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

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**Serotonin reuptake inhibitor antidepressants, including selective serotonin reuptake inhibitors (SSRIs; i.e., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), serotonin and norepinephrine reuptake inhibitors (i.e., desvenlafaxine, duloxetine, levomilnacipran, milnacipran, and venlafaxine), and serotonin modulators with SSRI-like properties (i.e., vilazodone and vortioxetine) are primary pharmacologic treatments for major depressive and anxiety disorders. Genetic variation in *CYP2D6*, *CYP2C19*, and *CYP2B6* influences the metabolism of many of these antidepressants, which may potentially affect dosing, efficacy, and tolerability. In addition, the pharmacodynamic genes *SLC6A4* (serotonin transporter) and *HTR2A* (serotonin-2A receptor) have been examined in relation to efficacy and side effect profiles of these drugs. This guideline updates and expands the 2015 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* genotypes and SSRI dosing and summarizes the impact of *CYP2D6*, *CYP2C19*, *CYP2B6*, *SLC6A4*, and *HTR2A* genotypes on antidepressant dosing, efficacy, and tolerability. We provide recommendations for using *CYP2D6*, *CYP2C19*, and *CYP2B6* genotype results to help inform prescribing these antidepressants and describe the existing data for *SLC6A4* and *HTR2A*, which do not support their clinical use in antidepressant prescribing.**

This document updates and expands the 2015 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* genotypes and selective serotonin reuptake inhibitor (SSRI) antidepressants.[1] The current guideline includes updated evidence reviews for SSRIs, as well as evidence reviews for serotonin and norepinephrine reuptake inhibitors

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(SNRIs; i.e., desvenlafaxine, duloxetine, levomilnacipran, milnacipran, and venlafaxine), and serotonin modulators with SSRI-like properties (i.e., vilazodone and vortioxetine). New evidence reviews were conducted for these antidepressants and variants in the *CYP2B6*, serotonin transporter (*SLC6A4*), and serotonin-2A receptor (*HTR2A*) genes. This guideline informs the interpretation of existing genotype test results and provides recommendations to guide antidepressant dosing or selection. Other clinical variables that may influence antidepressant therapy, as well as which patients to test, test selection, and genotyping cost-effectiveness, are beyond the scope of this document and discussed elsewhere.[2,3] CPIC guidelines are periodically updated at cpicpgx.org.

## FOCUSED LITERATURE REVIEW

A systematic literature review focusing on *CYP2D6*, *CYP2C19*, *CYP2B6*, *SLC6A4*, and *HTR2A* genotypes and their influence on antidepressant (citalopram, escitalopram, desvenlafaxine, duloxetine, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, paroxetine, sertraline, venlafaxine, vilazodone, and vortioxetine) therapy was conducted (**Supplementary Material S1**). The evidence is summarized in **Tables S1–S4**.

## GENES: *CYP2D6*, *CYP2C19*, *CYP2B6*, *SLC6A4*, AND *HTR2A*

### Background

***CYP2D6***. To date, over 170 haplotypes (or star (*) alleles) have been defined by the Pharmacogene Variation (PharmVar) Consortium[4] (***CYP2D6* Allele Definition Table**[5,6]). *CYP2D6* alleles have been extensively studied across ancestrally diverse populations, and significant differences in allele frequencies have been observed (***CYP2D6* Allele Functionality and Frequency Tables**[5,6]). The most commonly interrogated alleles are categorized into functional groups as follows: normal function (e.g., *CYP2D6*1* and **2*), decreased function (e.g., *CYP2D6*9*, **10*, and **41*), and no function (e.g., *CYP2D6*3–*6*).[6] Given that *CYP2D6* is also prone to structural variation, including gene deletions, duplications, multiplications, and rearrangements with *CYP2D7*, many clinical laboratories also report *CYP2D6* copy number variants. Notably, *CYP2D6*5* represents a gene deletion, whereas gene duplications and multiplications are denoted as xN (e.g., *CYP2D6*1x2*, indicating two gene copies of the **1* allele).

***CYP2C19***. The *CYP2C19* gene has more than 35 star alleles defined by PharmVar,[7] including rare gene deletions (***CYP2C19* Allele Definition Table**[5,6]). The frequencies of these alleles differ considerably across ancestrally diverse populations (***CYP2C19* Allele Frequency Table**[5,6]). Alleles are categorized into functional groups as follows: normal function (e.g., *CYP2C19*1*), decreased function (e.g., *CYP2C19*9*), no function (e.g., *CYP2C19*2* and **3*), and increased function (e.g., *CYP2C19*17*) (***CYP2C19* Allele Functionality Table**[5,6]). Emerging data suggest that some individuals with *CYP2C19*1* alleles have a *CYP2C:TG* haplotype (rs2860840 and rs11188059) associated with increased CYP2C19 enzyme activity.[8] However, this haplotype resides in *CYP2C18* (~25 kilobase (kb) upstream of *CYP2C19*) and is not currently interrogated by clinical genotyping platforms; additional information is provided as **Supplementary Material S1**.

***CYP2B6***. *CYP2B6* is also highly polymorphic with over 45 star alleles currently defined by PharmVar[9] (***CYP2B6* Allele Definition Table**[5]). Substantial differences in allele frequencies occur across ancestrally diverse groups (***CYP2B6* Frequency Table**[5,6]). 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*). Additional information is provided as **Supplementary Material S1**.

***SLC6A4***. The *SLC6A4* gene encodes the serotonin transporter (5-HTT) that terminates the action of serotonin via reuptake of the neurotransmitter from the synaptic spaces into presynaptic neurons. Serotonin reuptake inhibitor antidepressants (e.g., SSRIs, SNRIs, vortioxetine, and vilazodone) directly bind to the serotonin transporter, blocking serotonin reuptake. The most studied variant is (rs4795541/5-HTTLPR) in the *SLC6A4* promoter region, with the most common alleles referred to as "long" (16 repeats) and "short" (14 repeats). The long (L) allele has been associated with 1.9-fold to 2.2-fold greater serotonin reuptake activity compared with the short allele.[10] An additional promoter variant in *SLC6A4* (rs25531A>G) is often used to subdivide the long allele into long-A ($L_A$) or long-G ($L_G$) alleles, where some evidence suggests that $L_A$ carriers retain the expected long-allele reuptake activity, and $L_G$ carriers have decreased activity similar to those with the short (S) allele;[10] however, consensus on the function of this promoter variant is lacking.[10] While *SLC6A4* genotype has been commonly studied for associations with antidepressants, epigenetic patterns have also been investigated and shown to contribute to 5-HTT expression and brain activity.[11]

***HTR2A***. The *HTR2A* gene encodes the postsynaptic serotonin-2A receptor ($5\text{-HT}_{2A}$), which is involved in postsynaptic serotonin signaling. Two of the most widely studied *HTR2A* variants are in the promoter region and are in strong linkage disequilibrium (rs6311A>G, rs6313C>T). Both variants have been associated with altered $5\text{-HT}_{2A}$ expression in human prefrontal and temporal cortices.[12,13] Another variant in intron 2 (rs7997012A>G) with unknown function has also been extensively investigated in relation to antidepressant treatment outcomes.[12–14]

### Genetic test interpretation

**CYP2D6, CYP2C19, and CYP2B6.** Clinical laboratories typically interrogate *CYP2D6*, *CYP2C19*, and *CYP2B6* variants with known functional consequences that are of appreciable frequencies in the general population and assign genotype using star (*) allele nomenclature.[4,7,9] Each star (*) allele (or haplotype) represents a specific combination of variants identified by the test for each gene. The ***CYP2D6*, *CYP2C19*, and *CYP2B6* Allele Functionality Tables** provide lists of alleles and their functional status determined based on reported *in vitro* and/or *in vivo* data when available.[5,6] Genetic test results are commonly

reported as the combination of the inherited maternal and paternal star (*) alleles, which is referred to as a diplotype (e.g., *CYP2D6*1/*2*, *CYP2C19*1/*3*, *CYP2B6*1/*6*).[4,7] The predicted phenotype (**Table 1**) is influenced by the expected function of each reported allele in the diplotype. An activity scoring (AS) system is commonly used to assign the functional capacity of *CYP2D6* alleles (the AS represents the sum of the activity values assigned to each allele) and is used to assign poor metabolizers (PMs) (AS = 0), intermediate metabolizers (IMs) (AS = 0.25–1), normal metabolizers (NMs) (AS 1.25–2.25), or ultrarapid metabolizers (UMs) (AS >2.25)[15] (**Table 1**). The **Supplementary Material S1** (Genetic Test Interpretation Section) contains additional information regarding *CYP2D6*, *CYP2C19*, and *CYP2B6* genetic test interpretation and phenotype assignment, including a discussion regarding activity scores for *CYP2D6*.

**SLC6A4 and HTR2A.** Clinical testing of *SLC6A4* is available; however, most laboratories only test for the long/short 5-HTTLPR promoter variant (rs4795541), and a minority also test for the additional promoter variant rs25531. Not testing or testing for rs25531 can result in SLC6A4 phenotype discrepancies for 4–23% of long/long and 4–16% of long/short individuals, depending on race and ethnicity.[16] Clinical testing of *HTR2A* is also available; however, most laboratories only test for rs6311, rs6313, and/or rs7997012. To date, no standardized genotype to phenotype categories have been proposed for *SLC6A4* or *HTR2A*. As such, laboratory test results for these two genes, and their implications for antidepressant response, vary across commercially available tests.[17]

### Available genetic test options

See **Supplementary Material S1** and www.ncbi.nlm.nih.gov/gtr/ for more information on commercially available clinical testing options.

### Incidental findings

Some studies have reported associations between genetic variants in *CYP2D6*, *CYP2C19*, *CYP2B6*, *SLC6A4*, and *HTR2A* and psychiatric or medical conditions. However, none of these variants are considered clinically useful predictors of any common conditions, nor are they implicated in any Mendelian genetic disorders. See **Supplementary Material S1** for more information.

### Other considerations

CYP2D6, CYP2C19, and CYP2B6 are the primary enzymes responsible for the metabolism of many other commonly used medications. It is important to note that CPIC guidelines exist for other drugs metabolized by CYP2D6, CYP2C19, and CYP2B6.[18]

**Modification of the predicted phenotype by drug–drug interactions.** Phenoconversion refers to the mismatch between an individual's genetically predicted phenotype and observed phenotype due to the presence of an inducer or inhibitor of an enzyme's activity.[19] The degree of phenoconversion may depend on the individual's innate metabolizer phenotype as well as the strength and duration of the inducer or inhibitor.[20] A list of CYP2D6, CYP2C19, and CYP2B6 inducers and strong, moderate, or weak inhibitors is maintained by the US Food and Drug Administration (FDA).[21] Consensus approaches for adjusting CYP2D6, CYP2C19, or CYP2B6 predicted phenotypes in the presence of inhibitors or inducers have not been established (see **Supplementary Material S1** for further discussion).

## DRUGS: SEROTONIN REUPTAKE INHIBITORS

### Background

Approximately one-half of adults with major depressive disorder have inadequate response to initial pharmacotherapy.[22] Furthermore, an estimated 25,000 patients per year in the United States present to emergency departments due to antidepressant-related adverse events.[23] Utilizing pharmacogenetic test results to guide antidepressant therapy may help improve treatment response and decrease adverse events.[24] SSRIs and SNRIs are first-line pharmacotherapy options for major depressive and anxiety disorders and may be used to treat other psychiatric conditions. Serotonin modulators with SSRI-like properties (e.g., vilazodone and vortioxetine) are newer antidepressants for treating major depressive disorder. Although pharmacokinetic properties vary among these agents, they are all serotonin reuptake inhibitors that increase serotonergic activity by decreasing presynaptic serotonin reuptake. The most common adverse effects of these drugs include central nervous system effects (e.g., insomnia, headache), gastrointestinal dysfunction, and sexual dysfunction; however, the incidence of specific side effects may differ with each drug and condition being treated. Serious adverse events, such as serotonin syndrome and arrhythmias caused by QT prolongation, have been associated with some SSRIs.[25,26]

Patients may be predisposed to poor therapeutic outcomes due to having *CYP2D6*, *CYP2C19*, or *CYP2B6* allelic variants that alter antidepressant biotransformation. CYP2D6 extensively metabolizes fluvoxamine, paroxetine, venlafaxine, and vortioxetine into less active metabolites, or in the case of venlafaxine, an active metabolite that has SNRI activity (**Table S5**). Altered CYP2D6 activity may result in lower or greater exposure to these drugs. For other antidepressants that are major or minor CYP2D6 substrates (i.e., citalopram, sertraline, duloxetine, fluoxetine, levomilnacipran, venlafaxine, vilazodone, and vortioxetine), multiple drug metabolism pathways and/or active metabolites result in complex and unclear relationships between genotype-defined metabolizer groups and drug exposure or outcomes (**Table S5**).[27] Because citalopram, escitalopram, and sertraline are extensively metabolized by CYP2C19, variants impacting CYP2C19 activity may alter drug exposure. CYP2C19 extensively metabolizes citalopram and escitalopram to much less potent metabolites (**Table S5**).[28] Sertraline is metabolized by CYP2D6, CYP2C19, CYP2B6, and other CYP enzymes, with pharmacokinetic studies suggesting that CYP2C19 is the major metabolic pathway (**Table S5**).[27] There is evidence that *CYP2B6* genetic variation is associated with sertraline exposure,[8] but studies have found little to no effect of *CYP2D6* genetic variation on sertraline exposure and dose (**Table S1**).

**Table 1 Assignment of predicted phenotypes based on diplotypes**

| Phenotype | Activity score range | Activity score/diplotypes | Examples of *CYP2D6* diplotypes[a] |
|---|---|---|---|
| Assignment of predicted CYP2D6 phenotypes based on diplotypes | | | |
| CYP2D6 ultrarapid metabolizer | >2.25 | >2.25 | **1/*1xN*, **1/*2xN*, **2/*2xN* |
| CYP2D6 normal metabolizer | $1.25 \leq x \leq 2.25$ | 1.25<br>1.5<br>1.75<br>2.0<br>2.25 | **1/*10*, **1/*9*, **1/*41*<br>**1/*17*, **1/*29*<br>**1/*10x3*<br>**1/*1*, **1/*2*<br>**2x2/*10* |
| CYP2D6 intermediate metabolizer | $0 < x < 1.25$ | 0.25<br>0.5<br>0.75<br>1 | **4/*10*, **4/*41*<br>**10/*10*, **10/*41*<br>**10/*29*, **9/*14*, **17/*41*<br>**1/*5*, **1/*4*, **1/*5* |
| CYP2D6 poor metabolizer | 0 | 0 | **3/*4*, **4/*4*, **5/*5*, **5/*6* |
| CYP2D6 indeterminate | n/a | An individual carrying one or two uncertain and/or unknown function alleles | **1/*22*, **1/*25*, **22/*25* |
| Assignment of predicted CYP2C19 phenotypes based on diplotypes | | | |
| CYP2C19 ultrarapid metabolizer | n/a | An individual carrying two increased function alleles | **17/*17* |
| CYP2C19 rapid metabolizer | n/a | An individual carrying one normal function allele and one increased function allele | **1/*17* |
| CYP2C19 normal metabolizer | n/a | An individual carrying two normal function alleles | **1/*1* |
| CYP2C19 likely intermediate metabolizer | n/a | An individual carrying one normal function allele and one decreased[b] function allele or one increased function allele and one decreased[b] function allele or two decreased[b] function alleles | **1/*9*, **9/*17*, **9/*9* |
| CYP2C19 intermediate metabolizer | n/a | An individual carrying one normal function allele and one no function allele or one increased function allele and one no function allele | **1/*2*, **1/*3*, **2/*17*, **3/*17* |
| CYP2C19 likely poor metabolizer | n/a | An individual carrying one decreased[b] function allele and one no function allele | **2/*9*, **3/*9* |
| CYP2C19 poor metabolizer | n/a | An individual carrying two no function alleles | **2/*2*, **3/*3*, **2/*3* |
| CYP2C19 indeterminate | n/a | An individual carrying one or two uncertain function alleles | **1/*12*, **2/*12*, **12/*14* |
| Assignment of predicted CYP2B6 phenotypes based on diplotypes | | | |
| CYP2B6 ultrarapid metabolizer | n/a | An individual carrying two increased function alleles | **4/*4* |
| CYP2B6 rapid metabolizer | n/a | An individual carrying one normal function allele and one increased function allele | **1/*4* |
| CYP2B6 normal metabolizer | n/a | An individual carrying two normal function alleles | **1/*1* |
| CYP2B6 intermediate metabolizer | n/a | An individual carrying one normal function allele and one decreased function allele OR one normal function allele and one no function allele OR one increased function allele and one decreased function allele OR one increased function allele and one no function allele | **1/*6*, **1/*18*, **4/*6*, **4/*18* |
| CYP2B6 poor metabolizer | n/a | An individual carrying two decreased function alleles OR two no function alleles OR one decreased function allele and one no function allele | **6/*6*, **18/*18*, **6/*18* |
| CYP2B6 indeterminate | n/a | An individual carrying one or two uncertain and/or unknown function alleles | **3/*6*, **3/*10* |

CYP, cytochrome P450; n/a, not applicable.
[a]Please refer to the Diplotype-Phenotype Table online for a complete list.[5,6] [b]There are limited data to characterize the function of decreased function alleles.

### Linking genetic variability to variability in drug-related phenotypes

**CYP2D6, CYP2C19, and CYP2B6.** There is substantial evidence linking *CYP2D6* or *CYP2C19* genotype to phenotypic variability in pharmacokinetic parameters or treatment outcomes for some, but not all, of the antidepressants evaluated in this guideline (**Supplementary Material S1**). *CYP2B6* genotype has been associated with pharmacokinetic parameters of sertraline. The application of a grading system to the evidence linking *CYP2D6*, *CYP2C19*, or *CYP2B6* genotypes to pharmacokinetic variability, dose, and clinical outcomes indicates a moderate to high quality of evidence for the majority of data (**Tables S1 and S2**). This body of evidence, which includes retrospective pharmacogenetic analyses of prospective trials, as well as large population studies identifying relationships across genotype, drug exposure associations, and treatment discontinuation or switching, provides the basis for the recommendations in **Tables 2–5**.

**HTR2A and SLC6A4.** Variants in *HTR2A* and *SLC6A4* have been independently associated with response variability, remission, and side effects of many antidepressants (**Tables S3 and S4**). However, the evidence supporting these associations is currently mixed and insufficient to support clinical utility. Some meta-analyses revealed statistically significant antidepressant class associations (for *HTR2A*) or SSRI class associations (*SLC6A4*) with response, remission, or side effects, but individual studies often did not account for differences in medications, dose, exposure, or genetic variants that affect the pharmacokinetics of these medications.[14,29,30] While there are statistical associations and biological plausibility given the pharmacodynamic properties of antidepressants, how to translate these relationships to clinical action is currently unclear. Contextual factors influencing this assessment include an unclear relationship of pharmacodynamic antidepressant–gene associations with drug dose requirement, incomplete evidence regarding alternative treatments, lack of consensus on genotype to phenotype translation, inconsistent *SLC6A4* L/S stratification by subvariants (e.g., $L_A/L_G$), and differences in the magnitude and direction of associations observed across biogeographic groups.

### Therapeutic recommendations

**Tables 2–4** describe recommended clinical actions based on genetic information. Drug interactions and other clinical factors can substantially influence prescribing decisions for antidepressants and should be considered before initiating drug therapy. Based on the current literature, *CYP2D6*-guided recommendations are made for paroxetine, fluvoxamine, venlafaxine, and vortioxetine; *CYP2C19*-guided recommendations are made for citalopram, escitalopram, and sertraline; and *CYP2B6*-guided recommendations are made for sertraline. Considerations regarding other antidepressants included in the evidence review are also discussed below.

**CYP2D6-paroxetine, fluvoxamine, venlafaxine, and vortioxetine dosing recommendations.** **Table 2** summarizes the dosing recommendations for paroxetine (**Table 2a**), fluvoxamine (**Table 2b**), venlafaxine (**Table 2c**), and vortioxetine (**Table 2d**) based on CYP2D6 phenotype. In multiple studies, CYP2D6 UMs had low or undetectable plasma concentrations of paroxetine[31–34] and vortioxetine[35] when compared with NMs.[31–34] Those with undetectable or low plasma concentrations had a lower probability of clinical benefit, although the minimal effective paroxetine therapeutic concentration is not well defined.[36] Because of the decreased probability of clinical benefit due to lower drug exposure for paroxetine and vortioxetine, an alternative antidepressant not predominantly metabolized by CYP2D6 should be considered. Regarding venlafaxine, increased metabolism to the active metabolite (O-desmethylvenlafaxine) is seen in UMs; however, there is minimal evidence to suggest that this is clinically significant. In addition, there are insufficient data to assess whether there is a meaningful impact of CYP2D6 ultrarapid metabolism on fluvoxamine exposure or clinical outcomes. Therefore, no dosing recommendations are provided for venlafaxine or fluvoxamine for CYP2D6 UMs.

Due to the increased risk of side effects, a lower paroxetine starting dose and slower titration may be considered for CYP2D6 IMs (**Table 2a** and **Table S1**). Autoinhibition of CYP2D6 and potential phenoconversion were considered in the interpretation of these data, resulting in an optional designation for this recommendation. Adjustments to fluvoxamine, venlafaxine, or vortioxetine therapy are not warranted for CYP2D6 IMs.

When administered similar doses, CYP2D6 PMs had significantly greater drug exposure or parent to metabolite ratios for paroxetine, fluvoxamine, venlafaxine, and vortioxetine when compared with NMs (**Table S1**). Increased drug exposure increases the risk for dose-dependent or concentration-dependent side effects.[37] To potentially prevent adverse effects, dose extrapolations based on differences in pharmacokinetic parameters between phenotype groups suggest a 50% dose reduction of paroxetine (**Table 2a**) and vortioxetine (**Table 2d**) and a 30% dose reduction of fluvoxamine is warranted.[27] However, reducing the fluvoxamine dose by 30% may not be feasible, given the currently available formulations. Therefore, a 25–50% reduction may help prevent adverse events by limiting high drug exposures (**Table 2b**). Data for venlafaxine suggest increased concentration-dependent side effects in CYP2D6 PMs (**Table S2**). The paucity of prospective studies, uncommon clinical use of therapeutic drug monitoring for antidepressants,[38] and the potential that decreasing the dose may compromise medication efficacy was the basis for the optional recommendation to consider alternatives to venlafaxine in CYP2D6 PMs (**Table 2c**). Moreover, the FDA Table of Pharmacogenetic Associations[39] lists venlafaxine and vortioxetine as drugs warranting dose adjustments in CYP2D6 PMs. In addition, the FDA notes paroxetine and fluvoxamine as drugs for which CYP2D6 PMs may have altered systemic concentrations.

**CYP2C19-citalopram, escitalopram, and sertraline dosing recommendations.** **Table 3** summarizes the dosing recommendations for citalopram, escitalopram, and sertraline based on CYP2C19 phenotype. CYP2C19 UMs had significantly lower citalopram and escitalopram exposure compared with NMs

**Table 2 Dosing recommendations antidepressants based on CYP2D6 phenotype**

| Phenotype | Implication | Therapeutic recommendation | Classification of recommendation[a] | Considerations |
|---|---|---|---|---|
| (a) Dosing recommendations for paroxetine based on CYP2D6 phenotype | | | | |
| CYP2D6 ultrarapid metabolizer | Increased metabolism of paroxetine to less active compounds when compared with CYP2D6 normal metabolizers. Lower plasma concentrations decrease the probability of clinical benefit. The extent to which ultrarapid metabolizers phenoconvert to normal, intermediate, or poor metabolizers due to paroxetine autoinhibition of CYP2D6 is unclear | Select alternative drug not predominantly metabolized by CYP2D6 | Moderate | Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy |
| CYP2D6 normal metabolizer | Normal metabolism of paroxetine to less active compounds. Paroxetine-associated phenoconversion of normal metabolizers to intermediate or poor metabolizers due to CYP2D6 autoinhibition may occur and is dose-dependent and greater at steady state concentrations | Initiate therapy with recommended starting dose | Strong | |
| CYP2D6 intermediate metabolizer | Reduced metabolism of paroxetine to less active compounds when compared with CYP2D6 normal metabolizers when starting treatment or at lower doses. Higher plasma concentrations may increase the probability of side effects. Paroxetine-associated phenoconversion of intermediate metabolizers to poor metabolizers due to CYP2D6 autoinhibition may occur and is dose-dependent and greater at steady-state concentrations | Consider a lower starting dose and slower titration schedule as compared with normal metabolizers | Optional | Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy |
| CYP2D6 poor metabolizer | Greatly reduced metabolism when compared with CYP2D6 normal metabolizers. Higher plasma concentrations may increase the probability of side effects. The impact of paroxetine-associated autoinhibition of CYP2D6 is minimal in poor metabolizers | Consider a 50% reduction in recommended starting dose, slower titration schedule, and a 50% lower maintenance dose as compared with normal metabolizers | Moderate | Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy |
| CYP2D6 indeterminate | n/a | No recommendation | No recommendation | |
| (b) Dosing recommendations for fluvoxamine based on CYP2D6 phenotype | | | | |
| CYP2D6 ultrarapid metabolizer | No data available for CYP2D6 ultrarapid metabolizers | No recommendation due to lack of evidence | No recommendation | |
| CYP2D6 normal metabolizer | Normal metabolism | Initiate therapy with recommended starting dose | Strong | |
| CYP2D6 intermediate metabolizer | Reduced metabolism of fluvoxamine to less active compounds when compared with CYP2D6 normal metabolizers. Higher plasma concentrations may increase the probability of side effects | Initiate therapy with recommended starting dose | Moderate | |

**Table 2 (Continued)**

| Phenotype | Implication | Therapeutic recommendation | Classification of recommendation[a] | Considerations |
|---|---|---|---|---|
| CYP2D6 poor metabolizer | Greatly reduced metabolism of fluvoxamine to less active compounds when compared with CYP2D6 normal metabolizers. Higher plasma concentrations may increase the probability of side effects | Consider a 25–50% lower starting dose and slower titration schedule as compared with normal metabolizers or consider a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2D6 | Optional | Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy |
| CYP2D6 indeterminate | n/a | No recommendation | No recommendation | |
| (c) Dosing recommendations for venlafaxine based on CYP2D6 phenotype | | | | |
| CYP2D6 ultrarapid metabolizer | Increased metabolism of venlafaxine to the active metabolite O-desmethylvenlafaxine (desvenlafaxine) and increased O-desmethylvenlafaxine:venlafaxine ratio as compared with CYP2D6 normal metabolizers. There is insufficient evidence supporting the clinical impact of increased O-desmethylvenlafaxine:venlafaxine ratio in CYP2D6 ultrarapid metabolizers | No action recommended based on genotype for venlafaxine because of minimal evidence regarding the impact on efficacy or side effects | No recommendation | |
| CYP2D6 normal metabolizer | Normal metabolism | Initiate therapy with recommended starting dose | Strong | |
| CYP2D6 intermediate metabolizer | Decreased metabolism of venlafaxine to active metabolite O-desmethylvenlafaxine (desvenlafaxine) and decreased O-desmethylvenlafaxine:venlafaxine ratio as compared with CYP2D6 normal metabolizers. There is insufficient evidence supporting the clinical impact of the decreased O-desmethylvenlafaxine:venlafaxine ratio in CYP2D6 intermediate metabolizers | No action recommended based on genotype for venlafaxine because of minimal evidence regarding the impact on efficacy or side effects | No recommendation | |
| CYP2D6 poor metabolizer | Decreased metabolism of venlafaxine to the active metabolite O-desmethylvenlafaxine (desvenlafaxine) and greatly decreased O-desmethylvenlafaxine:venlafaxine ratio as compared with CYP2D6 normal and intermediate metabolizers. The clinical impact of increased venlafaxine and decreased O-desmethylvenlafaxine:venlafaxine ratio in CYP2D6 poor metabolizers is unclear, but CYP2D6 PM genotype has been associated with adverse effects | Consider a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2D6 | Optional | Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy |
| CYP2D6 indeterminate | n/a | No recommendation | No recommendation | |

(Continued)

**Table 2 (Continued)**

| Phenotype | Implication | Therapeutic recommendation | Classification of recommendation[a] | Considerations |
|---|---|---|---|---|
| (d) Dosing recommendations for vortioxetine based on CYP2D6 phenotype | | | | |
| CYP2D6 ultrarapid metabolizer | Increased metabolism of vortioxetine to inactive compounds when compared with CYP2D6 normal metabolizers. Lower plasma concentrations decrease the probability of clinical benefit | Select alternative drug not predominantly metabolized by CYP2D6. If vortioxetine use is warranted, initiate therapy at standard starting dose and titrate to maintenance dose based on efficacy and side effects. Increasing the target maintenance dose by 50% or more may be needed for efficacy | Optional | Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy |
| CYP2D6 normal metabolizer | Normal metabolism | Initiate therapy with recommended starting dose | Strong | |
| CYP2D6 intermediate metabolizer | Reduced metabolism of vortioxetine to less active compounds when compared with CYP2D6 normal metabolizers. Higher plasma concentrations may increase the probability of side effects | Initiate therapy with recommended starting dose | Moderate | |
| CYP2D6 poor metabolizer | Greatly reduced metabolism of vortioxetine to inactive compounds when compared with CYP2D6 normal metabolizers. Higher plasma concentrations may increase the probability of side effects | Initiate 50% of starting dose (e.g., 5 mg) and titrate to the maximum recommended dose of 10 mg or consider a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2D6 | Moderate | Drug–drug interactions, indication and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy |
| CYP2D6 indeterminate | n/a | No recommendation | No recommendation | |

CYP, cytochrome P450; n/a, not applicable.
[a]Rating scheme described in **Supplementary Material S1**.

**Table 3 Dosing recommendations for antidepressants based on CYP2C19 phenotype**

| Phenotype | Implication | Therapeutic Recommendation | Classification of Recommendation[a] | Considerations |
|---|---|---|---|---|
| (a) Dosing recommendations for citalopram and escitalopram based on CYP2C19 phenotype | | | | |
| CYP2C19 ultrarapid metabolizer | Increased metabolism of citalopram and escitalopram to less active compounds when compared with CYP2C19 rapid and normal metabolizers. Lower plasma concentrations decrease the probability of clinical benefit | Consider a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2C19. If citalopram or escitalopram are clinically appropriate, and adequate efficacy is not achieved at standard maintenance dosing, consider titrating to a higher maintenance dose | Strong | Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy |
| CYP2C19 rapid metabolizer | Increase in metabolism of citalopram and escitalopram to less active compounds when compared with CYP2C19 normal metabolizers. Lower plasma concentrations decrease the probability of clinical benefit | Initiate therapy with recommended starting dose. If patient does not adequately respond to recommended maintenance dosing, consider titrating to a higher maintenance dose or switching to a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2C19 | Optional | Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy |
| CYP2C19 normal metabolizer | Normal metabolism | Initiate therapy with recommended starting dose | Strong | |
| CYP2C19 intermediate metabolizer | Reduced metabolism when compared with CYP2C19 normal metabolizers. Higher plasma concentrations may increase the probability of side effects | Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose than normal metabolizers | Moderate | Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose |
| CYP2C19 likely intermediate metabolizer | Reduced metabolism when compared with CYP2C19 normal metabolizers. Higher plasma concentrations may increase the probability of side effects | Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose than normal metabolizers | Moderate | Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose |
| CYP2C19 likely poor metabolizer | Reduced metabolism of citalopram and escitalopram to less active compounds when compared with CYP2C19 normal and intermediate metabolizers. Higher plasma concentrations may increase the probability of side effects | Consider a clinically appropriate antidepressant not predominantly metabolized by CYP2C19. If citalopram or escitalopram are clinically appropriate, consider a lower starting dose, slower titration schedule, and 50% reduction of the standard maintenance dose as compared with normal metabolizers | Strong | Per the FDA warning, citalopram 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation. FDA product labeling additionally cautions that citalopram dose should be limited to 20 mg/day in patients with hepatic impairment, those taking a CYP2C19 inhibitor, and patients greater than 60 years of age |

(Continued)

**Table 3 (Continued)**

| Phenotype | Implication | Therapeutic Recommendation | Classification of Recommendation[a] | Considerations |
|---|---|---|---|---|
| CYP2C19 poor metabolizer | Reduced metabolism of citalopram and escitalopram to less active compounds when compared with CYP2C19 normal and intermediate metabolizers. Higher plasma concentrations may increase the probability of side effect | Consider a clinically appropriate antidepressant not predominantly metabolized by CYP2C19. If citalopram or escitalopram are clinically appropriate, consider a lower starting dose, slower titration schedule, and 50% reduction of the standard maintenance dose as compared with normal metabolizers | Strong | Per the FDA warning, citalopram 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation. FDA product labeling additionally cautions that citalopram dose should be limited to 20 mg/day in patients with hepatic impairment, those taking a CYP2C19 inhibitor, and patients >60 years of age |
| CYP2C19 indeterminate | n/a | No recommendation | No recommendation | |
| (b) Dosing recommendations for sertraline based on CYP2C19 phenotype | | | | |
| CYP2C19 ultrarapid metabolizer | Small increase in metabolism of sertraline to less active compounds when compared with CYP2C19 normal metabolizers | Initiate therapy with recommended starting dose | Strong | CYP2B6 metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered |
| CYP2C19 rapid metabolizer | Small increase in metabolism of sertraline to less active compounds when compared with normal metabolizers | Initiate therapy with recommended starting dose | Strong | CYP2B6 metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered |
| CYP2C19 normal metabolizer | Normal metabolism | Initiate therapy with recommended starting dose | Strong | CYP2B6 metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered |
| CYP2C19intermediate metabolizer | Reduced metabolism of sertraline to less active compounds when compared with CYP2C19 normal metabolizers | Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose than CYP2C19 normal metabolizers | Moderate | CYP2B6 metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered |
| CYP2C19 likely intermediate metabolizer | Reduced metabolism of sertraline to less active compounds when compared with CYP2C19 normal metabolizers | Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose than CYP2C19 normal metabolizers | Moderate | CYP2B6 metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered |

**Table 3 (Continued)**

| Phenotype | Implication | Therapeutic Recommendation | Classification of Recommendation[a] | Considerations |
|---|---|---|---|---|
| CYP2C19 likely poor metabolizer | Greatly reduced metabolism of sertraline to less active compounds when compared with CYP2C19 normal metabolizers. Higher plasma concentrations may increase the probability of side effects | Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose as compared with CYP2C19 normal metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2C19 | Moderate | CYP2B6 metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy |
| CYP2C19 poor metabolizer | Greatly reduced metabolism of sertraline to less active compounds when compared with CYP2C19 normal metabolizers. Higher plasma concentrations may increase the probability of side effects | Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose as compared with CYP2C19 normal metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2C19 | Moderate | CYP2B6 metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy |
| CYP2C19 indeterminate | n/a | No recommendation | No recommendation | CYP2B6 metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy |

CYP, cytochrome P450; FDA, US Food and Drug Administration; n/a, not applicable.
[a]Rating scheme described in **Supplementary Material S1**.

and may experience less symptomatic improvement (Table S1). There are insufficient data to calculate an initial citalopram or escitalopram dose for CYP2C19 UMs, and UMs had greater discontinuation or medication switching compared with NMs (Table S1). Therefore, an alternative clinically appropriate antidepressant not extensively metabolized by CYP2C19 is recommended for CYP2C19 UMs (Table 3a). If citalopram or escitalopram is clinically warranted and adequate efficacy is not achieved at standard maintenance dosing, consider titrating to a higher maintenance dose. Although some data suggest small increases in sertraline metabolism in CYP2C19 UMs,[40] the small effect sizes and a lack of clinical outcomes in relation to this genotype group were the basis for no recommendation to alter sertraline dosing in UMs.

CYP2C19 rapid metabolizers (RMs) may have increased metabolism of citalopram and escitalopram (Table S1); however, these pharmacokinetic effects and clinical associations are less pronounced than in UMs. This was the basis for an optional recommendation to initiate citalopram or escitalopram with a standard starting dose but to consider dose increases or alternatives if patients do not adequately respond to usual maintenance doses (Table 3a). Adjustments to sertraline dosing are not warranted for RMs (Table 3b). CYP2C19 IMs may have reduced metabolism and elevated plasma concentrations of citalopram, escitalopram, and sertraline. Existing data do not support adjusting starting doses for IMs, but reduced metabolism may warrant a slower titration and a lower maintenance dose than NMs.

Elevated concentrations of citalopram, escitalopram, and sertraline have been observed in CYP2C19 PMs, which may increase the risk of adverse drug reactions (Table S1). A growing body of literature also demonstrates that CYP2C19 PMs have worse clinical outcomes, including increased drug discontinuation or switching and increased side effects (Table S1). To minimize unfavorable clinical outcomes with citalopram, escitalopram, or sertraline, a clinically appropriate alternative antidepressant not extensively metabolized by CYP2C19 is recommended in CYP2C19 PMs, or dose adjustments can be considered. If citalopram, escitalopram, or sertraline is clinically indicated in CYP2C19 PMs, a lower starting dose, slower titration, and a 50% reduction of standard maintenance doses should be considered.[27] For citalopram, the FDA recommends a 50% dose reduction (or a maximum dose of 20 mg/day in adults) for CYP2C19 PMs due to the risk of QT prolongation.[26] While the FDA labeling does not include a similar recommendation for escitalopram, it may also have a risk for QT prolongation.[26,41] Although limited data are available describing the relationship between SSRI concentrations and therapeutic effect and tolerability, this is a strong recommendation due to the apparent risk for arrhythmias combined with the FDA providing specific dose recommendations.

**Considerations for other drugs evaluated in relation to CYP2D6 and CYP2C19.** CYP2D6 converts fluoxetine to S-norfluoxetine, while CYP2D6 and CYP2C9 convert fluoxetine to R-norfluoxetine (Table S5). Fluoxetine and S-norfluoxetine modulate serotonin reuptake with similar activity, while R-norfluoxetine is less pharmacologically active.[42] CYP2D6 UMs or PMs have been demonstrated to possess significantly different parent to metabolite ratios (Table S1), but the sum total of fluoxetine plus norfluoxetine plasma concentrations may not vary significantly by CYP2D6 metabolizer groups.[43] Little data are available describing how CYP2D6 phenotype status influences the sum total of fluoxetine plus norfluoxetine concentrations over time or if an imbalance between fluoxetine and norfluoxetine concentrations caused by CYP2D6 phenotype status affects patient outcomes or safety. Therefore, no gene-based dosing recommendations are provided for fluoxetine (CPIC level C, Table S6).

Duloxetine is a substrate of CYP1A2 and CYP2D6; however, existing data do not support a clinically meaningful impact of CYP2D6 on duloxetine and thus was assigned CPIC level C (no recommendation, Table S11). Because other SNRIs such as desvenlafaxine (SNRI metabolized by CYP3A4), levomilnacipran (SNRI predominantly metabolized by CYP3A4 with minor contributions by CYP2C8, CYP2C19, and CYP2D6), milnacipran (SNRI eliminated primarily by renal excretion), and vilazodone (serotonin-modulator metabolized primarily by CYP3A4 with minor contributions from CYP2C19 and CYP2D6) are not significantly impacted by altered CYP2D6 and/or CYP2C19 metabolism, recommendations and CPIC levels were not assigned (Table S5).

**CYP2B6-sertraline dosing recommendations.** Table 4 summarizes the dosing recommendations for sertraline based on CYP2B6 phenotype. Because of the small increase in metabolism in CYP2B6 UMs and RMs, no pre-emptive dose increase is recommended. CYP2B6 IMs may have reduced metabolism and slightly elevated plasma concentrations of sertraline. Existing data do not support adjusting starting doses for CYP2B6 IMs, but reduced metabolism may warrant a slower titration and a lower maintenance dose than NMs. CYP2B6 PMs have greatly reduced metabolism and higher elevated plasma concentrations; thus, a lower starting dose, slower titration, and a 25% reduction of standard maintenance doses should be considered. Because these data supporting decreased metabolism in CYP2B6 IMs and PMs are derived from two pharmacokinetic studies and there is a lack of clinical outcome data (i.e., toxicity) (Table S1), these recommendations are optional.

**CYP2B6 and CYP2C19-sertraline dosing recommendations.** Because CPIC recommendations are provided with the assumption that the test results are available prior to prescribing, we have provided recommendations when only *CYP2C19* (Table 3b) or only *CYP2B6* (Table 4) are available, or when both *CYP2C19* and *CYP2B6* genotype results are available (Table 5). Although a change in dose or therapy may not be warranted based on results for a single gene, treatment modification may be warranted given the combination of a non-normal CYP2C19 and CYP2B6 phenotype (Table 5). Dosing recommendations for CYPC19/CYP2B6 and sertraline are based on Braten *et al.*[8] and are based on the reported or calculated percentage differences in exposure from normal metabolizers.

**Table 4 Dosing recommendations for sertraline based on CYP2B6 phenotype**

| Phenotype | Implication | Therapeutic recommendation | Classification of recommendation[a] | Considerations |
|---|---|---|---|---|
| CYP2B6 ultrarapid metabolizer | Increase in metabolism of sertraline to less active compounds when compared with CYP2B6 normal metabolizers | Initiate therapy with recommended starting dose | Moderate | CYP2C19 metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered |
| CYP2B6 rapid metabolizer | Small increase in metabolism of sertraline to less active compounds when compared with CYP2B6 normal metabolizers | Initiate therapy with recommended starting dose | Strong | CYP2C19 metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered |
| CYP2B6 normal metabolizer | Normal metabolism of sertraline to less active compounds | Initiate therapy with recommended starting dose | Strong | CYP2C19 metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should also be considered |
| CYP2B6 intermediate metabolizer | Reduced metabolism of sertraline to less active compounds when compared with CYP2B6 normal metabolizers | Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose than CYP2B6 normal metabolizers | Optional | CYP2C19 metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should be also considered |
| CYP2B6 poor metabolizer | Greatly reduced metabolism of sertraline to less active compounds when compared with CYP2B6 normal metabolizers. Higher plasma concentrations may increase the probability of side effects | Consider a lower starting dose, slower titration schedule, and 25% reduction of standard maintenance dose as compared with CYP2B6 normal metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2B | Optional | CYP2C19 metabolizer status, drug–drug interactions, and other patient characteristics (e.g., age, renal function, liver function) should be considered when adjusting dose or selecting an alternative therapy |
| CYP2B6 indeterminate | n/a | No recommendation | No recommendation | |

CYP, cytochrome P450; n/a, not applicable.
[a]Rating scheme described in **Supplementary Material S1**.

**Table 5 Dosing recommendations for sertraline based on CYP2C19 and CYP2B6 phenotypes**

| Phenotype | CYP2B6 ultrarapid or rapid metabolizer | CYP2B6 normal metabolizers | CYP2B6 intermediate metabolizers | CYP2B6 poor metabolizers | CYP2B6 indeterminate |
|---|---|---|---|---|---|
| CYP2C19 ultrarapid or rapid metabolizers | Initiate therapy with recommended starting dose. If patient does not adequately respond to recommended maintenance dosing, consider titrating to a higher maintenance dose or switching to a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2C19 or CYP2B6. Classification of recommendation ratings described in **Supplementary Material S1**: Optional | Initiate therapy with recommended starting dose. Classification of recommendation ratings described in **Supplementary Material S1**: Strong | Initiate therapy with recommended starting dose. Classification of recommendation ratings described in **Supplementary Material S1**: Moderate | Initiate therapy with recommended starting dose. Classification of recommendation ratings described in **Supplementary Material S1**: Optional | Initiate therapy with recommended starting dose. Classification of recommendation ratings described in **Supplementary Material S1**: Strong |
| CYP2C19 normal metabolizers | Initiate therapy with recommended starting dose. Classification of recommendation ratings described in **Supplementary Material S1**: Moderate | Initiate therapy with recommended starting dose. Classification of recommendation ratings described in **Supplementary Material S1**: Strong | Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose. Classification of recommendation ratings described in **Supplementary Material S1**: Moderate | Consider a lower starting dose, slower titration schedule, and 25% reduction of standard maintenance dose as compared with CYP2B6 normal metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2B6. Classification of recommendation ratings described in **Supplementary Material S1**: Optional | Initiate therapy with recommended starting dose. Classification of recommendation ratings described in **Supplementary Material S1**: Strong |
| CYP2C19 intermediate metabolizers Or CYP2C19 likely intermediate metabolizers | Initiate therapy with recommended starting dose. Classification of recommendation ratings described in **Supplementary Material S1**: Moderate | Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose. Classification of recommendation ratings described in **Supplementary Material S1**: Moderate | Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose than normal metabolizers. Classification of recommendation ratings described in **Supplementary Material S1**: Optional | Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose as compared with CYP2B6 normal metabolizers. Classification of recommendation ratings described in **Supplementary Material S1**: Optional | Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose. Classification of recommendation ratings described in **Supplementary Material S1**: Moderate |

(Continued)

**Table 5 (Continued)**

| Phenotype | CYP2B6 ultrarapid or rapid metabolizer | CYP2B6 normal metabolizers | CYP2B6 intermediate metabolizers | CYP2B6 poor metabolizers | CYP2B6 indeterminate |
|---|---|---|---|---|---|
| CYP2C19 poor metabolizers<br>Or<br>CYP2C19 likely poor metabolizers | Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose as compared with CYP2C19 normal metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2C19.<br>Classification of recommendation ratings described in **Supplementary Material S1**: Optional | Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose as compared with CYP2C19 normal metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2C19.<br>Classification of recommendation ratings described in **Supplementary Material S1**: Moderate | Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose as compared with CYP2C19 normal metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2C19.<br>Classification of recommendation ratings described in **Supplementary Material S1**: Moderate | Select an alternative antidepressant not primarily metabolized by CYP2C19 or CYP2B6.<br>Classification of recommendation ratings described in **Supplementary Material S1**: Optional | Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose as compared with CYP2C19 normal metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2C19.<br>Classification of recommendation ratings described in **Supplementary Material S1**: Moderate |
| CYP2C19 indeterminate | Initiate therapy with recommended starting dose.<br>Classification of recommendation ratings described in **Supplementary Material S1**: Moderate | Initiate therapy with recommended starting dose.<br>Classification of recommendation ratings described in **Supplementary Material S1**: Moderate | Initiate therapy with recommended starting dose. Consider a slower titration schedule and lower maintenance dose.<br>Classification of recommendation ratings described in **Supplementary Material S1**: Moderate | Consider a lower starting dose, slower titration schedule, and 25% reduction of standard maintenance dose as compared with CYP2B6 normal metabolizers or select a clinically appropriate alternative antidepressant not predominantly metabolized by CYP2B6.<br>Classification of recommendation ratings described in **Supplementary Material S1**: Optional | No recommendation |

CYP, cytochrome P450.

**HTR2A and SLC6A4.** Clinical recommendations are not provided for serotonin reuptake inhibitor antidepressants based on *HTR2A* (**Tables S7 and S8**) and *SLC6A4* (**Table S9**) genotypes because the evidence supporting an association is mixed and/or insufficient to support clinical validity and utility at this time (CPIC level C: no recommendation).

**Pediatrics.** Citalopram, escitalopram, and sertraline had the most pharmacogenetic data supporting potential genotype-guided prescribing changes in children (**Table S1**). Based on this evidence, the recommendations for these drugs are relevant to pediatric patients and are consistent with smaller pharmacokinetic studies available for this population. Children and adolescents were underrepresented in pharmacogenetic studies of the other drugs included in this guideline. Therefore, the generalizability of other recommendations to pediatric patients needs to be established. As such, clinicians treating children and adolescents should determine their applicability to younger patients while considering the unique and more limited evidence base for these medications in youth, as well as pediatric-specific differences in tolerability (e.g., activation)[44] and disorder-specific response trajectory.[45] Because CYP2D6, CYP2C19, and CYP2B6 activity reach adult levels by early childhood,[46–48] it may be appropriate to extrapolate genotype-guided recommendations for antidepressants related to *CYP2D6*, *CYP2C19*, and *CYP2B6* to adolescents or possibly younger children with close monitoring. Ultimately, additional research and clinical trials in pediatric patients investigating the association between *CYP2D6*, *CYP2C19*, or *CYP2B6* and antidepressant systemic exposure, treatment response and tolerability are needed.

**Biogeographic groups.** The recommendations provided herein are largely derived from studies that primarily included individuals with European or East Asian ancestry as defined elsewhere.[49] Although studies including individuals from other ancestry groups are needed, there is no reason to suspect that the effects of *CYP2C19*, *CYP2D6*, and/or *CYP2B6* genetic variation on SSRI or SNRI exposure or treatment outcomes will not apply across biogeographic groups. Differential effects of *HTR2A* or *SLC6A4* variants on SSRI or SNRI treatment outcomes between European and East Asian ancestry groups have been described,[14,29] but further research is required before firm conclusions can be made as differences in pharmacokinetics (that may be related to allele frequencies of CYP enzymes) were not accounted for in these studies.

### Recommendations for incidental findings

Not applicable.

### Other considerations

Drug–drug interactions and other patient characteristics (e.g., age, renal function, liver function, diet, substance use, and a patient's past history of medication response and tolerability) should be considered when adjusting dose or selecting alternative therapies. See the **Supplementary Material S1** for additional information.

Paroxetine and fluoxetine are potent inhibitors of CYP2D6, albeit involving different mechanisms.[50] Several studies suggest that CYP2D6 UMs may not undergo phenoconversion by paroxetine. However, some of these studies were brief, and patients may not have been at steady state.[31–34] Further, most research studies and clinically available tests for *CYP2D6* do not determine the exact number of gene copies, which may include duplications and multiplications; the impact of these subtypes of UMs on susceptibility to phenoconversion is unclear. CYP2D6 NMs and IMs may be more susceptible to paroxetine-induced phenoconversion (from NM/IM to IM/PM due to autoinhibition) than UMs. The evidence presented in **Table S1** demonstrates that in CYP2D6 PMs, paroxetine pharmacokinetics are significantly different compared with NMs. However, some of these studies are limited by relatively short study periods (see **Supplementary Material S1** for more information).

Many of the antidepressants evaluated herein are substrates for other enzymes such as CYP1A2, CYP2C9, and CYP3A4 (**Table S5**). Currently, there is limited evidence supporting gene-based dosing recommendations for these CYPs for the drugs reviewed here.

Some commercially available tests targeting antidepressants use proprietary combinatorial algorithms to generate clinical decision support based on genotypes for the genes included in this evidence review and other genotypes.[51] Clinical trial data are accumulating for these approaches with collectively positive but modest results.[52] However, the opaque nature of these proprietary combinatorial approaches place this evidence beyond the scope of evaluation using the standardized CPIC Guideline development process.

## POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

Existing *CYP2D6*, *CYP2C19*, and/or *CYP2B6* genotype results may provide the potential benefit of identifying patients who are at an increased risk of experiencing adverse drug reactions or inadequate response to serotonin reuptake inhibitor antidepressant therapy. A potential risk is the missed identification of rare or novel variants that are typically not interrogated on clinically used testing platforms (e.g., CYP2C:TG). If an individual carries a rare variant, the actual phenotype may differ from the predicted phenotype. An individual's CYP2D6, CYP2C19, and/or CYP2B6 metabolizer status may also depend on other factors, including epigenetic variation, age, diet, comorbidities, smoking, pregnancy, or concomitant medications.[19] Although *CYP2D6*, *CYP2C19*, and/or *CYP2B6* genotype results are reliable when performed in qualified laboratories, there is a possibility for rare human and/or laboratory errors. Another limitation is that different laboratory tests may interrogate different sets of variants, which could result in different predicted phenotypes. As antidepressant medications are often prescribed to patients with liver or hematopoietic stem cell transplants, caution should be used to ensure that the tissue used for genotyping is representative of the enzymes in the liver.

## CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

Patients on stable and effective antidepressant medication doses without significant tolerability concerns may not benefit from

dose modifications based on *CYP2D6*, *CYP2C19*, and/or *CYP2B6* genotype results. Pharmacogenetic test results are one of many pieces of clinical information to be considered when optimizing antidepressant drug therapy.

## SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).


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## CONFLICT OF INTEREST

C.A.B. has equity in Sequence2Script Inc. A.B.S. has equity in Incite Health Pty Ltd. J.R.B. has served as consultant to OptumRx. All other authors declared no competing interests for this work.

## DISCLAIMER

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