38.
349. Baumer FM, Howe M, Gallelli K, Simeonova DI, Hallmayer J, Chang KD. A pilot study of antidepressant-induced mania in pediatric bipolar disorder: Characteristics, risk factors, and the serotonin transporter gene. Biol Psychiatry. 2006;60(9):1005-12.
350. Kim DK, Lim SW, Lee S, Sohn SE, Kim S, Hahn CG, et al. Serotonin transporter gene polymorphism and antidepressant response. Neuroreport. 2000;11(1):215-9.
351. Serretti A, Zanardi R, Franchini L, Artioli P, Dotoli D, Pirovano A, et al. Pharmacogenetics of selective serotonin reuptake inhibitor response: a 6-month follow-up. Pharmacogenetics. 2004;14(9):607-13.
352. Smits KM, Smits LJ, Peeters FP, Schouten JS, Janssen RG, Smeets HJ, et al. The influence of 5-HTTLPR and STin2 polymorphisms in the serotonin transporter gene on treatment effect of selective serotonin reuptake inhibitors in depressive patients. Psychiatric genetics. 2008;18(4):184-90.
353. Illi A, Poutanen O, Setala-Soikkeli E, Kampman O, Viikki M, Huhtala H, et al. Is 5-HTTLPR linked to the response of selective serotonin reuptake inhibitors in MDD? Eur Arch Psychiatry Clin Neurosci. 2011;261(2):95-102.
354. Myung W, Lim SW, Kim S, Kim H, Chung JW, Seo MY, et al. Serotonin transporter genotype and function in relation to antidepressant response in Koreans. Psychopharmacology (Berl). 2013;225(2):283-90.
355. Seripa D, Pilotto A, Paroni G, Fontana A, D'Onofrio G, Gravina C, et al. Role of the serotonin transporter gene locus in the response to SSRI treatment of major depressive disorder in late life. J Psychopharmacol. 2015;29(5):623-33.
356. Serretti A, Cusin C, Rossini D, Artioli P, Dotoli D, Zanardi R. Further evidence of a combined effect of SERTPR and TPH on SSRIs response in mood disorders. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics. 2004;129B(1):36-40.
357. Yevtushenko OO, Oros MM, Reynolds GP. Early response to selective serotonin reuptake inhibitors in panic disorder is associated with a functional 5-HT1A receptor gene polymorphism. J Affect Disord. 2010;123(1-3):308-11.
358. Serretti A, Mandelli L, Lorenzi C, Pirovano A, Olgiati P, Colombo C, et al. Serotonin transporter gene influences the time course of improvement of "core" depressive and somatic anxiety symptoms during treatment with SSRIs for recurrent mood disorders. Psychiatry Res. 2007;149(1-3):185-93.

359. Erzegovesi S, Riboldi C, Di Bella D, Di Molfetta D, Mapelli F, Negri B, et al. Bulimia nervosa, 5-HTTLPR polymorphism and treatment response to four SSRIs: a single-blind study. Journal of clinical psychopharmacology. 2004;24(6):680-2.
360. Monteleone P, Santonastaso P, Tortorella A, Favaro A, Fabrazzo M, Castaldo E, et al. Serotonin transporter polymorphism and potential response to SSRIs in bulimia nervosa. Molecular psychiatry. 2005;10(8):716-8.
361. Stein MB, Seedat S, Gelernter J. Serotonin transporter gene promoter polymorphism predicts SSRI response in generalized social anxiety disorder. Psychopharmacology (Berl). 2006;187(1):68-72.
362. Dreimuller N, Tadic A, Dragicevic A, Boland K, Bondy B, Lieb K, et al. The serotonin transporter promoter polymorphism (5-HTTLPR) affects the relation between antidepressant serum concentrations and effectiveness in major depression. Pharmacopsychiatry. 2012;45(3):108-13.
363. Takahashi H, Higuchi H, Sato K, Kamata M, Yoshida K, Nishimura K. Association between serotonin transporter polymorphisms (5-HTTLPR) and the MADRS Dysphoria, Retardation, and Vegetative Subscale scores in the treatment of depression. Neuropsychiatr Dis Treat. 2017;13:1463-9.
364. Kao WT, Chang CL, Lung FW. 5-HTT mRNA level as a potential biomarker of treatment response in patients with major depression in a clinical trial. J Affect Disord. 2018;238:597-608.
365. Stamm TJ, Adli M, Kirchheiner J, Smolka MN, Kaiser R, Tremblay PB, et al. Serotonin transporter gene and response to lithium augmentation in depression. Psychiatric genetics. 2008;18(2):92-7.
366. Gressier F, Bouaziz E, Verstuyft C, Hardy P, Becquemont L, Corruble E. 5-HTTLPR modulates antidepressant efficacy in depressed women. Psychiatric genetics. 2009;19(4):195-200.
367. Domschke K, Tidow N, Schwarte K, Deckert J, Lesch KP, Arolt V, et al. Serotonin transporter gene hypomethylation predicts impaired antidepressant treatment response. Int J Neuropsychopharmacol. 2014;17(8):1167-76.
368. Nonen S, Kato M, Takekita Y, Wakeno M, Sakai S, Serretti A, et al. Polymorphism of rs3813034 in Serotonin Transporter Gene SLC6A4 Is Associated With the Selective Serotonin and Serotonin-Norepinephrine Reuptake Inhibitor Response in Depressive Disorder: Sequencing Analysis of SLC6A4. Journal of clinical psychopharmacology. 2016;36(1):27-31.
369. Garfield LD, Muller DJ, Kennedy JL, Mulsant BH, Reynolds CF, 3rd, Teitelbaum SL, et al. Genetic variation in the serotonin transporter and HTR1B receptor predicts reduced bone formation during serotonin reuptake inhibitor treatment in older adults. World J Biol Psychiatry. 2014;15(5):404-10.
370. Rawson KS, Dixon D, Civitelli R, Peterson TR, Mulsant BH, Reynolds CF, 3rd, et al. Bone Turnover with Venlafaxine Treatment in Older Adults with Depression. J Am Geriatr Soc. 2017;65(9):2057-63.
371. Lapid MI, Kung S, Frye MA, Biernacka JM, Geske JR, Drake MT, et al. Association of the serotonin transporter-linked polymorphic region genotype with lower bone mineral density. Transl Psychiatry. 2017;7(8):e1213.
372. Smith RM, Papp AC, Webb A, Ruble CL, Munsie LM, Nisenbaum LK, et al. Multiple regulatory variants modulate expression of 5-hydroxytryptamine 2A receptors in human cortex. Biol Psychiatry. 2013;73(6):546-54.
373. Amitai M, Kronenberg S, Carmel M, Michaelovsky E, Frisch A, Brent D, et al. Pharmacogenetics of citalopram-related side effects in children with depression and/or anxiety disorders. J Neural Transm (Vienna). 2016;123(11):1347-54.
374. Demirbugen Oz M, Uckun Z, Yuce-Artun N, Baskak B, Ozdemir H, Kizil Ozel T, et al. The relationship between the serotonin 2A receptor gene -1438A/G and 102T/C polymorphisms and citalopram/sertraline-induced nausea in major depressed patients. Human psychopharmacology. 2018;33(5):e2673.
375. Choi MJ, Kang RH, Ham BJ, Jeong HY, Lee MS. Serotonin receptor 2A gene polymorphism (-1438A/G) and short-term treatment response to citalopram. Neuropsychobiology. 2005;52(3):155-62.

376. McMahon FJ, Buervenich S, Charney D, Lipsky R, Rush AJ, Wilson AF, et al. Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. Am J Hum Genet. 2006;78(5):804-14.
377. Peters EJ, Slager SL, Jenkins GD, Reinalda MS, Garriock HA, Shyn SI, et al. Resequencing of serotonin-related genes and association of tagging SNPs to citalopram response. Pharmacogenet Genomics. 2009;19(1):1-10.
378. Su YA, Li JT, Dai WJ, Liao XM, Dong LC, Lu TL, et al. Genetic variation in the tryptophan hydroxylase 2 gene moderates depressive symptom trajectories and remission over 8 weeks of escitalopram treatment. International clinical psychopharmacology. 2016;31(3):127-33.
379. Brunoni AR, Carracedo A, Amigo OM, Pellicer AL, Talib L, Carvalho AF, et al. Association of BDNF, HTR2A, TPH1, SLC6A4, and COMT polymorphisms with tDCS and escitalopram efficacy: ancillary analysis of a double-blind, placebo-controlled trial. Braz J Psychiatry. 2020;42(2):128-35.
380. Paddock S, Laje G, Charney D, Rush AJ, Wilson AF, Sorant AJ, et al. Association of GRIK4 with outcome of antidepressant treatment in the STAR*D cohort. The American journal of psychiatry. 2007;164(8):1181-8.
381. Uher R, Huezo-Diaz P, Perroud N, Smith R, Rietschel M, Mors O, et al. Genetic predictors of response to antidepressants in the GENDEP project. The pharmacogenomics journal. 2009;9(4):225-33.
382. Brasch-Andersen C, Moller MU, Christiansen L, Thinggaard M, Otto M, Brosen K, et al. A candidate gene study of serotonergic pathway genes and pain relief during treatment with escitalopram in patients with neuropathic pain shows significant association to serotonin receptor2C (HTR2C). European journal of clinical pharmacology. 2011;67(11):1131-7.
383. Perlis RH, Fijal B, Adams DH, Sutton VK, Trivedi MH, Houston JP. Variation in catechol-O-methyltransferase is associated with duloxetine response in a clinical trial for major depressive disorder. Biol Psychiatry. 2009;65(9):785-91.
384. Fijal BA, Kohler J, Ostbye K, Ahl J, Houston JP. Association of candidate gene polymorphisms with diastolic blood pressure change in patients treated with duloxetine. Psychiatry Res. 2013;206(2-3):313-4.
385. Gasso P, Blazquez A, Rodriguez N, Boloc D, Torres T, Mas S, et al. 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. Journal of child and adolescent psychopharmacology. 2018;28(10):711-8.
386. Yoshida K, Naito S, Takahashi H, Sato K, Ito K, Kamata M, et al. Monoamine oxidase A gene polymorphism, 5-HT 2A receptor gene polymorphism and incidence of nausea induced by fluvoxamine. Neuropsychobiology. 2003;48(1):10-3.
387. Sina M, Ahmadiani A, Asadi S, Shams J. Association of serotonin receptor 2a haplotypes with obsessive-compulsive disorder and its treatment response in Iranian patients: a genetic and pharmacogenetic study. Neuropsychiatr Dis Treat. 2018;14:1199-209.
388. Sato K, Yoshida K, Takahashi H, Ito K, Kamata M, Higuchi H, et al. Association between -1438G/A promoter polymorphism in the 5-HT(2A) receptor gene and fluvoxamine response in Japanese patients with major depressive disorder. Neuropsychobiology. 2002;46(3):136-40.
389. Lohoff FW, Aquino TD, Narasimhan S, Multani PK, Etemad B, Rickels K. Serotonin receptor 2A (HTR2A) gene polymorphism predicts treatment response to venlafaxine XR in generalized anxiety disorder. The pharmacogenomics journal. 2013;13(1):21-6.
390. Yuan R, Yuan F, Ren D, Zhu Y, Bi Y, Hu J, et al. HTR1A and HTR2A variants may not predict venlafaxine treatment response in China Han population with major depressive disorder. Psychiatry Res. 2018;270:1179-80.
391. Daud ANA, Bergman JEH, Kerstjens-Frederikse WS, van der Vlies P, Hak E, Berger RMF, et al. Prenatal exposure to serotonin reuptake inhibitors and congenital heart anomalies: an exploratory pharmacogenetics study. Pharmacogenomics. 2017;18(10):987-1001.

392. Liang CS, Ho PS, Chiang KT, Su HC. 5-HT2A receptor -1438 G/A polymorphism and serotonergic antidepressant-induced sexual dysfunction in male patients with major depressive disorder: a prospective exploratory study. J Sex Med. 2012;9(8):2009-16.
393. Badamasi IM, Lye MS, Ibrahim N, Abdul Razaq NA, Ling KH, Stanslas J. Serotonergic receptor gene polymorphism and response to selective serotonin reuptake inhibitors in ethnic Malay patients with first episode of major depressive disorder. The pharmacogenomics journal. 2021;21(4):498-509.
394. Bishop JR, Moline J, Ellingrod VL, Schultz SK, Clayton AH. Serotonin 2A -1438 G/A and G-protein Beta3 subunit C825T polymorphisms in patients with depression and SSRI-associated sexual side-effects. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2006;31(10):2281-8.
395. Masiran R, Sidi H, Mohamed Z, Mohamed Saini S, Nik Jaafar NR. Association between 5HT2A polymorphism and selective serotonin re-uptake inhibitor (SSRI)-induced sexual desire disorder (SDD) among Malaysian women. Asia Pac Psychiatry. 2013;5 Suppl 1:41-9.
396. Masiran R, Sidi H, Mohamed Z, Mohd Nazree NE, Nik Jaafar NR, Midin M, et al. Female sexual dysfunction in patients with major depressive disorder (MDD) treated with selective serotonin reuptake inhibitor (SSRI) and its association with serotonin 2A-1438 G/A single nucleotide polymorphisms. J Sex Med. 2014;11(4):1047-55.
397. Deumic Shultz E, Mills JA, Ellingrod VL, Bishop JR, Calarge CA. Sexual Functioning in Adolescents With Major Depressive Disorder: A Prospective Study. J Clin Psychiatry. 2021;82(6).
398. Illi A, Setala-Soikkeli E, Viikki M, Poutanen O, Huhtala H, Mononen N, et al. 5-HTR1A, 5-HTR2A, 5-HTR6, TPH1 and TPH2 polymorphisms and major depression. Neuroreport. 2009;20(12):1125-8.
399. Horstmann S, Lucae S, Menke A, Hennings JM, Ising M, Roeske D, et al. Polymorphisms in GRIK4, HTR2A, and FKBP5 show interactive effects in predicting remission to antidepressant treatment. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2010;35(3):727-40.
400. Kishi T, Yoshimura R, Kitajima T, Okochi T, Okumura T, Tsunoka T, et al. HTR2A is associated with SSRI response in major depressive disorder in a Japanese cohort. Neuromolecular Med. 2010;12(3):237-42.
401. Viikki M, Huuhka K, Leinonen E, Illi A, Setala-Soikkeli E, Huuhka M, et al. Interaction between two HTR2A polymorphisms and gender is associated with treatment response in MDD. Neurosci Lett. 2011;501(1):20-4.
402. Qesseveur G, Petit AC, Nguyen HT, Dahan L, Colle R, Rotenberg S, et al. Genetic dysfunction of serotonin 2A receptor hampers response to antidepressant drugs: A translational approach. Neuropharmacology. 2016;105:142-53.
403. Corregiari FM, Bernik M, Cordeiro Q, Vallada H. Endophenotypes and serotonergic polymorphisms associated with treatment response in obsessive-compulsive disorder. Clinics (Sao Paulo). 2012;67(4):335-40.
404. Cusin C, Serretti A, Zanardi R, Lattuada E, Rossini D, Lilli R, et al. Influence of monoamine oxidase A and serotonin receptor 2A polymorphisms in SSRI antidepressant activity. Int J Neuropsychopharmacol. 2002;5(1):27-35.
405. Li HF, Yu X, Yang K, He CY, Kou SJ, Cao SX, et al. The relationship between single nucleotide polymorphisms in 5-HT2A signal transduction-related genes and the response efficacy to selective serotonin reuptake inhibitor treatments in Chinese patients with major depressive disorder. Genet Test Mol Biomarkers. 2012;16(7):667-71.
406. Noordam R, Direk N, Sitlani CM, Aarts N, Tiemeier H, Hofman A, et al. Identifying genetic loci associated with antidepressant drug response with drug-gene interaction models in a population-based study. J Psychiatr Res. 2015;62:31-7.

407. Dong ZQ, Li XR, He L, He G, Yu T, Sun XL. 5-HTR1A and 5-HTR2A genetic polymorphisms and SSRI antidepressant response in depressive Chinese patients. Neuropsychiatr Dis Treat. 2016;12:1623-9.
408. Sun Y, Tao S, Tian S, Shao J, Mo Z, Wang X, 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;283:130-8.
409. Kao CF, Kuo PH, Yu YW, Yang AC, Lin E, Liu YL, et al. Gene-Based Association Analysis Suggests Association of HTR2A With Antidepressant Treatment Response in Depressed Patients. Front Pharmacol. 2020;11:559601.
410. Milosavljevic F, Bukvic N, Pavlovic Z, Miljevic C, Pesic V, Molden E, et al. Association of CYP2C19 and CYP2D6 Poor and Intermediate Metabolizer Status With Antidepressant and Antipsychotic Exposure: A Systematic Review and Meta-analysis. JAMA psychiatry. 2021;78(3):270-80.
411. Lin XQ, Wang P, Cai WK, Xu GL, Yang M, Zhou MD, et al. The Associations Between CYP2D6 Metabolizer Status and Pharmacokinetics and Clinical Outcomes of Venlafaxine: A Systematic Review and Meta-Analysis. Pharmacopsychiatry. 2019;52(5):222-31.
412. Fabbri C, Tansey KE, Perlis RH, Hauser J, Henigsberg N, Maier W, et al. Effect of cytochrome CYP2C19 metabolizing activity on antidepressant response and side effects: Meta-analysis of data from genome-wide association studies. Eur Neuropsychopharmacol. 2018;28(8):945-54.
413. Chang M, Tybring G, Dahl ML, Lindh JD. Impact of cytochrome P450 2C19 polymorphisms on citalopram/escitalopram exposure: a systematic review and meta-analysis. Clinical pharmacokinetics. 2014;53(9):801-11.
414. Areberg J, Petersen KB, Chen G, Naik H. Population pharmacokinetic meta-analysis of vortioxetine in healthy individuals. Basic & clinical pharmacology & toxicology. 2014;115(6):552-9.
415. Kato M, Serretti A. Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. Molecular psychiatry. 2010;15(5):473-500.
416. Niitsu T, Fabbri C, Bentini F, Serretti A. Pharmacogenetics in major depression: a comprehensive meta-analysis. Progress in neuro-psychopharmacology & biological psychiatry. 2013;45:183-94.
417. Wan YS, Zhai XJ, Tan HA, Ai YS, Zhao LB. Associations between the 1438A/G, 102T/C, and rs7997012G/A polymorphisms of HTR2A and the safety and efficacy of antidepressants in depression: a meta-analysis. The pharmacogenomics journal. 2021;21(2):200-15.
418. Du D, Tang Q, Han Q, Zhang J, Liang X, Tan Y, et al. Association between genetic polymorphism and antidepressants in major depression: a network meta-analysis. Pharmacogenomics. 2020;21(13):963-74.
419. Ren F, Ma Y, Zhu X, Guo R, Wang J, He L. Pharmacogenetic association of bi- and triallelic polymorphisms of SLC6A4 with antidepressant response in major depressive disorder. J Affect Disord. 2020;273:254-64.
420. Stein K, Maruf AA, Muller DJ, Bishop JR, Bousman CA. Serotonin Transporter Genetic Variation and Antidepressant Response and Tolerability: A Systematic Review and Meta-Analysis. J Pers Med. 2021;11(12).
421. Crawford AA, Lewis G, Lewis SJ, Munafo MR. Systematic review and meta-analysis of serotonin transporter genotype and discontinuation from antidepressant treatment. Eur Neuropsychopharmacol. 2013;23(10):1143-50.
422. Porcelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. Eur Neuropsychopharmacol. 2012;22(4):239-58.
423. Serretti A, Kato M, De Ronchi D, Kinoshita T. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. Molecular psychiatry. 2007;12(3):247-57.

424. Serretti A, Cusin C, Rausch JL, Bondy B, Smeraldi E. Pooling pharmacogenetic studies on the serotonin transporter: a mega-analysis. Psychiatry Res. 2006;145(1):61-5.