Supplement to:

Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for *CYP2D6* and *CYP2C19* Genotypes and Tricyclic Antidepressants: 2016 Update

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Table of Contents

GUIDELINE UPDATES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* genotypes and the dosing of tricyclic antidepressants **(TCAs)** is published in full on the PharmGKB website (www.pharmgkb.org) and cpicpgx.org (1). Relevant information will be reviewed periodically and updated guidelines published online.

LITERATURE REVIEW

2012 guideline

We searched the PubMed® database (1966 to September 2012) for the following keywords: (cytochrome P450 2D6 or CYP2D6) OR (cytochrome P450 2C19 or CYP2C19) AND (tricyclic antidepressants OR amitriptyline OR clomipramine OR desipramine OR doxepin OR imipramine OR nortriptyline OR trimipramine) for the association between *CYP2D6* and/or *CYP2C19* genotypes and metabolism of tricyclic antidepressant drugs or tricyclic antidepressant-related adverse drug events or clinical outcomes. For key publications pertaining to clinical pharmacogenetic studies on tricyclic antidepressant response or adverse effects, and reviews or consensus statements, see references (2-6). Using these search terms, 353 publications were identified. Study inclusion criteria included publications that included analyses for the association between *CYP2C19* and *CYP2D6* genotypes and metabolism of TCAs or TCA-related adverse drug events or clinical outcomes. Non-English manuscripts were excluded. Following application of these inclusion criteria, 74 publications were reviewed and included in the evidence tables (**Supplemental Tables S5 to S16**).

2016 guideline update

We searched PubMed® database as described above between September 2012 and July 2016. Using these search terms, 46 publications were identified. Following application of the inclusion criteria, 5 additional publications were reviewed and included in the evidence tables (**Supplemental Tables S5 to S16**).

The *CYP2D6* (7) and *CYP2C19* (8) Frequency Tables are updates of those previously published in CPIC guidelines (9-12). Updates to the *CYP2D6* and *CYP2C19* Frequency Tables were made by searching the PubMed® database (1995 to July 2016). The following criteria were used for

CYP2D6: (CYP2D6 or 2D6 or cytochrome P4502D6) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity) with filter limits set to retrieve "full-text" and "English" literature. The following criteria were used for *CYP2C19*: (CYP2C19 or 2C19 or cytochrome P4502C19) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity) with filter limits set to retrieve "full-text" and "English" literature. In addition, reports were also identified from citations by others or review articles. Studies were considered for inclusion in the *CYP2D6* or *CYP2C19* Frequency Table if: (1) the ethnicity of the population was clearly indicated, (2) either allele frequencies or genotype frequencies were reported, (3) the method by which the genes were genotyped was indicated, (4) the sample population consisted of at least 50 individuals with a few exceptions (e.g., smaller cohorts that were part of larger studies) and (5) the study represented an original publication (no reviews or meta-analyses).

CYP2C19 diplotype and phenotype frequencies were estimated using the equation describing Hardy Weinberg equilibrium based on reported allele frequencies. *CYP2D6* allele frequency data have been utilized by Gaedigk *et al.* (13) to predict phenotype frequencies across world populations.

GENES: CYP2D6 AND CYP2C19

Genetic Test Interpretation

CYP2D6 and *CYP2C19* genetic variants are typically reported as haplotypes, which are defined by a specific combination of single nucleotide polymorphisms (SNPs) and/or other sequence variants including insertions and deletions that are interrogated by genotype analysis. *CYP2D6* and *CYP2C19* haplotypes are assigned a star-allele (*) nomenclature to allow for the standardization of genetic polymorphism annotation (14). A complete list of *CYP2D6* and *CYP2C19* star-allele nomenclature along with the genetic variants that define each star-allele is available at http://www.cypalleles.ki.se/cyp2d6.htm and http://www.cypalleles.ki.se/cyp2c19.htm, respectively. Information regarding *CYP2D6* (7) or *CYP2C19* haplotypes (8) (star-alleles) is also available at PharmGKB (www.pharmgkb.org). Knowing which SNPs or other genetic variants a particular test interrogates is important as the

inclusion or exclusion of certain genetic variants in a pharmacogenetic test could affect the reported star-allele result.

Clinical laboratories usually report a diplotype, which is the summary of inherited maternal and paternal star-alleles (e.g. *CYP2C19*1/*2*, where an individual inherited a **1* allele and a **2* allele). Commonly reported *CYP2D6* and *CYP2C19* star-alleles are categorized into functional groups (e.g., normal function, decreased function, increased function or no function) based on the predicted activity of the encoded enzyme (*CYP2C19* Allele Definition Table (8) and *CYP2D6* Allele definition Table (7)). The predicted phenotype (**Table 1, main manuscript**) is influenced by the expected function of each reported allele in the diplotype. CYP2D6 and CYP2C19 phenotype-predicting tools, such as pharmacogenetic translation tables, are being developed by CPIC and can be accessed at www.pharmgkb.org.

Calculating CYP2D6 Activity Score. Gaedigk *et al*. developed a scoring system to provide a uniform approach to assigning a predicted CYP2D6 phenotype (15). *CYP2D6* alleles are assigned an activity value as detailed in **Supplemental Table S1**. The activity value of each allele reported in the diplotype is added together to calculate the CYP2D6 activity score. For example, to calculate the activity score of a *CYP2D6*1/*17* diplotype, the activity value of **1* (activity value = 1) and the activity value of **17* (activity value = 0.5) are totaled to provide the CYP2D6 activity score of 1.5. Note that a value of 0.5 indicates decreased activity and not that the activity conveyed by an allele is half of that encoded by a normal function allele. For this guideline, the CYP2D6 activity score is used to assign a predicted phenotype as follows: activity score of 0 = poor metabolizer, activity score of 0.5 = intermediate metabolizer, activity scores ranging from 1.0-2.0 = normal metabolizer, and activity score greater than 2.0 = ultrarapid metabolizer. Therefore, a pharmacogenetic test result of *CYP2D6*1/*17* yields a CYP2D6 activity score of 1.5 and predicts a normal metabolizer phenotype.

There is a lack of consensus in regards to whether patients with a CYP2D6 activity score of 1.0 should be assigned a normal or intermediate phenotype. Pharmacokinetic data suggest that patients with an activity score of 1.0 have a higher CYP2D6 metabolic capacity compared to patients with an activity score of 0.5, but less CYP2D6 enzyme activity compared to patients

with an activity score of 2.0 (15-17). Herein, we classified patients with a CYP2D6 activity score of 1.0 as normal metabolizers, which is consistent with the CPIC guidelines for codeine and the selective serotonin reuptake inhibitors (SSRIs). (18, 19)

CYP2D6 Structural and Gene Copy Number Variants. Because *CYP2D6* is subject to copy number variation (gene duplications, multiplications, or deletions), clinical laboratories may report gene copy number if directly tested. Most patients will have a normal copy number of 2, with one gene copy inherited maternally and one gene copy inherited paternally. When two *CYP2D6* gene copies are present, the diplotype may be reported as follows: *CYP2D6*1/*1* or *CYP2D6 (*1/*1)2N*, where "2" represents the gene copy number. A copy number of "1" indicates the presence of a *CYP2D6* gene deletion (the patient possesses only one gene copy), and a copy number of "0" indicates both *CYP2D6* genes are deleted. *CYP2D6* gene deletions are indicated by the *CYP2D6*5* allele. A gene deletion that is present on one chromosome may be reported as follows: *CYP2D6*2/*5* or *CYP2D6 (*2/*2)1N*, where "1" represents gene copy number and the *CYP2D6*5* allele is inferred. Typically, clinical laboratories will report a homozygous gene deletion as *CYP2D6*5/*5* or *CYP2D6 (*5/*5)0N*.

A copy number greater than two indicates the presence of a *CYP2D6* gene duplication or multiplication. When a *CYP2D6* gene duplication is present, the diplotype may be reported as *CYP2D6 (*1/*2)3N*, where "3" represents gene copy number. A clinical laboratory may not report an exact copy number, but rather indicate that additional copies of the *CYP2D6* gene are present (e.g., *CYP2D6*1/*2* duplication or *CYP2D6 (*1/*2)xN*). In instances where a duplication/multiplication is present and the exact copy number is not reported, most patients will likely have a *CYP2D6* gene copy number of 3. However, individuals carrying as many as 13 *CYP2D6* gene copies have been reported (20). Clinical laboratories typically do not determine which allele is duplicated; therefore, when calculating the CYP2D6 activity score, the duplication must be considered for each allele reported in the diplotype (21). For example, a genotype result of *CYP2D6 (*1/*4)3N* indicates a patient has three copies of the *CYP2D6* gene, with either two copies of the *CYP2D6*1* allele and one copy of the *CYP2D6*4* allele, or one copy of the *CYP2D6*1* allele and two copies of the *CYP2D6*4* allele. If the *CYP2D6*1* allele carries the duplication, the CYP2D6 activity score of this diplotype will be 2, whereas if the

*CYP2D6*4* allele carries the duplication, the activity score will be 1. Likewise, if the number of gene copies is not determined and it remains unknown which allele carries the duplication/multiplication, a *CYP2D6 (*4/*9)xN* genotype for example, can be consistent with an IM (intermediate metabolizer) phenotype (*CYP2D6*4xN/*9*; activity score of 0.5) or an NM (normal metabolizer) phenotype (*CYP2D6*4/*9xN* assuming that *xN* does not exceed four copies in which case the activity score is 1 for *xN*=2, 1.5 for *xN*=3 and 2 for *xN*=4). As these examples illustrate, phenotype prediction will be considerably more accurate if testing determines which allele carries the duplication/multiplication and determines the number of gene copies present. Studies have been published describing the translation of *CYP2D6* genotypes into predicted phenotypes when gene duplications or multiplications are present (10, 13, 15, 21, 22).

Note that a duplication may not be detected by copy number assays when paired with the *CYP2D6*5* allele (gene deletion). A *CYP2D6*2x2/*5* diplotype, for example, has a gene duplication on one allele and a gene deletion on the other for a total number of two gene copies. This diplotype may be reported as *CYP2D6*2/*2*.

Other structural variants include gene copies that consist of *CYP2D6* and *CYP2D7*-derived sequences (23, 24). The no function *CYP2D7-2D6* hybrid genes, collectively assigned as *CYP2D6*13*(25), may not be detected by a particular genotype test or gene copy number testing. In such cases, the test may detect only the allele present on the second chromosome and report the diplotype as homozygous for that allele. For example, a test that does not detect *CYP2D6*13* will report a *CYP2D6*1/*13* diplotype as *CYP2D6*1/*1*. Hybrid genes can also occur in duplication configurations and cause positive gene duplication test results that may lead to an overestimation of activity and false-positive prediction of ultrarapid metabolism (24, 26). For example, a *CYP2D6*1/*13+*2* diplotype (activity score = 2 predicting normal metabolism) may be assigned as *CYP2D6*1/*2xN* (activity score = 3 predicting ultrarapid metabolism).

Limitations of the Star (*) Nomenclature and Allele Assignments. The star (*) nomenclature has defined multiple subvariants for an allele (e.g., *CYP2D6*2* and **4*), but generally, these are not distinguished by current genotype testing. This is of no consequence for *CYP2D6*4*, because all **4* subvariants share 1846G>A causing aberrant splicing and absence of functional protein.

For *CYP2D6*2*, however, it is uncertain whether any of the sequence variations defining the suballeles convey a functional consequence. Also, there is no, or little, information regarding their frequencies because test laboratories do not discriminate the suballeles. In addition, there are numerous known variants and subvariants of uncertain function that have not been designated by the nomenclature committee.

It also needs to be realized that the accuracy of a genotype test depends on the number of sequence variations/allelic variants tested. If no variation is found, a *CYP2D6*1* will be the default assignment. Depending on which sequence variations are found, the default assignment can also be *CYP2D6*2* (or other). For example, if 2850C>T is present, but 1023C>T (which is found on the *CYP2D6*17* allele) is not, the default assignment is *CYP2D6*2*. Also see 'CYP2D6 Other Considerations' below.

Recent findings indicate that a SNP in a distal enhancer region impacts allele activity on the transcriptional level (27, 28). It is not fully understood on which allelic variants this enhancer SNP is located; emerging knowledge, however, suggests that a majority of *CYP2D6*2* alleles, at least in Caucasians, may have lower than normal activity. Presence of this enhancer SNP may also impact the activity encoded by *CYP2D6*2xN* (duplications and multiplications). However, this SNP is not included in current test panels. The activity score will be updated, if warranted, as new information becomes available**.**

CYP2C19 predicted phenotype. The predicted phenotype for a patient carrying the *CYP2C19*17* increased function allele in combination with a no function allele (e.g., *CYP2C19*2*) is less clear. Limited data suggest that increased activity conferred by the *CYP2C19*17* allele may not compensate for the loss of activity conferred by the *CYP2C19*2* allele (8). Herein, we classified carriers of the *CYP2C19*17* allele in combination with a no function allele as intermediate metabolizers, which is consistent with the CPIC guideline for the SSRIs (19).

Limited data are available to assess the predicted phenotypes for rare *CYP2C19* diplotype combinations that include *CYP2C19* alleles with decreased function and low frequencies in the general population (e.g., **9, *10*). Therefore, for the purpose of this guideline the following

assignments have been proposed: patients with two decreased function alleles OR patients with one normal/increased function allele AND one decreased function allele are categorized as "likely intermediate metabolizers" (e.g., *CYP2C19*1/*9, *9/*9, *9/*17*) and patients with one decreased function allele and one no function allele are categorized as "likely poor metabolizers" (*CYP2C19*2/*9*). For many rare alleles, no information regarding enzyme activity is currently available, and those with functional data have only been determined by in vitro studies. Consequently, the proposed "likely intermediate" and "likely poor" metabolizer assignments were developed for diplotypes that contain one allele with an established effect on enzyme activity and a second allele with limited or no available activity data. The diplotypes in these new categories may be revised as new data become available, which will be updated on PharmGKB (www.pharmgkb.org) and cpicpgx.org as needed.

CYP2C19 Rapid Metabolizer Phenotype. The original CPIC TCA guideline defined CYP2C19 ultrarapid metabolizers as those who carry one *CYP2C19*17* allele in combination with a normal function allele or those who are *CYP2C19*17* homozygotes (29). The decision to group *CYP2C19*1/*17* and *CYP2C19*17/*17* diplotypes together as ultrarapid metabolizers was largely based on pharmacokinetic data demonstrating that *CYP2C19*17* carriers have higher metabolic capacity than *CYP2C19*1* homozygotes (30, 31). There was also limited pharmacokinetic data contrasting *CYP2C19*1/*17* with the more rare *CYP2C19*17/*17* diplotype. However, subsequent data has shown that for certain substrates (e.g., voriconazole), *CYP2C19*17* homozygotes clearly have distinct pharmacokinetic parameters when compared to *CYP2C19*1/*17* individuals that necessitates unique gene-based dosing recommendations (32).

To accommodate these differences, CPIC has recently introduced the term "CYP2C19 rapid metabolizer" to define those who carry one *CYP2C19*17* allele in combination with a normal function *CYP2C19*1* allele and using the CYP2C19 ultrarapid metabolizer term to identify *CYP2C19*17* homozygotes (33). The rapid metabolizer term allows for more granular gene-based dosing recommendations along with additional flexibility for phenotype-driven clinical decision support. Of note, the limited data available distinguishing rapid (**1/*17*) and ultrarapid (**17/*17*) *CYP2C19* metabolizers treated with TCAs prompted the same recommendation for both the rapid and ultrarapid CYP2C19 metabolizer phenotypes for this guideline.

Phenotyping CYP2D6 and CYP2C19. The TCAs were considered a first-line treatment option for depression during the 1960s and 1970s, but their use started to decline in the 1980s as new drugs with more tolerable side effect profiles were developed to treat depression (34). Much knowledge about the TCAs was gained during the height of their use, a time in which genotyping studies were mostly nonexistent. However, valuable information about how CYP2D6 or CYP2C19 metabolizer status affects pharmacokinetic properties and outcomes was acquired by phenotyping patients for CYP2D6 or CYP2C19 enzyme function. Probe drugs including dextromethorphan, sparteine, and debrisoquine were used for CYP2D6 phenotyping, while proguanil and mephenytoin were used for CYP2C19 phenotyping (35-38). In most instances patients were divided into two groups, either poor or normal metabolizers. Good concordance has been observed between assigned phenotypes based on probe drugs and genetic test results (39-45). Therefore, we consider outcome and pharmacokinetic data obtained from studies where individuals were phenotyped to be comparable to outcome and pharmacokinetic data obtained from studies where individuals were genotyped.

Available Genetic Test Options

Commercially available genetic testing options change over time. Additional information about pharmacogenetic testing can be found at the Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr/). The American College of Medical Genetics and Genomics (ACMG) established guidelines for laboratory testing of *CYP2D6* in relation to tamoxifen therapy (46).

Clinical laboratories may analyze different SNPs or other genetic variants, which are dependent on the genotyping platforms used and may affect the reported diplotype leading to discrepant results between methodologies. Additionally, laboratories may differ in how *CYP2D6* copy number variants are tested and/or reported, which can potentially affect phenotype prediction. Therefore, it is important to not only know the alleles interrogated by each laboratory, but also which sequence variants (e.g., SNPs, insertions, deletions) are tested and how copy number variants are reported. Clinical laboratories commonly give an interpretation of the genotype

result and provide a predicted phenotype. Phenotype assignment for this guideline is defined in the main manuscript and supplementary data, but may differ from some clinical laboratory interpretations. Any *CYP2D6* or *CYP2C19* genotyping results used to guide patient pharmacotherapy and/or deposited into patient medical records should be derived from validated genotyping platforms in clinical laboratories that implement the appropriate regulatory standards and best practices (e.g., CAP, CLIA).

Incidental Findings

A concern about genetic testing in clinical settings is that an individual's genotype may be predictive of an unrelated disease risk; however, variants in pharmacogenes generally have not been strongly associated with disease risk. Reports exist describing an association between CYP2D6 ultrarapid metabolizers and suicidality, though a recent study found no such association (47-49). For *CYP2C19*, associations between ultrarapid/rapid metabolizer genotypes and depressive symptoms and anxiety has been reported (50, 51). These associations are poorly understood and may be explained by alterations in either drug or endogenous substrate metabolism. A large candidate gene association study has identified a correlation between *CYP2C19* no function alleles (*CYP2C19*2*) and lower depressive symptoms in European twins (50). A subsequent study of transgenic mice suggested that *CYP2C19* overexpression in the brain was associated with reduced hippocampal volume and behavioral markers of anxiety (51). *CYP2D6* has been investigated in candidate gene studies of depression as well as personality traits (49, 52-63). Although some nominal associations were identified, *CYP2D6* genetic variants are not currently considered to be predictive of depression or personality traits. Notably, a recent meta-analysis of genome-wide association studies for major depressive disorder did not identify any significant association between depression risk and *CYP2C19* or *CYP2D6* genotypes. (64). Small, isolated studies on cancer susceptibility have been reported for *CYP2C19* and *CYP2D6* genotypes, yet neither gene is currently considered to be significantly predictive of cancer risk (65, 66).

Other Considerations

Due to the increasing adoption of pharmacogenetic genotyping arrays, and the eventual adoption of exome sequencing, it will become more likely a clinician has genetic test results for multiple genes

that affect a particular drug (22, 67, 68). Although dosing recommendations have been established for the genes-drug pair *VKORC1*/*CYP2C9*-warfarin (69), in most instances there are insufficient data available to develop other genes-drug pair guidelines. There has been interest in investigating the combined effects of *CYP2D6* and *CYP2C19* genetic variants on tricyclic dosing, but the frequency of certain phenotype combinations, such as a CYP2D6 ultrarapid metabolizer also having CYP2C19 poor metabolism, is expected to be low (70-73). Therefore, enrolling a sufficient number of patients on a clinical trial that represents all possible CYP2D6 and CYP2C19 phenotype combinations would be difficult. Steimer *et al*. demonstrated that particular *CYP2D6* and *CYP2C19* allele combinations have the potential to alter the pharmacokinetics of amitriptyline resulting in an increased risk of side effects (70). However, further studies are needed to develop moderate or strong dosing recommendations for tricyclics when considering combined CYP2D6/CYP2C19 phenotypes.

CYP2D6 Other Considerations

There are several factors that cause potential uncertainty in *CYP2D6* genotyping results and phenotype predictions as follows: **1)** Because it is currently impractical to test for every variation in the *CYP2D6* gene, genotyping tests may not detect rare variants resulting in patients being assigned a default genotype. It also needs to be stressed that genotyping tests are not designed to detect unknown/de novo sequence variations. Depending on the sequence variations (or alleles present) in a given patient, the default genotype may be *CYP2D6*1/*1* (or wild-type) or another diplotype. If the rare or *de novo* variant adversely affects CYP2D6 enzyme function, then the patient's actual phenotype may differ from the predicted phenotype. **2)** Sub-alleles of *CYP2D6*4* have been identified that harbor additional SNPs with limited or no added functional consequence (e.g., *CYP2D6*4A*, *4B*, *4C*, and *4D*). Therefore, only analyzing for the defining *CYP2D6*4* SNPs (100C>T and 1846G>A) is usually sufficient to determine a CYP2D6 phenotype. **3)** There are multiple gene units involved in duplication and other major rearrangements. Additionally, the pseudogenes *CYP2D7* and *CYP2D8* may be misinterpreted as functional duplications (74). If the specific gene units involved in the duplication or other rearrangements are not specifically tested for, the phenotype prediction may be inaccurate and CYP2D6 activity over-estimated. **4)** Some SNPs exist on multiple alleles. For example, *CYP2D6*69* carries the defining SNPs for *CYP2D6*41* (2850C>T, 2988G>A, and 4180G>C)

and the defining SNPs for *CYP2D6*10* (100C>T and 4180G>C) in addition to multiple other SNPs. If a patient carries these genetic variants (in the absence of 1846G>A), a *CYP2D6*10/*41* diplotype is typically assigned, because this is the most likely result based on allele frequencies. However, a *CYP2D6*1/*69* genotype cannot be excluded with certainty. Testing for additional SNPs (e.g., 1062A>G, 3384A>C, and 3584G>A) could exclude *CYP2D6*1/*69* with certainty. Therefore, to unequivocally determine the presence of certain alleles, testing for multiple SNPs may be required. **5)** Allele frequencies may vary considerably among individuals of different ethnic backgrounds. For instance, *CYP2D6*10* is common in Asian populations while *CYP2D6*17* is common in people of Sub-Saharan African ancestry. These alleles, however, have a considerably lower prevalence in other ethnic groups such as Caucasians of European ancestry. As another example, *CYP2D6*14* is present in Asian populations and therefore its defining SNP (1758G>A) has been incorporated into Asian genotyping panels (75). Thus, the alleles that should be tested for a given population may vary considerably. **6)** Certain alleles carry genes in tandem arrangements. One such example is *CYP2D6*36+*10* (one copy of the non-functional *CYP2D6*36* and one copy of the decreased function *CYP2D6*10*). This tandem can be found in Asians and is typically reported as a default assignment of *CYP2D6*10*.

CYP2C19 Other Considerations

There are several factors to consider when genotyping *CYP2C19*. Some of these factors may cause potential uncertainty in *CYP2C19* genotyping results and phenotype predictions and are listed as follows: **1)** *CYP2C19*2* is the most common loss-of-function allele. Sub-alleles of *CYP2C19*2* have been identified that harbor additional SNPs with limited or no added functional consequence (e.g., *CYP2C19*2A*, **2B*, **2C*, and **2D*). Therefore, only analyzing for the defining *CYP2C19*2* SNP (c.681G>A) is usually sufficient to determine a CYP2C19 phenotype. **2)** Many genotyping tests do not detect rare variants. Depending on the sequence variations (or alleles present) in a given patient, the default genotype may be *CYP2C19*1/*1* (or wild-type) or another diplotype. If a rare variant adversely affects CYP2C19 enzyme function, then the patient's actual phenotype may differ from the predicted phenotype. **3)** *CYP2C19* allele frequencies may vary considerably among individuals of different ethnic backgrounds. *CYP2C19*3* has a low prevalence among most ethnic groups, but has an allele frequency of approximately 15% in some Asian populations (*CYP2C19* Frequency Table (8, 9)). Thus, the

alleles that should be tested for a given population may vary considerably. For Asian populations, *CYP2C19*3* analysis should be included in a *CYP2C19* genotyping panel. **4)** The defining polymorphisms for *CYP2C19*2* (c.681G>A) and *CYP2C19*17* (c.-806C>T) are in linkage disequilibrium with each other (9). Therefore, it is difficult to determine whether these two variants function independently of each other. Published articles focusing on clopidogrel argue both for (30) and against (76, 77) independence. **5)** The no function *CYP2C19*4* allele has been identified in linkage disequilibrium with *CYP2C19*17* (c.-806C>T) in certain ethnic subpopulations and this haplotype is designated *CYP2C19*4B* (9, 78). *CYP2C19*17* is an increased function allele, while *CYP2C19*4B* is a no function allele. Probing for *CYP2C19*4* in addition to *CYP2C19*17* may improve CYP2C19 phenotype prediction accuracy. **6)** Certain genotyping platforms (e.g., Affymetrix DMET) analyze for over 15 *CYP2C19* star-alleles, many of which are rare and not well characterized. 7) A genotyping test only detects selected allelic variants and does not detect unknown/de novo sequence variations. Therefore, uncertainty exists when translating a genotype result into a predicted CYP2C19 phenotype in instances where a patient is found to carry a poorly characterized allele.

LEVELS OF EVIDENCE

The evidence summarized in **Supplemental Tables S5-16** is graded using a scale based on previously published criteria (79) that was applied to other CPIC guidelines (18, 19) as follows:

- **High**: Evidence includes consistent results from well-designed, well-conducted studies.
- **Moderate**: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
- **Weak**: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Every effort was made to present evidence from high-quality original research studies. In addition, we took into consideration all available peer-reviewed published literature including other gene-based dosing recommendations (2-6). This literature provided the framework for the strength of therapeutic recommendations.

STRENGTH OF THERAPEUTIC RECOMMENDATIONS

Multiple rating schemes for strength of recommendations in a number of clinical guidelines were evaluated. Ultimately, we chose to use a slight modification of a transparent and simple system for just three categories for recommendations:

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

CPIC's therapeutic recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: *in vivo* pharmacokinetic and pharmacodynamic data, *in vitro* enzyme activity of tissues expressing wild-type or variant-containing CYP2D6 or CYP2C19, *in vitro* CYP2D6 or CYP2C19 enzyme activity from tissues isolated from individuals of known *CYP2D6 or CYP2C19* genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

The therapeutic recommendations are simplified to allow rapid interpretation by clinicians. They have been adopted from the rating scale for evidence-based therapeutic recommendations on the use of antiretroviral agents found at **http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.** The recommendations are as follows:

Strong recommendation for the statement

Moderate recommendation for the statement

Optional recommendation for the statement

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

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (80-84). See https://cpicpgx.org/guidelines/guideline-for-tricyclic-antidepressants-and-cyp2d6-and-cyp2c19/ for resources to support the adoption of CPIC guidelines within an EHR (85). Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating the use of *CYP2D6* and/or C*YP2C19* genotype results to guide TCA dosing in an EHR.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (85, 86). To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main manuscript**). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient summary section; these phenotypes are best stored in the EHR at the "person level" rather than at the date-centric "encounter level". Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (67, 80).

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

relevant to the CPIC guideline (see https://www.pharmgkb.org/page/cyp2c19RefMaterials and https://www.pharmgkb.org/page/cyp2d6RefMaterials**)** (7, 8).

Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC is also providing gene-drug specific tables that provide guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for drugs relevant to the CPIC guideline (see https://cpicpgx.org/guidelines/guideline-for-tricyclic-antidepressants-and-cyp2d6-and-cyp2c19/).

SUPPLEMENTAL TABLE S1. ASSOCIATION BETWEEN ALLELIC VARIANTS[A] AND CYP2D6 ENZYME ACTIVITY

Functional Status (10, 15)	Activity Value[c,d]	Alleles
Increased function	>1	**1xN, *2xN, *35xN, *45xN*
Normal or Increased function	1 or >1[h]	**9xN, *10xN, *17xN, *29xN, *41xN*
Normal function[b]	1	**1*[e], **2, *27, *33, *34*[f], **35, *39*[f], **45*[g], **46*[g], **48, *53*
Decreased function	0.5	**9, *10, *14B,*17, *29, *41, *49, *50, *54, *55, *59, *72*
No function	0	**3, *3xN, *4, *4xN, *5, *6, *6xN, *7, *8, *11, *12, *13, *14A, *15, *18, *19, *20, *21, *31, *36, *36xN, *38, *40, *42, *44, *47, *51, *56, *57, *62,*68, *69, *92, *100, *101*
Unknown	N/A	**22, *23, *24, *25, *26, *28, *30, *32, *37, *43, *43xN, *52, *58, *60, *61, *63, *64, *65, *70, *71, *73, *74, *75, *81, *82, *83, *84, *85, *86, *87, *88, *89, *90, *91, *93, *94, *95, *96, *97, *98, *102, *103, *104, *105, *107, *108, *109*

[a]See http://www.cypalleles.ki.se/cyp2d6.htm and the *CYP2D6* Allele Definition Table (7) for updates on *CYP2D6* allelic variants and nomenclature.
[b]An important caveat for all genotyping tests is that the decision to assign an allele a wild-type status is based upon a genotyping test that interrogates only the most common and already-proven sites of functional variation. It is always possible that a new, previously undiscovered (and therefore un-interrogated) site of variation is defaulted to a functional allele assignment

(wild-type). There is a rare possibility that such variation confers reduced or no activity in an individual and that the person's CYP2D6 function is not accurately predicted.

[c]For some allelic variants there is no or sparse information regarding their activity; therefore no value can be assigned and no CYP2D6 activity score can be calculated. In such cases, the activity score may be estimated based on the second/known allele. A recent in vitro investigation using tamoxifen as substrate provides preliminary information for alleles listed here as unknown (87).

[d]For certain *CYP2D6* alleles *in vivo* data are lacking to unambiguously assign an activity value. For instance, the *CYP2D6*10* and **17* activity values may be substrate dependent, and for particular drugs the activity value could be closer to 1 (normal function) or 0 (no function). It should be noted that the CYP2D6 activity score is an ordinal scale. An allele with an activity score of 0.5 does not necessarily have half the metabolic activity of an allele with an activity score of 1. Rather the score of 0.5 indicates the allele has decreased metabolic activity when compared to the *CYP2D6*1* reference allele.

[e]*CYP2D6*1* serves as reference and is defined as wild-type.

[f] Function of *CYP2D6*34* and **39* is extrapolated from **2*. Both star alleles have SNP(s) that are part of the **2* haplotype.

[g]Limited data are available to determine the predicted activity value of *CYP2D6*45* and **46*. Although an activity value of 1 (functional) is assigned to *CYP2D6*45* and **46* in this guideline, others may assign an activity value of 0.5 (decreased function).

[h]Activity value is dependent on the number of duplications/multiplications present.

SUPPLEMENTAL TABLE S2. EXAMPLES OF *CYP2D6* GENOTYPES WITH RESULTING ACTIVITY SCORES AND PHENOTYPE CLASSIFICATION

Allele 1	Allele 2	*CYP2D6* Diplotype	CYP2D6 Activity Score[a]	Phenotype
**1*	**1xN*[b]	**1/*1xN*	≥3.0	UM
**2x2*[c]	**41*	**2x2/*41*	2.5	UM
**1*	**2*	**1/*2*	2.0	NM
**1*	**17*	**1/*17*	1.5	NM
**2*	**3*	**2/*3*	1.0	NM
**1*	**4x2*[d]	**1/*4x2*	1.0	NM
**10*	**10*	**10/*10*[e]	1.0	NM[e]
**4*[d]	**10*	**4/*10*	0.5	IM
**5*	**6*	**5/*6*[f]	0	PM

Abbreviations are as follows: NM = normal metabolizer, IM = intermediate metabolizer, PM = poor metabolizer, UM = ultrarapid metabolizer. Normal metabolizers with an activity score of 2.0 are expected to exhibit higher CYP2D6 enzyme activity versus individuals with activity scores of 1.5 and 1.0, respectively.

[a]The CYP2D6 activity score is calculated by summing the allele activity values for allele 1 and allele 2. The allele activity values are presented in **Supplemental Table S1**.

[b]**1xN* denotes that two or more copies of the *CYP2D6*1* allele are present. Because the activity value of *CYP2D6*1* is equal to 1, an activity value of 2 will be assigned to the **1xN* allele in instances where a duplication is present (the activity value of each copy would be added together to equal 2). If three gene copies are present, the **1xN* allele activity value would be equal to 3. Therefore, if **1xN* is paired with a second functional allele, the activity score would be ≥3 with an exact value depending on the number of gene copies.

[c]**2x2* denotes a duplication of a functional allele, therefore the allele activity value of **2x2* would be 2. In this example, the gene duplication is paired with *CYP2D6*41* (allele value = 0.5) resulting in a CYP2D6 activity score of 2.5.

[d]Regardless of the number of copies present, *CYP2D6*4* and **4xN* are always considered no function alleles.

[e]Note that some investigators may define patients with a *CYP2D6*10/*10* genotype as intermediate metabolizers

[f]The 1707delT variation will present as homozygous in a test due to the absence of a gene copy on the second allele. If no test is performed for the *CYP2D6*5* gene deletion, the genotype will be assigned as homozygous *CYP2D6 (*6/*6)* which is technically inaccurate, but correctly predicts a poor metabolizer phenotype. The same may occur in the presence of *CYP2D7/2D6* hybrid genes.

SUPPLEMENTAL TABLE S3. TRICYCLIC ANTIDEPRESSANT METABOLISM BY CYP2D6 AND CYP2C19

Parent drug	CYP2C19 metabolite[a]	CYP2D6 metabolite[b]	Therapeutic drug monitoring[c]
Amitriptyline	nortriptyline[d]	hydroxy-amitriptyline	amitriptyline + nortriptyline
Clomipramine	desmethyl-clomipramine	hydroxy-clomipramine	clomipramine + desmethyl-clomipramine
Desipramine[d]	--------	hydroxy-desipramine	desipramine
Doxepin	desmethyl-doxepin	hydroxy-doxepin	doxepin + desmethyl-doxepin
Imipramine	desipramine[d]	hydroxy-imipramine	imipramine + desmethyl-imipramine
Nortriptyline[d]	--------	hydroxy-nortriptyline	nortriptyline
Trimipramine	desmethyl-trimipramine	hydroxy-trimipramine	trimipramine + desmethyl-trimipramine

[a]The pharmacologically active CYP2C19 metabolites are hydroxylated by CYP2D6 to less active compounds.
[b]The hydroxylated metabolites are glucuronidated, rendering the lipophilic drugs to water-soluble compounds that are renally eliminated (34).
[c]The parent drug and CYP2C19 metabolite are both pharmacologically active compounds. As a part of therapeutic drug monitoring the plasma concentrations of both are monitored (88-90).
[d]Desipramine and nortriptyline are the CYP2C19 metabolites of imipramine and amitriptyline respectively. Both are also FDA approved drugs.

SUPPLEMENTAL TABLE S4. TRICYCLIC ANTIDEPRESSANT SIDE EFFECTS[A]

Amitriptyline	CYP2C19 metabolite (Nortriptyline)	CYP2D6 metabolites (hydroxy-amitriptyline, hydroxy-nortriptyline)
Anticholinergic Side Effects Blurred vision Constipation Dizziness Urinary retention Xerostomia Cardiotoxicity Arrhythmias Heart Block Orthostatic hypotension Tachycardia Central nervous system toxicity Delirium Seizures Dementia Headache Sedation	Anticholinergic Side Effects Blurred vision Constipation Dizziness Urinary retention Xerostomia Cardiotoxicity Arrhythmias Heart Block Tachycardia	Cardiotoxicity Arrhythmias Heart Block Tachycardia

[a]The more common and/or serious side effects associated with amitriptyline and its metabolites. The side effect profile of other tricyclics including clomipramine, desipramine, doxepin, imipramine and trimipramine is similar. [74]

Anticholinergic side effects are common with the tricyclic antidepressants, which are due to the binding of these drugs to cholinergic receptors. The ranking of cholinergic receptor binding of the tricyclics is as follows: tertiary amines > secondary amines (desmethyl-metabolites) > hydroxy-metabolites (34). Tricyclics also bind with α-adrenergic, serotonin and histamine receptors resulting in orthostatic hypotension and sedation (91). Although patients with amitriptyline plus nortriptyline plasma concentrations within the recommended therapeutic range (80-200 ng/ml) may experience such effects, higher plasma concentrations of tertiary or secondary amines may place a patient at an increased risk of anticholinergic side effects along with orthostatic hypotension and sedation (88). Amitriptyline plus nortriptyline plasma concentrations above the recommended therapeutic range are also associated with central nervous system and cardiac toxicity (92). Therefore, a CYP2D6 or CYP2C19 phenotype that may increase the plasma concentrations of tertiary or secondary amines (e.g., a CYP2D6 or

CYP2C19 poor metabolizer) will theoretically place a patient at an increased risk of adverse effects.

Tricyclic hydroxy-metabolites have lower binding affinities to muscarinic receptors, but have been associated with cardiotoxicity (93-96). In elderly depressed patients, plasma concentrations of hydroxy-nortriptyline metabolites were associated with increases in QRS duration and QTc intervals (97). Stern *et al*. found that desipramine and hydroxy-desipramine plasma concentrations may predict prolongation of cardiac conduction in young adults (98). Because CYP2D6 metabolizes tricyclics to hydroxy-metabolites, CYP2D6 ultrarapid metabolizers may have elevated hydroxy-metabolite plasma concentrations resulting in an increased risk for cardiotoxicity (99). It should be noted that therapeutic drug monitoring does not usually include measuring hydroxy-metabolite plasma concentrations; therefore, appropriate hydroxy-metabolite plasma concentrations have not been defined.

In addition to variation in the *CYP2D6* and *CYP2C19* genes, CYP inhibitors can increase the plasma concentration of tricyclic antidepressants. There are multiple publications describing patients who have elevated tricyclic plasma concentrations when taking a tricyclic concomitantly with a CYP2D6 inhibitor (100-103). It has been suggested that the CYP2D6 activity score should be adjusted to 0 during treatment with a strong CYP2D6 inhibitor, and that patients should be treated similarly to CYP2D6 poor metabolizers (18, 104). Patients taking strong inhibitors of CYP2D6, such as fluoxetine, in combination with a tricyclic might benefit from following the CYP2D6 poor metabolizer dosing recommendations in **Table 2** located in the main document.

Although the occurrence of adverse events has been related in part to tricyclic steady-state concentrations, it should be noted that side effects may occur even when patients are within the recommended therapeutic range (34, 92, 105). Similarly, it has been hypothesized that tricyclic plasma concentrations above or below the recommended therapeutic range, or an imbalance between parent drug and metabolite concentrations, may lead to treatment failure, but conflicting data are present (34, 91, 92, 105-113). Even though particular CYP2D6 or CYP2C19 phenotypes (e.g., ultrarapid or poor metabolizers) may place a patient at a higher risk of adverse effects or

treatment failure, it does not necessarily mean normal metabolizers are immune from side effects or treatment failure. Therefore, all patients should be monitored closely for side effects and treatment failure.

SUPPLEMENTAL TABLE S5. EVIDENCE LINKING *CYP2D6* GENOTYPE TO AMITRIPTYLINE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence[a]
Clinical	CYP2D6 poor metabolizers (as determined by genotyping or phenotyping) have decreased metabolism[b] of amitriptyline as compared to normal metabolizers.	Balant-Gorgia, *et al*. (1982)(114) Baumann, *et al*. (1986)(109) Tacke, *et al*. (1992)(115) Steimer, *et al*. (2004)(116) Koski, *et al*. (2006)(117) Halling, *et al*. (2008)(118) de Vos, *et al*. (2011)(119) Smith, *et al*. (2011)(120)	High
Clinical	Significant correlation between the number/resulting function of *CYP2D6* variant alleles and metabolism[b] of amitriptyline.	Steimer, *et al*. (2004)(116) Steimer, *et al*. (2005)(70) Halling, *et al*. (2008)(118) de Vos, *et al*. (2011)(119)	High
Clinical	No significant difference in metabolism[b] of amitriptyline is shown between carriers of only one *CYP2D6* functional allele or carriers of decreased function alleles compared to carriers of two *CYP2D6* normal function alleles.	Shimoda, *et al*. (2002)(110)	Weak
Clinical	CYP2D6 poor metabolizers (as determined by genotyping) require a decreased dose of amitriptyline as compared to normal metabolizers.	de Vos, *et al*. (2011)(119)	Moderate
Clinical	Carriers of *CYP2D6* no function alleles have an increased risk for side effects as compared to carriers of other *CYP2D6* alleles.	Steimer, *et al*. (2005)(70) Johnson, *et al*. (2006)(121) Forget, *et al*. (2008)(122)	Moderate
Clinical	CYP2D6 poor metabolizers (as determined by genotyping) are associated with early discontinuation (within 28 days to 45 days	Bijl, *et al*. (2008)(123) Peñas-Lledó, *et al*. (2013)(124)	Moderate

	after the start of the first prescription) of antidepressant therapy as compared to normal metabolizers.		
Clinical	CYP2D6 ultrarapid metabolizers (as determined by genotyping) have an increased risk for discontinuation of treatment and a decreased response.	Peñas-Lledó, *et al*. (2013)(124)	Moderate
Clinical	Correlation of desbrisoquine hydroxylation with amitriptyline metabolism.	Mellström, *et al*. (1986)(125)	Moderate
Clinical	Correlation of dextromethorphan metabolism with amitriptyline metabolism.	Breyer-Pfaff, *et al*. (1992)(126)	Moderate

[a]Rating scheme described in the *Levels of Evidence* section of the **Supplemental Material.**

[b"]Increased metabolism" or "decreased metabolism" defined as changes in pharmacokinetic variables based on area under the plasma concentration-time curve of amitriptyline or nortriptyline, elimination half-life of amitriptyline, metabolic ratio of amitriptyline/hydroxyamitriptyline and nortriptyline/hydroxynortriptyline, oral clearance of amitriptyline, plasma concentrations of amitriptyline and/or nortriptyline.

SUPPLEMENTAL TABLE S6. EVIDENCE LINKING *CYP2C19* GENOTYPE TO AMITRIPTYLINE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence[a]
Clinical	CYP2C19 poor metabolizers (as determined by genotyping) have a decreased metabolism[b] of amitriptyline as compared to CYP2C19 normal metabolizers.	Jiang, *et al*. (2002)(127) Shimoda, *et al*. (2002)(110) Steimer, *et al*. (2004)(116) Grasmäder, *et al*. (2004)(128) Steimer, *et al*. (2005)(70) van der Weide, *et al*. (2005)(129) Koski, *et al*. (2006)(117) de Vos, *et al*. (2011)(119)	High
Clinical	CYP2C19 intermediate metabolizers (as determined by genotyping) have a decreased metabolism[b] of amitriptyline as compared to CYP2C19 normal metabolizers.	Shimoda, *et al*. (2002)(110) Steimer, *et al*. (2004)(116) van der Weide, *et al*. (2005)(129) Steimer, *et al*. (2005)(70) Koski, *et al*. (2006)(117) de Vos, *et al*. (2011)(119)	High
Clinical	CYP2C19 ultrarapid metabolizers (as determined by genotyping) have an increased metabolism[b] of amitriptyline as compared to CYP2C19 normal metabolizers.	de Vos, *et al*. (2011)(119)	Moderate
Clinical	Correlation of mephenytoin metabolism with amitriptyline metabolism.	Breyer-Pfaff, *et al*. (1992)(126)	Moderate

[a]Rating scheme described in the *Levels of Evidence* section of the **Supplemental Material.**

[b]"Increased metabolism" or "decreased metabolism" defined as changes in pharmacokinetic variables based on area under the plasma concentration-time curve of amitriptyline, metabolic ratio of amitriptyline/nortriptyline, and/or plasma concentrations of amitriptyline and/or nortriptyline.

SUPPLEMENTAL TABLE S7. EVIDENCE LINKING *CYP2D6* GENOTYPE TO NORTRIPTYLINE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence[a]
Clinical	CYP2D6 poor metabolizers (as determined by genotyping or phenotyping) have decreased metabolism[b] of nortriptyline as compared to normal metabolizers.	Bertilsson, *et al*. (1981)(39) Dalén, *et al*. (1998)(130) Murphy, *et al*. (2001)(131) Hodgson, *et al*. (2014)(132) Berm, *et al*. (2016)(133)	High
Clinical	CYP2D6 intermediate metabolizers (as determined by genotyping) have decreased metabolism[b] of nortriptyline as compared to normal metabolizers.	Morita, *et al*. (2000)(134) Lee, *et al*. (2004)(135)	High
Clinical	CYP2D6 ultrarapid metabolizers (as determined by genotyping) have increased metabolism[b] of nortriptyline as compared to CYP2D6 normal metabolizers.	Bertilsson, *et al*. (1993)(136) Dalén, *et al*. (1998)(130) Laine, *et al*. (2001)(137) Hodgson, *et al*. (2014)(132)	High
Clinical	Correlation between the number of *CYP2D6* variant alleles and nortriptyline metabolism[b]	Dahl, *et al*. (1996)(112) Yue, *et al*. (1998)(138) Dalén, *et al*. (1998)(130) Morita, *et al*. (2000)(134) Murphy, *et al*. (2001)(131) Lee, *et al*. (2006)(139) Chua, *et al*. (2013)(140) Hodgson, *et al*. (2014)(132)	High
Clinical	CYP2D6 poor metabolizers (as determined by genotyping) require a decreased dose of nortriptyline as compared to normal metabolizers.	Murphy, *et al*. (2001)(131) Bijl, *et al*. (2008)(123) **No association reported:** Hodgson, *et al*. (2014)(132)	Moderate

Clinical	CYP2D6 ultrarapid metabolizers (as determined by genotyping) require an increased dose of nortriptyline.	Bertilsson, *et al*. (1993)(136)	Moderate
Clinical	Carriers of *CYP2D6* no function and decreased function alleles have an increased risk for side effects when receiving nortriptyline as compared to carriers of other *CYP2D6* alleles.	Bertilsson, *et al*. (1981)(39) Chen, *et al*. (1996)(141) Lee, *et al*. (2004)(135) Piatkov, *et al*. (2011)(142) **No association reported:** Hodgson, *et al*. (2014)(132)	Moderate
Clinical	CYP2D6 ultrarapid metabolizers (as determined by genotyping) experience decreased response when receiving nortriptyline.	Bertilsson, *et al*. (1985)(99) Bertilsson, *et al*. (1993)(136) Kawanishi, *et al*. (2004)(143)	Moderate
Clinical	Correlation of desbrisquine hydroxylation with nortriptyline metabolism.	Bertilsson, *et al*. (1980)(144) Mellström, *et al*. (1981)(145) Woolhouse, *et al*. (1984)(146) Nordin, *et al*. (1985)(93)	High
Clinical	A pharmacokinetic model using published data showed that the intrinsic clearance of nortriptyline is a linear function of the number of functional *CYP2D6* genes.	Kvist, *et al*. (2001)(147)	Moderate

[a]Rating scheme described in the *Levels of Evidence* section of the **Supplemental Material.**

[b"]Increased metabolism" or "decreased metabolism" defined as changes in pharmacokinetic variables based on area under the plasma concentration-time curve of nortriptyline, elimination half-life of nortriptyline, oral clearance of nortriptyline, plasma concentrations of nortriptyline and/or hydroxynortriptyline, maximal concentration (Cmax) of hydroxynortriptyline, and/or metabolic ratio (MR) of nortriptyline/hydroxynortriptyline.

SUPPLEMENTAL TABLE S8. EVIDENCE LINKING *CYP2D6* GENOTYPE TO IMIPRAMINE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence[a]
Clinical	CYP2D6 poor metabolizers (as determined by genotyping or phenotyping) have decreased metabolism[b] of imipramine as compared to normal metabolizers.	Brøsen, *et al*. (1986)(148) Brøsen, *et al.* (1986)(149) Balant-Gorgia, *et al.* (1989)(103) Koyama, *et al.* (1994)(73) Madsen, *et al.* (1995)(150) Madsen, *et al.* (1996)(151) Schenk, *et al.* (2008)(152)	High
Clinical	Correlation between the number/function of *CYP2D6* variant alleles and imipramine metabolism[b].	Schenk, *et al* (2008)(152)	High
Clinical	CYP2D6 poor metabolizers (as determined by genotyping) require a decreased dose of imipramine as compared to normal metabolizers.	Sindrup, *et al.* (1990)(153) Bijl, *et al.* (2008)(123) Schenk, *et al.* (2008)(152)	High
Clinical	CYP2D6 ultrarapid metabolizers (as determined by genotyping) require an increased dose of imipramine as compared to normal metabolizers.	Schenk, *et al.* (2008)(152)	High
Clinical	*CYP2D6* genotype is associated with variations in dose requirements for imipramine.	Schenk, *et al.* (2008)(152)	High
Clinical	Carriers of *CYP2D6* no function alleles have an increased risk for side effects when receiving imipramine as compared to carriers of other *CYP2D6* alleles.	Balant-Gorgia, *et al.* (1989)(103) Chen, *et al.* (1996)(141) Bijl, *et al.* (2008)(123)	Moderate
Clinical	Correlation of sparteine metabolism with imipramine metabolism.	Madsen, *et al.* (1995)(150)	High

In-vitro	CYP2D6 is involved in imipramine metabolism.	Brøsen, *et al.* (1991)(154)	Moderate

[a]Rating scheme described in the *Levels of Evidence* section of the **Supplemental Material.**

[b]"Increased metabolism" or "decreased metabolism" defined as changes in pharmacokinetic variables based on area under the plasma concentration-time curve of imipramine and desipramine, elimination half-life of imipramine, metabolic ratio of hydroxyimipramine/imipramine and hydroxydesipramine/desipramine, oral clearance of imipramine, and/or plasma or urinary concentrations of imipramine and/or desipramine.

SUPPLEMENTAL TABLE S9. EVIDENCE LINKING *CYP2C19* GENOTYPE TO IMIPRAMINE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence[a]
Clinical	CYP2C19 poor metabolizers (as determined by genotyping or phenotyping) have a decreased metabolism[b] of imipramine as compared to CYP2C19 normal metabolizers.	Skjelbo, *et al.* (1991)(155) Koyama, *et al.* (1994)(73) Koyama, *et al.* (1996)(156) Morinobu, *et al.* (1997)(157) Schenk, *et al.* (2008)(152)	High
Clinical	CYP2C19 intermediate metabolizers (as determined by genotyping) have a decreased metabolism[b] of imipramine as compared to CYP2C19 normal metabolizers.	Schenk, *et al.* (2008)(152) Schenk, *et al.* (2010)(158)	Moderate
Clinical	CYP2C19 ultrarapid metabolizers (as determined by genotyping) have an increased metabolism[b] of imipramine as compared to CYP2C19 normal metabolizers.	Schenk, *et al.* (2010)(158)	Moderate
Clinical	Correlation of mephenytoin metabolism with imipramine metabolism.	Skjelbo, *et al.* (1993)(159) Madsen, *et al.* (1995)(150) Madsen, *et al.* (1997)(160)	High

[a]Rating scheme described in the *Levels of Evidence* section of the **Supplemental Material.**

[b]"Increased metabolism" or "decreased metabolism" defined as changes in pharmacokinetic variables based on area under the plasma concentration-time curve of imipramine, metabolic ratio (MR) of desipramine/imipramine, oral clearance of imipramine, metabolic ratio of imipramine/desipramine and/or plasma concentrations of imipramine and desipramine.

SUPPLEMENTAL TABLE S10. EVIDENCE LINKING *CYP2D6* GENOTYPE TO DESIPRAMINE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence[a]
Clinical	CYP2D6 poor metabolizers (as determined by genotyping or phenotyping) have decreased metabolism[b] of desipramine as compared to normal metabolizers.	Spina, *et al.* (1984)(161) Brøsen, *et al.* (1986)(149) Spina, *et al.* (1987)(162) Steiner, *et al.* (1987)(102) Brøsen, *et al.* (1988)(163) Dahl, *et al.* (1992)(164) Spina, *et al.* (1997)(106) Nguyen, *et al.* (2016)(165)	High
Clinical	Correlation between the number/ function of *CYP2D6* variant alleles and metabolism[b] of desipramine.	Dahl, *et al.* (1992)(164) Shimoda, *et al.* (2000)(166) Bergmann, *et al.* (2001)(167) Furman, *et al.* (2004)(168)	Moderate
Clinical	CYP2D6 poor metabolizers (as determined by phenotyping) require a decreased dose of desipramine as compared to normal metabolizers.	Spina, *et al.* (1997)(106)	Moderate
Clinical	Carriers of *CYP2D6* no function and decreased function alleles have an increased risk for side effects when receiving desipramine as compared to carriers of other *CYP2D6* alleles.	Bluhm, *et al.* (1993)(169) Chen, *et al.* (1996)(141) Spina, *et al.* (1997)(106)	Moderate
Clinical	Correlation of desbrisquine hydroxylation with desipramine metabolism.	Bertilsson, *et al.* (1983)(170) Spina, *et al.* (1984)(161)	Moderate

[a]Rating scheme described in the *Levels of Evidence* section of the **Supplemental Material.**

[b]"Increased metabolism" or "decreased metabolism" defined as changes in pharmacokinetic variables based on area under the plasma concentration-time curve of desipramine, elimination half-life of desipramine, metabolic ratio of desipramine/hydroxydesipramine, oral or systematic clearance of desipramine, plasma or urinary concentrations of desipramine and/or hydroxydesipramine).

SUPPLEMENTAL TABLE S11. EVIDENCE LINKING *CYP2D6* GENOTYPE TO CLOMIPRAMINE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence[a]
Clinical	CYP2D6 poor metabolizers (as determined by genotyping or phenotyping) have decreased metabolism[b] of clomipramine as compared to normal metabolizers.	Balant-Gorgia, *et al.* (1987)(171) Balant-Gorgia, *et al.* (1989)(103) Nielsen, *et al.* (1992)(172) Tacke, *et al.* (1992)(115) Nielsen, *et al.* (1994)(71) DUAG, *et al.* (1999)(173) Stephan, *et al.* (2006)(174)	High
Clinical	CYP2D6 ultrarapid metabolizers (as determined by genotyping) have decreased metabolism[b] of clomipramine.	Bertilsson, *et al.* (1993)(136) Baumann, *et al.* (1998)(175)	Moderate
Clinical	No significant difference in plasma concentrations of clomipramine and desmethylclomipramine and the number of variant *CYP2D6* alleles.	de Vos, *et al.* (2011)(119)	Moderate
Clinical	CYP2D6 poor metabolizers (as determined by genotyping) require a decreased dose of clomipramine as compared to normal metabolizers.	Bijl, *et al.* (2008)(123)	Weak
Clinical	Carriers of *CYP2D6* no function alleles have an increased risk for side effects as compared to carriers of other *CYP2D6* alleles.	Balant-Gorgia, *et al.* (1989)(103) Chen, *et al.* (1996)(141) Stephan, *et al.* (2006)(174) Vandel, *et al.* (2004)(176) Bijl, *et al.* (2008)(123)	High
Clinical	CYP2D6 ultrarapid metabolizers (as determined by genotyping) experience decrease response when receiving clomipramine.	Bertilsson, *et al.* (1993)(136)	Moderate

[a]Rating scheme described in the *Levels of Evidence* section of the **Supplemental Material.**
[b]"Increased metabolism" or "decreased metabolism" defined as changes in pharmacokinetic variables based on metabolic ratio (MR) of desmethyclomipramine/hydroxydesmethyclomipramine, oral clearance of clomipramine, and/or plasma concentrations of clomipramine and/or desmethyclomipramine or hydroxyclomipramine.

SUPPLEMENTAL TABLE S12. EVIDENCE LINKING *CYP2C19* GENOTYPE TO CLOMIPRAMINE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence[a]
Clinical	CYP2C19 poor metabolizers (as determined by genotyping or phenotyping) have a decreased metabolism[b] of clomipramine as compared to CYP2C19 normal metabolizers.	Nielsen, *et al.* (1994)(71) Yokono, *et al.* (2001)(177) de Vos, *et al.* (2011)(119)	High
Clinical	CYP2C19 intermediate metabolizers (as determined by genotyping) have a decreased metabolism of clomipramine as compared to CYP2C19 normal metabolizers.	Yokono, *et al.* (2001)(177)	High
Clinical	CYP2C19 intermediate or rapid metabolizers (*1/*17) (as determined by genotyping) are not associated with significant differences in metabolism of clomipramine as compared to normal metabolizers.	de Vos, *et al.* (2011)(119)	Moderate
Clinical	CYP2C19 ultrarapid metabolizer have a higher frequency of clomipramine concentrations below the therapeutic range.	de Vos, *et al.* (2011)(119)	Moderate

[a]Rating scheme described in the *Levels of Evidence* section of the **Supplemental Material.**

[b]"Increased metabolism" or "decreased metabolism" defined as changes in pharmacokinetic variables based on metabolic ratio of clomipramine/desmethylclomipramine, oral clearance of clomipramine, and/or plasma concentrations of clomipramine.

SUPPLEMENTAL TABLE S13. EVIDENCE LINKING *CYP2D6* GENOTYPE TO TRIMIPRAMNE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence[a]
Clinical	CYP2D6 poor metabolizers (as determined by genotyping or phenotyping) have decreased metabolism[b] of trimipramine as compared to normal metabolizers or ultrarapid metabolizers.	Tacke, *et al.* (1992)(115) Eap, *et al.* (2000)(178) Kirchheiner, *et al.* (2003a)(179) Kirchheiner, *et al.* (2003b)(180)	High
Clinical	Correlation between the number/ function of *CYP2D6* variant alleles and metabolism[b] of trimipramine.	Kirchheiner, *et al.* (2003a)(179) Kirchheiner, *et al.* (2003b)(180)	High
Clinical	Reduction of trimipramine metabolism by CYP2D6 inhibitor quinidine.	Eap, *et al.* (1992)(101)	Moderate

[a]Rating scheme described in the *Levels of Evidence* section of the **Supplemental Material.**

[b]"Increased metabolism" or "decreased metabolism" defined as changes in pharmacokinetic variables based on area under the plasma concentration-time curve of trimipramine, elimination half-life of trimipramine, oral clearance of trimipramine, plasma concentrations of trimipramine and desmethyltrimipramine, and/or systemic availability.

SUPPLEMENTAL TABLE S14. EVIDENCE LINKING *CYP2C19* GENOTYPE TO TRIMIPRAMINE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence[a]
Clinical	Significant correlation between the number of *CYP2C19* no function alleles (*2) and metabolism[b] of trimipramine.	Eap, *et al.* (2000)(178) Kirchheiner, *et al.* (2003b)(180)	High

[a]Rating scheme described in the *Levels of Evidence* section of the **Supplemental Material.**

[b]"Increased metabolism" or "decreased metabolism" defined as changes in pharmacokinetic variables based on area under the plasma concentration-time curve of trimipramine, elimination half-life of trimipramine, oral clearance of trimipramine, plasma concentrations of trimipramine and/or desmethyltrimipramine.

SUPPLEMENTAL TABLE S15. EVIDENCE LINKING *CYP2D6* GENOTYPE TO DOXEPIN PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence[a]
Clinical	CYP2D6 poor metabolizers (as determined by genotyping or phenotyping) have decreased metabolism[b] of doxepin as compared to normal metabolizers.	Tacke, *et al.* (1992)(115) Haritos, *et al.* (2000)(181) Kirchheiner, *et al.* (2002)(72) Koski, *et al.* (2007)(182)	High
Clinical	Correlation between the number/ function of *CYP2D6* variant alleles and metabolism[b] of doxepin.	Kirchheiner, *et al.* (2002)(72) Kirchheiner, *et al.* (2005)(183)	High
Clinical	CYP2D6 ultrarapid metabolizers (as determined by genotyping) have increased metabolism[b] of doxepin as compared to normal metabolizers.	Kirchheiner, *et al.* (2005)(183)	High
Clinical	CYP2D6 poor metabolizers (as determined by genotyping) require a decreased dose of doxepin as compared to normal metabolizers.	Bijl, *et al.* (2008)(123)	Weak
Clinical	Carriers of *CYP2D6* no function and decreased function alleles have an increased risk for side effects when receiving doxepin as compared to carriers of other *CYP2D6* alleles.	Koski, *et al.* (2007)(182) Bijl, *et al.* (2008)(123) Neukamm, *et al.* (2013)(184)	Moderate

[a]Rating scheme described in the *Levels of Evidence* section of the **Supplemental Material.**

[b"]Increased metabolism" or "decreased metabolism" defined as changes in pharmacokinetic variables based on area under the plasma concentration-time curve of desmethyldoxepin, elimination half-life of doxepin and desmethyldoxepin, oral clearance of doxepin, and/or plasma concentrations of doxepin and/or desmethyldoxepin.

SUPPLEMENTAL TABLE S16. EVIDENCE LINKING *CYP2C19* GENOTYPE TO DOXEPIN PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence[a]
Clinical	Significant correlation between the number of *CYP2C19* no function alleles (*2) and oral clearance of doxepin.	Kirchheiner, *et al.* (2002)(72)	Moderate
In-vitro	CYP2C19 contributes to the N-demethylation of doxepin.	Härtter, *et al.* (2002)(185)	Moderate

[a]Rating scheme described in the *Levels of Evidence* section of the **Supplemental Material.**

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