Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors

JK Hicks[1], JR Bishop[2], K Sangkuhl[3], DJ Müller[4], Y Ji[5], SG Leckband[6], JS Leeder[7], RL Graham[8], DL Chiulli[9], A LLerena[10], TC Skaar[11], SA Scott[12], JC Stingl[13], TE Klein[3], KE Caudle[14] and A Gaedigk[7]

Selective serotonin reuptake inhibitors (SSRIs) are primary treatment options for major depressive and anxiety disorders. *CYP2D6* and *CYP2C19* polymorphisms can influence the metabolism of SSRIs, thereby affecting drug efficacy and safety. We summarize evidence from the published literature supporting these associations and provide dosing recommendations for fluvoxamine, paroxetine, citalopram, escitalopram, and sertraline based on *CYP2D6* and/or *CYP2C19* genotype (updates at www.pharmgkb.org).

Interindividual differences in pharmacokinetic parameter values and treatment outcomes with the selective serotonin reuptake inhibitors (SSRIs) are associated with *CYP2D6* or *CYP2C19* polymorphisms.[1] The purpose of this guideline is to provide information to allow the interpretation of existing *CYP2D6* and/or *CYP2C19* genotype tests to guide SSRI dosing, particularly focusing on fluvoxamine, paroxetine, citalopram, escitalopram, and sertraline. Other clinical variables that may influence SSRI therapy as well as genotyping cost-effectiveness are beyond the scope of this article. CPIC guidelines are periodically updated at http://www.pharmgkb.org.

FOCUSED LITERATURE REVIEW

A systematic literature review focusing on *CYP2D6* and *CYP2C19* genotype and the influence on SSRI therapy was conducted (**Supplemental Data**).

GENES: *CYP2D6* AND *CYP2C19*

CYP2D6 background

CYP2D6 is highly polymorphic with over 100 known allelic variants and subvariants identified (http://www.cypalleles.ki.se/cyp2d6.htm; **Supplemental Tables S1** and **S2**). *CYP2D6* alleles have been extensively studied in multiple geographically, racially, and ethnically diverse groups and significant differences in allele frequencies have been observed (**Supplemental Table S3**). The most commonly reported 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*).[2,3] Because *CYP2D6* is subject to deletions, gene duplications, or multiplications, many clinical laboratories also report copy number variations. *CYP2D6*5* represents a gene deletion whereas gene duplications and multiplications are denoted by "xN" (e.g., *CYP2D6*1xN* with *xN* representing the number of *CYP2D6* gene copies).

[1]Department of Pharmacy, Cleveland Clinic, Cleveland, Ohio, USA; Genomic Medicine Institute, Cleveland Clinic, Cleveland, Ohio, USA; and Department of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio, USA; [2]University of Minnesota College of Pharmacy, Department of Experimental and Clinical Pharmacology, Minneapolis, Minnesota, USA; [3]Department of Genetics, Stanford University, Stanford, California, USA; [4]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; [5]Department of Laboratory Medicine and Pathology, Division of Laboratory Genetics, Mayo Clinic, Rochester, Minnesota, USA; [6]Veterans Affairs San Diego Healthcare System, Mental Health Care Line, University of California, San Diego, Skaggs School of Pharmacy and Pharmaceutical Sciences and Department of Psychiatry, San Diego, California, USA; [7]Division of Clinical Pharmacology, Toxicology & Innovative Therapeutics, Children's Mercy Hospital, Kansas City, Missouri and Department of Pediatrics, University of Missouri-Kansas City, Kansas City, Missouri, USA; [8]Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania, USA; [9]Veterans Affairs Palo Alto Health Care System, San Jose Division, San Jose, California, USA; [10]CICAB Clinical Research Center, Extremadura University Hospital and Medical School, Badajoz, Spain; [11]Division of Clinical Pharmacology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA; [12]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, USA; [13]Federal Institute of Drugs and Medical Devices, Bonn, Germany; [14]Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA. Correspondence: A Gaedigk (agaedigk@cmh.edu or cpic@pharmgkb.org)

Received 18 February 2015; accepted 8 May 2015; advance online publication 13 May 2015. doi:10.1002/cpt.147

CYP2C19 background

Similar to *CYP2D6*, the *CYP2C19* gene is highly polymorphic, with significant differences in allele frequencies observed among populations. Over 30 allelic variants and subvariants have been identified (http://www.cypalleles.ki.se/cyp2c19.htm; **Supplemental Tables S4** and **S5**); however, the majority of patients will carry *CYP2C19*1*, **2*, or **17* alleles. *CYP2C19*1* encodes a normal function enzyme, while *CYP2C19*2* is the most common no function allele followed by *CYP2C19*3*. The *CYP2C19*17* allele is defined by a variant in the promoter region resulting in enhanced gene transcription leading to increased metabolic capacity.[4] Allele frequencies are provided in **Supplemental Table S6**.

Genetic test interpretation

Clinical laboratories usually test for the more frequently observed *CYP2D6* and *CYP2C19* genetic variants and translate the results into star-allele (*) nomenclature. Each star-allele, or haplotype, is defined by a specific combination of single-nucleotide polymorphisms and/or other genetic variants within the *CYP2D6* or *CYP2C19* gene locus.[2,5] **Supplemental Tables S2** and **S5** provide a list of *CYP2D6* and *CYP2C19* alleles and their functional status. Genetic test results are reported as the summary of inherited maternal and paternal star-alleles referred to as a diplotype (e.g., *CYP2D6*1/*2* and *CYP2C19*1/*1*). **Supplemental Data** (Genetic Test Interpretation Section) contains additional information regarding *CYP2D6* and *CYP2C19* genetic test interpretation and phenotype assignment.

Different clinical laboratories may use varying methods to predict phenotype from genotype data. Therefore, before any pharmacotherapy modifications are made based on this guideline, it is advisable to predict a patient's phenotype from genotype as described above and in the **Supplemental Data**.

Available genetic test options

Information on commercially available clinical testing options can be found in the **Supplemental Data**, www.pharmgkb.org, or the Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr/).

Incidental findings

Some studies have reported an association between *CYP2D6* and *CYP2C19* genetic variants and risk for depression or suicide (**Supplemental Data**). These associations are poorly understood and may be due to either alterations in endogenous physiology or drug metabolism. At present *CYP2D6* and *CYP2C19* are not considered to be clinically useful predictors of depression or suicide risk, nor have they been directly implicated in any Mendelian disorders.

Other considerations

One of the limitations inherent in a genotype-only test is that rare or *de novo* variants will most likely not be included in any commercially available genotyping test. Other important considerations pertaining to genetic testing and genetic test interpretation are contained within the **Supplemental Data**.

DRUGS: SSRIs

Background

SSRIs are a first-line treatment option for major depressive and anxiety disorders, and may be used to treat other psychiatric conditions such as obsessive-compulsive disorder. Although pharmacokinetic properties vary among this drug class, all of the SSRIs selectively increase serotonergic activity by decreasing presynaptic serotonin reuptake. The more common adverse effects induced by this drug class include central nervous system effects (e.g., insomnia, headache), gastrointestinal dysfunction, and sexual dysfunction; however, the incidence of side effect occurrence differs with each drug. Serious adverse events such as arrhythmias caused by QT prolongation have been associated with SSRIs, particularly for individuals prescribed citalopram who are CYP2C19 poor metabolizers.[6]

Patients may be predisposed to poor therapeutic outcomes due to *CYP2D6* or *CYP2C19* polymorphisms that alter SSRI biotransformation. Paroxetine and fluvoxamine are extensively metabolized by CYP2D6 to compounds with little pharmacological activity towards serotonin reuptake inhibition (**Supplemental Figure S1**).[7,8] Variations in CYP2D6 activity may result in lower or greater exposure to these drugs. Fluoxetine metabolism is more complex, as both CYP2D6 and CYP2C9 convert fluoxetine to pharmacologically active norfluoxetine enantiomers (**Supplemental Figure S1**).[9]

Citalopram is a racemic mixture of R- and S-enantiomers, with the pharmacologically active S-enantiomer marketed as escitalopram. Citalopram and escitalopram are extensively metabolized by CYP2C19 to compounds that confer less serotonin reuptake inhibition (**Supplemental Figure S1**).[10] Sertraline is metabolized by CYP2D6, CYP2C19, and other polymorphic cytochrome P450 enzymes, with pharmacokinetic data suggesting that CYP2C19 is the major metabolic pathway (**Supplemental Figure S1**).[1] Because citalopram, escitalopram, and sertraline are extensively catalyzed by CYP2C19, variations in CYP2C19 activity may result in altered drug exposure.

Linking genetic variability to variability in drug-related phenotypes

For those diagnosed with major depressive disorder, approximately 50% will fail initial SSRI therapy.[11] Furthermore, an estimated 25,000 patients per year in the United States will seek medical treatment in emergency departments due to adverse events associated with antidepressants.[12] Utilizing existing pharmacogenetic results to guide SSRI therapy could potentially improve treatment response and decrease the occurrence of adverse events.[13–15] There is substantial evidence linking *CYP2D6* or *CYP2C19* genotype to phenotypic variability in SSRI pharmacokinetic parameters or treatment outcomes (**Supplemental Data**). The application of a grading system to the evidence linking *CYP2D6* and *CYP2C19* genotypes to SSRI pharmacokinetic variability indicates a moderate to high quality of evidence for the majority of data (**Supplemental Tables S7–S11**). This body of evidence, rather than randomized clinical trials, provides the basis for SSRI pharmacotherapy recommendations in **Tables 2** and **3**.

Therapeutic recommendations

The recommendations below and in **Tables 2** and **3** apply primarily to actions based on genetic tests only; drug interactions and other clinical factors can have a major influence for prescribing decisions for SSRIs and should be taken into consideration before initiating drug therapy. Based on the current literature, recommendations are made for paroxetine, fluvoxamine, citalopram, escitalopram, and sertraline. Considerations regarding fluoxetine are discussed below and can be found in the **Supplemental Material**.

***CYP2D6*-paroxetine and fluvoxamine dosing recommendations.** **Table 2** summarizes the dosing recommendations for paroxetine (**Table 2a**) and fluvoxamine (**Table 2b**) based on CYP2D6 phenotype. Multiple studies have demonstrated that CYP2D6 ultrarapid metabolizers have low or undetectable paroxetine plasma concentrations when compared to CYP2D6 extensive metabolizers.[16–19] Those with undetectable paroxetine plasma concentrations are likely at risk of therapeutic failure. Low paroxetine plasma concentrations may be a risk factor for therapy failure, although the minimal paroxetine therapeutic concentration is not well defined.[20] Because of the risk for therapy failure due to lower drug exposure, an alternative SSRI not extensively metabolized by CYP2D6 should be considered. There are insufficient data to calculate an initial paroxetine dose for CYP2D6 ultrarapid metabolizers. Data are lacking describing the effect of CYP2D6 ultrarapid metabolism on fluvoxamine therapy, therefore no dosing recommendations are provided for fluvoxamine in the context of CYP2D6 ultrarapid metabolizers. It may be reasonable, though, to select an alternative SSRI not extensively metabolized by CYP2D6 due to the lack of data describing how CYP2D6 ultrarapid metabolizer status influences fluvoxamine therapy.

Adjustments to paroxetine or fluvoxamine therapy are not warranted based on CYP2D6 status for those who are CYP2D6 extensive or intermediate metabolizers. Self-inhibition of CYP2D6, and potential phenoconversion, may lead to nonlinear kinetics at common doses in certain genotypes. Although CYP2D6 intermediate metabolizers may be expected to have a modest increase in drug exposure and may be more susceptible to CYP2D6 inhibition by paroxetine, existing evidence does not support paroxetine or fluvoxamine therapy adjustments. In addition, because *CYP2D6* diplotypes are inconsistently categorized as extensive or intermediate metabolizers, the literature is difficult to evaluate, thus resulting in a moderate recommendation classification for intermediate metabolizers.

When administered similar doses, CYP2D6 poor metabolizers have significantly greater drug exposure to paroxetine and fluvoxamine when compared to extensive metabolizers.[16,21–23] This increase in drug exposure may be a risk factor for drug-induced side effects. The US Food and Drug Administration (FDA) states that fluvoxamine should be used cautiously in patients known to have reduced levels of CYP2D6 activity (http://www.pharmgkb.org/label/PA166104854). To potentially prevent an adverse effect, an alternative SSRI not extensively metabolized by CYP2D6 should be considered for poor metabolizers. If paroxetine or fluvoxamine is warranted, dose extrapolations based on differences in pharmacokinetic parameters between phenotype groups suggest a 50% dose reduction of paroxetine and a 30% dose reduction of fluvoxamine.[1] However, a 30% decrease in fluvoxamine dose may not be feasible given the dosage forms; therefore, decreasing the dose of fluvoxamine by 25–50% may help prevent adverse events by limiting high drug exposures. Because therapeutic drug monitoring is not common for SSRIs,[20] limited data are available describing the linearity of the dose–concentration relationship and the relation between paroxetine or fluvoxamine concentrations and therapeutic effect and tolerability. Therefore, this recommendation is considered optional.

Fluoxetine considerations. CYP2D6 converts fluoxetine to S-norfluoxetine while both CYP2D6 and CYP2C9 convert fluoxetine to R-norfluoxetine (**Supplemental Figure S1**). Fluoxetine and R/S-norfluoxetine modulate serotonin reuptake, although R-norfluoxetine is thought be less pharmacologically active. CYP2D6 poor metabolizers have been demonstrated to possess significantly higher fluoxetine plasma concentrations than extensive metabolizers (**Supplemental Table S10**). However, the total sum of fluoxetine plus norfluoxetine plasma concentrations may not vary significantly by CYP2D6 phenotypes. Few data are available describing how CYP2D6 phenotype status influences the total sum of fluoxetine plus norfluoxetine concentrations over time, or if an imbalance between fluoxetine and norfluoxetine concentrations caused by CYP2D6 phenotype status affects patient outcome or safety. Therefore, no gene-based dosing recommendations are provided for fluoxetine. For CYP2D6 ultrarapid and poor metabolizers, it may be reasonable to monitor these patients more closely if they are prescribed fluoxetine or to select an alternative SSRI not extensively metabolized by CYP2D6 due to conflicting/inconclusive data describing how CYP2D6 status influences fluoxetine therapy. It is important to note that the prescribing information for fluoxetine states that the drug "should be used with caution in patients with congenital long QT syndrome" and that caution is warranted in situations that may prolong QT such as "conditions that predispose to increased fluoxetine exposure (overdose, hepatic impairment, use of CYP2D6 inhibitors, CYP2D6 poor metabolizer status, or use of other highly protein-bound drugs)."

***CYP2C19*-citalopram, escitalopram, and sertraline dosing recommendations.** **Table 3** summarizes the dosing recommendations for citalopram and escitalopram based on CYP2C19 phenotype. CYP2C19 ultrarapid metabolizers have significantly lower exposure to these drugs when compared to extensive metabolizers, and therefore may have an increased probability of failing therapy.[10,24,25] Because there are insufficient data to calculate an initial citalopram or escitalopram dose for CYP2C19 ultrarapid metabolizers, an alternative SSRI not extensively metabolized by CYP2C19 may be an option if deemed appropriate given other medications and clinical considerations. Drug–drug interactions should be considered if selecting an alternative SSRI, such as paroxetine, which inhibits CYP2D6. *CYP2C19*17* homozygotes have a greater metabolic capacity than *CYP2C19*17*

Table 1 Assignment of likely phenotypes based on diplotypes

Table 1a Assignment of CYP2D6 predicted phenotypes

Likely phenotype	Activity score	Genotypes	Examples of *CYP2D6* diplotypes
Ultrarapid metabolizer (~1–2% of patients)[a]	> 2.0	An individual carrying duplications of functional alleles	**1/*1xN, *1/*2xN, *2/*2xN*[b]
Extensive metabolizer (~77–92% of patients)	2.0-1.0[c]	An individual carrying two normal function alleles or two decreased function alleles or one normal function and one no function allele or one normal function and one decreased function allele	**1/*1, *1/*2, *1/*4, *1/*5, *1/*9, *1/*41, *2/*2,*41/*41*
Intermediate metabolizer (~2–11% of patients)	0.5	An individual carrying one decreased function and one no function allele	**4/*10, *4/*41, *5/*9*
Poor metabolizers (~5–10% of patients)	0	An individual carrying only no functional alleles	**3/*4, *4/*4, *5/*5, *5/*6*

Table 1b Assignment of CYP2C19 predicted phenotypes

Likely phenotype	Genotypes	Examples of *CYP2C19* diplotypes
Ultrarapid metabolizer (~5–30% of patients)[d]	An individual carrying two increased function alleles or one normal function allele and one increased function allele	**17/*17, *1/*17*
Extensive metabolizer (~35–50% of patients)	An individual carrying two normal function alleles	**1/*1*
Intermediate metabolizer (~18–45% of patients)	An individual carrying one normal function allele or one increased function allele and one no function allele	**1/*2, *1/*3, *2/*17*[e]
Poor metabolizer (~2–15% of patients)	An individual carrying two no function alleles	**2/*2, *2/*3, *3/*3*

[a]CYP2D6 metabolizer status frequencies are based on data from Caucasians and may differ from other ethnicities. See **Supplemental Tables S3** and **S6** note for information on the chances of observing specific diplotypes in different major race/ethnic groups. [b]Where *xN* represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see **Supplemental Data** for additional information on how to translate diplotypes into phenotypes. [c]Patients with an activity score of 1.0 may be classified as intermediate metabolizers by some reference laboratories. [d]CYP2C19 metabolizer status frequencies are based on average multiethnic frequency. [e]The predicted metabolizer phenotype for the**2/*17* diplotypes is a provisional classification. The currently available evidence indicates that the *CYP2C19*17* increased function allele is unable to completely compensate for the no function *CYP2C19*2* allele.[36] See **Supplemental Materials** for a more comprehensive list of predicted metabolizer phenotypes.

heterozygotes, and may benefit more from alternative therapy.[24,25] Given that there may be clinically significant differences among CYP2C19 ultrarapid metabolizers based on diplotype (i.e., *CYP2C19*1/*17* vs. *CYP2C19*17/*17*), this is a moderate recommendation.

Adjustments to citalopram or escitalopram therapy are not warranted based on CYP2C19 status for those who are CYP2C19 extensive metabolizers. Although CYP2C19 intermediate metabolizers may have elevated plasma concentrations, dose extrapolations suggest that minimal dose adjustments are warranted for intermediate metabolizers.[1] Elevated concentrations of these drugs have been observed in poor metabolizers, which may increase the risk of adverse drug reactions.[25–28] To potentially prevent an adverse effect, an alternative SSRI not extensively metabolized by CYP2C19 should be considered. If citalopram or escitalopram is warranted, an initial dosage decrease of 50% should be considered.[1] For citalopram, the FDA recommends a 50% dose reduction (or a maximum dose of 20 mg/day in adults) for CYP2C19 poor metabolizers due to risk of QT prolongation (the FDA recommendation does not apply to escitalopram).[6] Although limited data are available describing the relationship between SSRI concentrations and therapeutic effect and tolerability, this is a moderate recommendation due to apparent risk of arrhythmias combined with the FDA providing specific dose recommendations.

Pharmacokinetic data show reduced oral clearance of sertraline in CYP2C19 poor metabolizers[29,30] but only slightly increased metabolism in ultrarapid metabolizers.[29] Side effects in CYP2C19 poor metabolizers have also been reported to be more frequent than in normal metabolizers.[31] Therefore, in CYP2C19 poor metabolizers a dose reduction of 50% is recommended or an alternative SSRI not extensively metabolized by CYP2C19 should be considered (**Table 3**). No dose adjustment is recommended for CYP2C19 ultrarapid metabolizers; however, if a patient is not responding to adequate maintenance doses of sertraline, consider an alternative SSRI not predominantly metabolized by CYP2C19. Due to the limited available evidence, this recommendation is optional.

Pediatrics. Data describing the relationship between *CYP2D6* or *CYP2C19* genotype and SSRI systemic exposure or steady-state plasma concentrations in pediatric patients are scarce (**Supplemental Data**). Because CYP2D6 activity is fully mature by early childhood,[32] it may be appropriate to extrapolate these recommendations to adolescents or possibly younger children with close monitoring. CYP2C19 activity may be increased in children relative to adults;

Table 2 Dosing recommendations for CYP2D6 and SSRIs

Table 2a Dosing recommendation for paroxetine based on CYP2D6 phenotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]
CYP2D6 Ultrarapid metabolizer	Increased metabolism to less active compounds when compared to extensive metabolizers. Lower/undetectable plasma concentrations may increase probability of pharmacotherapy failure.	Select alternative drug not predominantly metabolized by CYP2D6.[b]	Strong
CYP2D6 Extensive metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
CYP2D6 Intermediate metabolizer	Reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Initiate therapy with recommended starting dose.	Moderate
CYP2D6 Poor metabolizer	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Select alternative drug not predominantly metabolized by CYP2D6[b] or if paroxetine use warranted, consider a 50% reduction of recommended starting dose and titrate to response.	Optional

Table 2b Dosing recommendation for fluvoxamine based on CYP2D6 phenotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]
CYP2D6 Ultrarapid metabolizer	No data available for CYP2D6 ultrarapid metabolizers.	No recommendation due to lack of evidence.[c]	Optional
CYP2D6 Extensive metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
CYP2D6 Intermediate metabolizer	Reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Initiate therapy with recommended starting dose.	Moderate
CYP2D6 Poor metabolizer	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a 25–50% reduction[d] of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6.[b]	Optional

[a]Rating scheme described in **Supplemental Material**. [b]Drug-drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy. [c]Data are lacking describing the effect of CYP2D6 ultrarapid metabolism on fluvoxamine therapy; therefore no dosing recommendations are provided for fluvoxamine use for CYP2D6 ultrarapid metabolizers. It may be reasonable, though, to select an alternative SSRI not extensively metabolized by CYP2D6 due to the lack of data describing how CYP2D6 ultrarapid metabolizer status influences fluvoxamine therapy. [d]Dose extrapolations based on differences in pharmacokinetic parameters between phenotype groups suggest a 30% dose reduction of fluvoxamine (1). However, a 30% decrease in dose may not be feasible given the dosage forms, therefore, decreasing the starting dose of fluvoxamine by 25–50% should be considered.

therefore, these recommendations should be used with caution in children and accompanied by close monitoring. Ultimately, additional research and clinical trials in pediatric patients investigating the association between CYP2D6 or CYP2C19 and SSRI systemic exposure or treatment outcomes is needed.

Recommendations for incidental findings

Not applicable.

Other considerations

Paroxetine and fluoxetine are strong inhibitors of CYP2D6, albeit involving different mechanisms.[33] Several studies have suggested that CYP2D6 ultrarapid metabolizers may not undergo phenoconversion by paroxetine, although some of these studies were short in duration and may not be representative of steady-state conditions.[16–19] CYP2D6 extensive and intermediate metabolizers may be more susceptible to paroxetine-induced phenoconversion (from extensive/intermediate to intermediate/poor metabolizers due to autoinhibition). Evidence presented in **Supplemental Table S8** demonstrates that paroxetine pharmacokinetic parameters are significantly different among CYP2D6 poor metabolizers when compared to extensive metabolizers. Some of these studies, however, are limited by relatively short study periods (see **Supplemental Material** for more information).

Table 3 Dosing recommendations for CYP2C19 and SSRIs

Table 3a Dosing recommendations for citalopram and escitalopram based on CYP2C19 phenotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]
CYP2C19 Ultrarapid metabolizer	Increased metabolism when compared to extensive metabolizers. Lower plasma concentrations will increase probability of pharmacotherapy failure.	Consider an alternative drug not predominantly metabolized by CYP2C19.[b]	Moderate
CYP2C19 Extensive metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
CYP2C19 Intermediate metabolizer	Reduced metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose.	Strong
CYP2C19 Poor metabolizer	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a 50% reduction[c,d] of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.[b]	Moderate

Table 3b Dosing recommendations for sertraline based on CYP2C19 phenotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]
CYP2C19 Ultrarapid metabolizer	Increased metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19.[b]	Optional
CYP2C19 Extensive metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
CYP2C19 Intermediate metabolizer	Reduced metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose.	Strong
CYP2C19 Poor metabolizer	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a 50% reduction[d] of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.[b]	Optional

[a]Rating scheme described in **Supplemental Materials**. [b]Drug-drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy. [c]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. [d]Percent dose adjustments corresponding to percent difference in oral clearances have been calculated/estimated by Stingl *et al*. (1).

Many of the SSRIs are substrates for other metabolic enzymes such as CYP1A2, CYP2C9, and CYP3A4. There is currently no strong evidence supporting gene-based dosing recommendations for other cytochrome P450 enzymes that metabolize SSRIs. There is increasing evidence that variations in the genes encoding the serotonin transporter (5-HTT, SLC6A4) and the serotonin 2A receptor (HTR2A) are associated with SSRI response and adverse effects.[34] As additional studies are published, gene-based dosing recommendations for *SLC6A4* and/or *HTR2A* may be warranted.

The guideline supplement contains examples of clinical decision support (CDS) tools that can be used within electronic health records (EHRs) to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see **Supplemental Material**). Clinical implementation resources include cross-references for drug and gene names to widely used terminologies and standardized nomenclature systems (**Supplemental Tables S12** and **S13**), workflow diagrams (**Supplemental Figures S2** and **S3**), tables that translate genotype test results into a predicted phenotype (**Supplemental Tables S14** and **S15**), and example text for documentation in the EHR and point-of-care alerts (**Supplemental Table S16**).

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

Existing *CYP2D6* and/or *CYP2C19* genotype results may provide the potential benefit of identifying patients who are at an increased risk of experiencing adverse drug reactions or therapeutic failure. A potential risk is the misinterpretation of

genetic test results, as rare or novel variants are typically not interrogated. If an individual carries a rare variant, the actual phenotype may differ from the predicted phenotype. An individual's CYP2D6 and/or CYP2C19 metabolizer status may also depend on other factors including epigenetic phenomena, diet, comorbidities, or comedications.[35] Although *CYP2D6* and/or *CYP2C19* genotyping is usually reliable when performed in qualified laboratories, the possibility for error in genotyping, contamination, or mislabeling of the sample remains.

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

Patients on a stable and effective dose of an SSRI most likely will not benefit from additional dose modifications based on *CYP2D6* or *CYP2C19* genotype results. Similar to all diagnostic tests, genetic tests are one of several pieces of clinical information that should be considered before initiating drug therapy.

DISCLAIMER

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written, and are intended only to assist clinicians in decision-making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

Additional supporting information may be found in the online version of this article.

ACKNOWLEDGMENTS

We acknowledge the critical input of members of the Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network, funded by the National Institutes of Health/National Institute of General Medical Science (NIH/NIGMS), PAAR4Kids (U01 GM92666), PharmGKB (R24 GM61374), and U01 HL0105198. We acknowledge the critical input of Dr. Mary V. Relling (St Jude Children's Research Hospital), Houda Hachad (Translational Software), and Andria L. Del Tredici (Millennium Health). This work is also funded by NIH grants K08MH083888 (to JRB), K23GM104401 (to SAS), and 2R01GM088076 (to TCS/AG). On behalf of CPIC, the authors are dedicating this guideline to the late David A. Mrazek, MD, a pioneer and advocate of psychiatric pharmacogenetics.

CONFLICT OF INTEREST

J.R.B. is an advisory board member for Physician's Choice Laboratory Services. S.A.S. is a paid consultant for USDS, Inc., and is an associate director of a clinical laboratory that performs *CYP2D6* and *CYP2C19* genetic testing. A.G. is a paid consultant for Millennium Health, LLC, San Diego, CA. T.E.K. is stockholder in Personalis Inc. All other authors declare no conflicts.

1. Stingl, J.C., Brockmoller, J. & Viviani, R. Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. *Mol. Psychiatry* **18**, 273–287 (2013).
2. Crews, K.R. *et al*. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin. Pharmacol. Ther.* **95**, 376–382 (2014).
3. Gaedigk, A., Simon, S.D., Pearce, R.E., Bradford, L.D., Kennedy, M.J. & Leeder, J.S. The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype. *Clin. Pharmacol. Ther.* **83**, 234–242 (2008).
4. Sim, S.C. *et al*. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin. Pharmacol. Ther.* **79**, 103–113 (2006).
5. Scott, S.A. *et al*. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clin. Pharmacol. Ther.* **94**, 317–323 (2013).
6. Funk, K.A. & Bostwick, J.R. A comparison of the risk of QT prolongation among SSRIs. *Ann. Pharmacother.* **47**, 1330–1341 (2013).
7. Mandrioli, R., Mercolini, L., Saracino, M.A. & Raggi, M.A. Selective serotonin reuptake inhibitors (SSRIs): therapeutic drug monitoring and pharmacological interactions. *Curr. Med. Chem.* **19**, 1846–1863 (2012).
8. Tang, S.W. & Helmeste, D. Paroxetine. *Expert Opin. Pharmacother.* **9**, 787–794 (2008).
9. Whirl-Carrillo, M. *et al*. Pharmacogenomics knowledge for personalized medicine. *Clin. Pharmacol. Ther.* **92**, 414–417 (2012).
10. Huezo-Diaz, P. *et al*. CYP2C19 genotype predicts steady state escitalopram concentration in GENDEP. *J. Psychopharmacol.* **26**, 398–407 (2012).
11. Barak, Y., Swartz, M. & Baruch, Y. Venlafaxine or a second SSRI: switching after treatment failure with an SSRI among depressed inpatients: a retrospective analysis. *Progr. Neuropsychopharmacol. Biol. Psychiatry* **35**, 1744–1747 (2011).
12. Hampton, L.M., Daubresse, M., Chang, H.Y., Alexander, G.C. & Budnitz, D.S. Emergency department visits by adults for psychiatric medication adverse events. *JAMA Psychiatry* **71**, 1006–1014 (2014).
13. Altar, C.A., Hornberger, J., Shewade, A., Cruz, V., Garrison, J. & Mrazek, D. Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy. *Int. Rev. Psychiatry* **25**, 509–533 (2013).
14. Brandl, E.J., Kennedy, J.L. & Muller, D.J. Pharmacogenetics of antipsychotics. *Can. J. Psychiatry* **59**, 76–88 (2014).
15. Muller, D.J., Kekin, I., Kao, A.C. & Brandl, E.J. Towards the implementation of CYP2D6 and CYP2C19 genotypes in clinical practice: update and report from a pharmacogenetic service clinic. *Int. Rev. Psychiatry* **25**, 554–571 (2013).
16. 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. *Ther. Drug Monit.* **25**, 738–742 (2003).
17. Gex-Fabry, M. *et al*. CYP2D6 and ABCB1 genetic variability: influence on paroxetine plasma level and therapeutic response. *Ther. Drug Monit.* **30**, 474–482 (2008).
18. Guzey, C. & Spigset, O. Low serum concentrations of paroxetine in CYP2D6 ultrarapid metabolizers. *J. Clin. Psychopharmacol.* **26**, 211–212 (2006).
19. Lam, Y.W., Gaedigk, A., Ereshefsky, L., Alfaro, C.L. & 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* **22**, 1001–1006 (2002).

20. Hiemke, C. *et al*. AGNP Consensus Guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry* **44**, 195–235 (2011).
21. Carrillo, J.A., Dahl, M.L., Svensson, J.O., Alm, C., Rodriguez, I. & Bertilsson, L. Disposition of fluvoxamine in humans is determined by the polymorphic CYP2D6 and also by the CYP1A2 activity. *Clin. Pharmacol. Ther.* **60**, 183–190 (1996).
22. Sawamura, K., Suzuki, Y. & Someya, T. Effects of dosage and CYP2D6-mutated allele on plasma concentration of paroxetine. *Eur. J. Clin. Pharmacol.* **60**, 553–557 (2004).
23. Spigset, O., Granberg, K., Hagg, S., Norstrom, A. & Dahlqvist, R. Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms. *Eur. J. Clin. Pharmacol.* **52**, 129–133 (1997).
24. Hodgson, K. *et al*. Genetic differences in cytochrome P450 enzymes and antidepressant treatment response. *J. Psychopharmacol.* **28**, 133–141 (2014).
25. 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. *Clin. Pharmacol. Ther.* **83**, 322–327 (2008).
26. Chen, B. *et al*. Estimation of CYP2D6*10 genotypes on citalopram disposition in Chinese subjects by population pharmacokinetic assay. *J. Clin. Pharm. Ther.* **38**, 504–511 (2013).
27. Fudio, S. *et al*. Evaluation of the influence of sex and CYP2C19 and CYP2D6 polymorphisms in the disposition of citalopram. *Eur. J. Pharmacol.* **626**, 200–204 (2010).
28. Noehr-Jensen, L. *et al*. Impact of CYP2C19 phenotypes on escitalopram metabolism and an evaluation of pupillometry as a serotonergic biomarker. *Eur. J. Clin. Pharmacol.* **65**, 887–894 (2009).
29. Rudberg, I., Hermann, M., Refsum, H. & Molden, E. Serum concentrations of sertraline and N-desmethyl sertraline in relation to CYP2C19 genotype in psychiatric patients. *Eur. J. Clin. Pharmacol.* **64**, 1181–1188 (2008).
30. Wang, J.H. *et al*. Pharmacokinetics of sertraline in relation to genetic polymorphism of CYP2C19. *Clin. Pharmacol. Ther.* **70**, 42–47 (2001).
31. Grasmader, K. *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. *Eur. J. Clin. Pharmacol.* **60**, 329–336 (2004).
32. Blake, M.J. *et al*. Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. *Clin. Pharmacol. Ther.* **81**, 510–516 (2007).
33. Bertelsen, K.M., Venkatakrishnan, K., Von Moltke, L.L., Obach, R.S. & Greenblatt, D.J. Apparent mechanism-based inhibition of human CYP2D6 in vitro by paroxetine: comparison with fluoxetine and quinidine. *Drug Metab. Dispos.* **31**, 289–293 (2003).
34. Gvozdic, K., Brandl, E.J., Taylor, D.L. & Muller, D.J. Genetics and personalized medicine in antidepressant treatment. *Curr. Pharm. Des.* **18**, 5853–5978 (2012).
35. LLerana, A., Berecz, R., de la Rubia, A., Fernandez-Salguero, P. & Dorado, P. Effect of thioridazine dosage on the debrisoquine hydroxylation phenotype in psychiatric patients with different CYP2D6 genotypes. *Ther. Drug Monit.* **23**, 616–620 (2001).
36. Sibbing, D. *et al*. Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. *Circulation* **121**, 512–518 (2010).