Supplement to:

Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants

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INTRODUCTION

Guideline Updates

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

Literature Review

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]

The *CYP2D6* and *CYP2C19* allele frequency tables are based on previously published CPIC guidelines.[7,8] Updates to the *CYP2D6* allele frequency table were made by searching the PubMed® database (1995 to June 2012) using the following key words: CYP2D6, CYP 2D6, cytochrome P4502D6, ethnic, ethnicity, race, population, and names of countries and populations (e.g., Spain, Spanish, Brazil, Brazilian). In addition, reports were also identified from citations by others or review articles. Studies were considered for inclusion if: (1) the ethnicity of the population was clearly indicated, (2) either *CYP2D6* allele frequencies or genotype frequencies were reported, (3) the method by which *CYP2D6* was 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).

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 variations including insertions and deletions that are interrogated during genotyping analysis. *CYP2D6* and *CYP2C19* haplotypes are assigned a star-allele nomenclature to allow for the standardization of genetic polymorphism annotation.[9] A complete list of *CYP2D6* and *CYP2C19* star-allele nomenclature along with the genetic variants that define each star-allele are available at http://www.cypalleles.ki.se/cyp2d6.htm and http://www.cypalleles.ki.se/cyp2c19.htm, respectively. Information regarding *CYP2D6* or *CYP2C19* haplotypes (star-alleles) is also available at PharmGKB (www.pharmgkb.org).[1] Knowing which SNPs or other genetic variants a particular test analyzes for is important. The

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

Reference laboratories usually report a diplotype, which is the summary of inherited maternal and paternal star-alleles (e.g., *CYP2C19*1/*2*, where the patient inherited a **1* allele and a **2* allele). Commonly reported *CYP2D6* and *CYP2C19* star-alleles are categorized into functional groups (e.g., functional, reduced function, or non-functional) based on the predicted activity of the encoded enzyme (Supplementary Tables S4 and S6). The predicted phenotype (Supplementary Tables S7-9) is influenced by the expected function of each reported allele in the diplotype. Phenotype-predicting tools including "look-up" or "translation" tables are being developed by the Translational Pharmacogenetics Project group and can be accessed at www.pharmgkb.org.[1] Hicks *et al.* describes the development of the CYP2D6 look-up table.[10]

Phenotyping CYP2D6 and CYP2C19. The tricyclic antidepressants 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 fewer side effects were developed to treat depression.[11] Much knowledge about the tricyclics 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.[12-15] The proton pump inhibitors have replaced proguanil and mephenytoin as the preferred probes for phenotyping CYP2C19. Omeprazole in an established CYP2C19 probe in adults, but pantoprazole may be a more suitable choice for CYP2C19 phenotyping in pediatric patients.[16,17] In most instances patients were divided into two groups, either poor or extensive metabolizers. Good concordance has been observed between assigned phenotypes based on probe drugs and genetic test results.[18-24] 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.

Calculating CYP2D6 Activity Score. Gaedigk *et al*. developed a scoring system to provide a uniform approach to assigning a predicted CYP2D6 phenotype.[25] *CYP2D6* alleles are assigned an activity value as detailed in Supplementary Table S4. 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. 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 = extensive metabolizer, and activity score greater than 2.0 = ultrarapid metabolizer. Therefore, a pharmacogenetic test result of *CYP2D6*1/*17* would result in a CYP2D6 activity score of 1.5 and a predicted phenotype of extensive metabolizer.

CYP2D6 Copy Number Variations. Because *CYP2D6* is subject to copy number variations (gene duplications, multiplications, or deletions), reference laboratories may report gene copy number. Most patients will have a copy number of 2, with one allele inherited maternally and one allele 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 copy number. A copy number of "1" indicates the presence of a single *CYP2D6* gene deletion, and a copy number of "0" indicates both *CYP2D6* genes are deleted. *CYP2D6* gene deletions are indicated by the **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 copy number and the **5* allele is inferred. Typically, reference laboratories will report two gene deletions 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 copy number. A reference 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). In instances where a duplication is present and the exact copy number is not reported, most patients will likely have a *CYP2D6* copy number of 3. However, individuals carrying as many as 13 *CYP2D6* copies have been reported.[26] Reference laboratories usually do not determine which allele is duplicated, therefore when calculating CYP2D6 activity score the duplication must be considered for each allele reported in the diplotype.[27] 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 **1* allele and one copy of the **4* allele, or one copy of the **1* allele and two copies of the **4* allele. If the **1* allele carries the duplication the CYP2D6 activity score of this diplotype will be 2, whereas if the **4* allele carries the duplication, the activity score will be 1. Studies have been published describing the translation of *CYP2D6* genotypes into predicted phenotypes when gene duplications or multiplications are present.[8,10,25,27]

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 assays may not detect rare or *de novo* variants resulting in patients being assigned a default genotype. 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.[28] 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*14A* is present in Asian populations and therefore its defining SNP (1758G>A) has been incorporated into Asian genotyping panels.[29] 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 reduced function *CYP2D6*10*). This tandem can be found in Asian populations and is typically reported as a default assignment of *CYP2D6*10*.

Available CYP2D6 Genetic Test Options. Commercially available genetic testing options change over time. Additional information about pharmacogenetic testing can be found at http://www.pharmgkb.org or the Genetic Testing Registry found at http://www.ncbi.nlm.nih.gov/gtr/.[1] The American College of Medical Genetics and Genomics (ACMG) established guidelines for laboratory testing of *CYP2D6* in relation to tamoxifen therapy.[30] The following list provides a selection of different platforms that are currently available for *CYP2D6* genotyping, some of which are approved by the U.S. Food and Drug Administration. It should be noted that some platforms may not include an assessment of *CYP2D6* copy number and thus cannot adequately predict CYP2D6 phenotype.

1. AmpliChip® CYP450 Test (Roche Molecular Systems, Inc., Pleasanton, CA)[31-33]
2. xTAG® CYP2D6 (Luminex® Molecular Diagnostics, Toronto, ON, Canada)[32]
3. INFINITI® CYP450 2D6 (AutoGenomics, Inc., Vista, CA)[32]
4. DMET™ (Affymetrix, Inc., Santa Clara, CA)[34]
5. VeraCode® ADME Core Panel (Illumina, Inc., San Diego, CA)[35]
6. TaqMan® Drug Metabolism Genotyping Assay Sets (Applied Biosystems, Inc., Foster City, CA)[36,37]

Clinical genotyping services for *CYP2D6* are available from multiple reference laboratories. Several examples are listed below.

1. LabCorp Laboratory Corporation of America®
2. Quest Diagnostics®
3. Mayo Medical Laboratories

4. ARUP®
5. PG$_{xL}$™ Laboratories

Reference laboratories may analyze for different SNPs or other genetic variants, which are dependent on the genotyping platform used and may affect the reported diplotype leading to discrepant results between methodologies. Additionally, reference laboratories may differ in how *CYP2D6* copy number variations are reported, which can potentially affect phenotype prediction. Therefore, it is important to know the genetic variants analyzed by each reference laboratory and how copy number variants are reported. Reference laboratories may give an interpretation of the *CYP2D6* genotype result and provide a predicted CYP2D6 phenotype. Phenotype assignment for this guideline is defined in the main manuscript and supplementary data, but may differ from reference laboratory interpretations. If the genotyping results will be reported in a patient's medical record, reference laboratories will need to implement genotyping platforms using CLIA standards.

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)** Because it is currently impractical to test for every variation in the *CYP2C19* gene, genotyping assays may not detect rare or *de novo* 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 the rare or *de novo* 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 (Supplemental Table S2).[7] 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.[7] Therefore, it is difficult to determine whether these two variants function independently of each other. Published articles focusing on clopidogrel argue both for[38] and against[39,40] independence. **5)** The *CYP2C19*4* loss-of-function allele has been identified in linkage disequilibrium with *CYP2C19*17* (c.-806C>T) in certain ethnic subpopulations and this haplotype is designated *CYP2C19*4B*.[7,41] *CYP2C19*17* is a gain-of-function allele, while *CYP2C19*4B* is a loss-of-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. 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.

Available CYP2C19 Genetic Test Options. Commercially available genetic testing options change over time. Additional information about pharmacogenetic testing can be found at http://www.pharmgkb.org or the Genetic Testing Registry found at http://www.ncbi.nlm.nih.gov/gtr/.[1] Some clinical laboratories perform *CYP2C19* testing using analyte-specific reagents as in-house validated Laboratory Developed Tests (LDTs).[7] Clinical trials are underway investigating *CYP2C19* point-of-care genetic testing.[42] A number of different platforms are currently available for *CYP2C19 genotyping*. The following list provides a selection of different platforms that are currently available, some of which are approved by the U.S. Food and Drug Administration.

1. AmpliChip® CYP450 Test (Roche Molecular Systems, Inc., Pleasanton, CA)[31-33]
2. INFINITI® CYP2C19 Assay (AutoGenomics, Inc., Vista, CA)[32,43]
3. DMET™ (Affymetrix, Inc., Santa Clara, CA)[34,44]
4. eSensor® 2C19 Test (GenMark Diagnostics, Inc., Carlsbad, CA)[43]
5. TaqMan® Drug Metabolism Genotyping Assay Sets (Applied Biosystems, Inc., Foster City, CA)[32,45]
6. SNPlex Genotyping System (Applied Biosystems, Inc., Foster City, CA)[37,46,47]
7. VeraCode® ADME Core Panel (Illumina, Inc., San Diego, CA)[35]

Clinical genotyping services for *CYP2C19* are available from multiple reference laboratories. Several examples are listed below.

1. LabCorp Laboratory Corporation of America®
2. Quest Diagnostics®
3. Mayo Medical Laboratories
4. ARUP®
5. PG_{xL}™ Laboratories

Reference laboratories may analyze for different SNPs or other genetic variants, which are dependent on the genotyping platform used and may affect the reported diplotype leading to discrepant results between methodologies. Therefore, it is important to know the genetic variants analyzed for by each reference laboratory. Reference laboratories may give an interpretation of the *CYP2C19* genotype result and provide a predicted CYP2C19 phenotype. Phenotype assignment for this guideline is defined in the main manuscript and supplementary data, but may differ from reference laboratory interpretations. If the genotyping results will be reported in a patient's medical record, reference laboratories will need to implement genotyping platforms using CLIA standards.

Levels of Evidence

The evidence summarized in Supplemental Tables S12-18 is graded using a scale based on previously published criteria[48] that was applied to other CPIC guidelines[7,8,49-52] 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

CPIC's therapeutic recommendations are based on weighting 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 gene-based dosing recommendations in this guideline takes into consideration the effects *CYP2D6* or *CYP2C19* genetic variants may have on both clinical outcomes and tricyclic plasma concentrations. Because the pharmacokinetic properties of tricyclic antidepressants do not differ between healthy volunteers and patients, we evaluated pharmacokinetic data acquired from studies performed on healthy subjects and patients to assist us in determining if *CYP2D6* or *CYP2C19* genetic variants affect tricyclic plasma concentrations.

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 retroviral agents found at **http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.**[53,54] The recommendations are as follows:

Strong recommendation for the statement
Moderate recommendation for the statement
Optional recommendation for the statement

Supplemental Table S1. Frequencies[a] of *CYP2D6* alleles in major race/ethnic groups[b]

Allele	African	African American	Caucasian (European + North American)	Middle Eastern	East Asian	South/Central Asian	Americas	Oceanian
***1**[c]	0.39	0.41	0.52	0.59	0.34	0.53	0.62	0.70
***2**[d]	0.20	0.12	0.27	0.24	0.12	0.31	0.24	0.012
***3**	0.0003	0.0034	0.013	0.0013	0.00	0.00	0.0052	0.00
***4**	0.033	0.06	0.18	0.076	0.0045	0.065	0.11	0.011
***5**	0.06	0.058	0.028	0.023	0.058	0.025	0.016	0.049
***6**	0.00	0.0027	0.0091	0.0096	0.0002	0.00	0.005	0.00
***7**	0.00	0.00	0.0012	0.00	0.00	ND	0.00	0.00
***8**	0.00	0.00	0.0003	0.00	0.00	ND	0.0015	0.00
***9**	0.0010	0.0054	0.02	0.00	0.0008	0.014	0.013	0.00
***10**[e]	0.067	0.043	0.028	0.035	0.42	0.19	0.034	0.016
***14**	0.0013	0.00	0.00	0.00	0.0092	0.00	0.0047	0.00
***17**[f]	0.19	0.18	0.0027	0.014	0.0002	0.0038	0.023	0.0005
***36**	0.00	0.0056	0.00	0.00	0.017	ND	ND	0.00
***41**[g]	0.10	0.10	0.092	0.22	0.022	0.10	0.057	0.00
***xN**[h]	0.075	0.043	0.028	0.067	0.015	0.013	0.033	0.088

***1xN*[i]	0.014	0.0044	0.0077	0.038	0.0031	0.0050	0.0078	0.11
***2xN*[i]	0.015	0.016	0.013	0.036	0.0042	0.0050	0.023	0.00
***4xN*[i]	0.014	0.020	0.0028	0.00	0.00	0.00	0.0036	0.00

Abbreviations are as follows: ND = not determined

[a]Average frequencies are based on the actual number of subjects with each allele reported in multiple studies. For full details and references please see http://www.pharmgkb.org/download.action?filename=CYP2D6_Literature_Table_and_Legend.pdf.

[b]Worldwide race/ethnic designations correspond to the Human Genome Diversity Project- Centre d'Etude du Polymorphisme Humain (HGDP-CEPH).[55,56]

[c]Because *CYP2D6*1* is not genotyped directly, all alleles that are negative for a sequence variation are defaulted to a *CYP2D6*1* assignment. Likewise, sequence variations of alleles that are not tested also default to a *CYP2D6*1* assignment and hence contribute to the frequencies reported for this allele. The inferred frequency for *CYP2D6*1* is calculated as: 1 - (sum of variant allele frequencies).

[d]*CYP2D6*2* is a 'default' assignment and, unless tested and discriminated for, *CYP2D6*8, *11, *17, *35,*41* along with other variants will default to a *CYP2D6*2* assignment. The frequencies shown here may therefore be over-estimated.

[e]*CYP2D6*10* is a 'default' assignment and, unless tested and discriminated for, *CYP2D6*14* and **36* along with other variants will default to a *CYP2D6*10* assignment. The frequencies shown here may therefore be over-estimated.

[f]*CYP2D6*17* is a 'default' assignment and, unless tested and discriminated for, *CYP2D6*40* and **58* will default to a *CYP2D6*17* assignment. The frequencies shown here may therefore be over-estimated.

[g]*CYP2D6*41* has not consistently been determined by its defining SNP (2988G>A) across studies; some platforms still use the -1584C>G SNP to discriminate between *CYP2D6*2* and **41*. This may lead to an overestimation of the *CYP2D6*41* frequency, especially in Africans and their descendants.

[h]*xN* denotes all gene duplications regardless of their nature. Alleles reported as *CYP2D6*2xN,* but not specifically discriminated from other duplications such as *CYP2D6*1xN or*4xN* were tabulated as *xN*.

[i]Frequencies calculated only from those studies which discriminated between gene duplications, that is studies that specified

duplications such as *CYP2D6*1xN, *2xN, or *4xN* were present. Because there may have been other duplications present and fewer studies had data for differentiated gene duplications, the sum of *CYP2D6*1xN, *2xN,* and **4xN* is less than the sum shown for *xN*. *xN* may also contain other alleles with gene rearrangements that test positive in a duplication assay, but do not carry duplications of identical gene units.

Supplemental Table S2. Frequencies[a] of *CYP2C19* alleles in major race/ethnic groups[b]

Allele	African	American	East Asian	European	Middle Eastern	Oceanian	South/Central Asian
***1*[c]	0.68	0.69	0.60	0.63	0.87	0.24	0.62
2	0.15	0.12	0.29	0.15	0.12	0.61	0.35
3	0.0052	0.00028	0.089	0.0042	0.011	0.15	0.024
4	0.00093	0.0024	0.00049	0.0025	ND	ND	0.00
5	ND	0.00	0.00062	0.000073	ND	ND	0.00
6	0.00	0.00	0.00	0.00017	ND	ND	0.00
8	0.00	0.0012	0.00	0.0035	ND	ND	ND
17	0.16	0.18	0.027	0.21	ND	ND	ND

Abbreviations are as follows: ND = not determined

[a]Average frequencies are based on the actual number of subjects with each allele reported in multiple studies.

[b]Worldwide race/ethnic designations correspond to the Human Genome Diversity Project- Centre d'Etude du Polymorphisme Humain (HGDP-CEPH)[55,56]

[c]Because *CYP2C19*1* is not genotyped directly, all alleles that are negative for a sequence variation are defaulted to a *CYP2C19*1* assignment. Likewise, sequence variations of alleles that are not tested also default to a *CYP2C19*1* assignment and hence contribute to the frequencies reported for this allele. The inferred frequency for *CYP2C19*1* is calculated as: 1 - (sum of variant allele frequencies).

Supplemental Table S3. Commonly tested polymorphisms defining *CYP2D6* variant alleles and their effect on CYP2D6 protein

Allele[a]	Major Nucleotide Variation[b,c]	dbSNP Number[d]	Effect on CYP2D6 Protein
1[e]	-	-	-
1xN	Gene duplication or multiplication	-	Increased protein expression
2[f]	2850C>T 4180G>C[g]	rs16947 rs1135840	R296C S486T
2xN	Gene duplication or multiplication	-	Increased protein expression
3	2549delA	rs35742686	Frameshift
4	100C>T, 1846G>A [4180G>C[g]]	rs1065852 rs3892097 rs1135840	P34S, splicing defect [S486T]
4xN	Gene duplication or multiplication	-	P34S, splicing defect
5	Gene deletion	N/A	Gene deletion
6	1707delT	rs5030655	Frameshift
9	2615delAAG	rs5030656	K281 deletion
10	100C>T 4180G>C[g]	rs1065852 rs1135840	P34S S486T
17	1023C>T 2850C>T 4180G>C[g]	rs28371706 rs16947 rs1135840	T107I R296C S486T
41	2850C>T 2988G>A 4180G>C[g]	rs16947 rs28371725 rs1135840	R296C Splicing defect S486T

[a]See Human Cytochrome P450 Allele Nomenclature Committee website (http://www.cypalleles.ki.se) for comprehensive haplotype definitions of *CYP2D6* variant alleles and updated allele information.

[b]All coordinates refer to accession #M33388 as detailed at http://www.cypalleles.ki.se/cyp2d6.htm. All variants are annotated to the negative DNA strand.

[c]Some alleles may carry multiple nucleotide variations. More specific details on the combinations of genetic variants present in each allele can be found at http://www.cypalleles.ki.se or http://www.pharmgkb.org. In addition, the specific genetic variants included in the genotyping assays that are used to distinguish each allele can be found in the assays' product insert.

[d]RefSNP accession ID number (*http://www.ncbi.nlm.nih.gov/snp/*).

[e]The *CYP2D6*1* allele is characterized by the absence of any sequence variations. Consequently, this allele cannot be identified by a SNP; rather *CYP2D6*1* is assigned by default when no SNPs are detected during testing.

[f]The *CYP2D6*2* allele is characterized by two amino acid changes; both, however also occur in many other alleles. Therefore, if an allele carries these two SNPs exclusively, it is designated *CYP2D6*2*. This is the only way to truly distinguish *CYP2D6*2* from other alleles (e.g., *CYP2D6*17* and **41*).

[g]This SNP is present on many allelic variants including functional and non-functional variants. Specifically, it has been found on some *CYP2D6*4* subvariants. While some tests include this SNP, it cannot be utilized to identify an allelic variant with certainty.

Supplemental Table S4. Association between allelic variants[a] and CYP2D6 enzyme activity

Functional Status[8,25]	Activity Value[b,c]	Alleles
Functional / normal activity / wild-type[d]	1	**1*[e], **2*, **27*, **33*, **35*, **45*[f], **46*[f], **39*, **48*, **53*
Reduced function / decreased activity	0.5	**9*, **10*, **17*, **29*, **41*, **49*, **50*, **54*, **55*, **59*, **69*, **72*
Non-functional / no activity	0	**3*, **4*, **5*, **6*, **7*, **8*, **11*, **12*, **13*, **14*, **15*, **16*, **18*, **19*, **20*, **21*, **31*, **36*, **38*, **40*, **42*, **44*, **47*, **51*, **56*, **57*, **62*

[a]See http://www.cypalleles.ki.se/cyp2d6.htm for updates on *CYP2D6* allelic variants and nomenclature.

[b]There are additional allelic variants for which the activity value is unknown, therefore no CYP2D6 activity score can be calculated. In such cases, the activity score may be estimated based on the second/known allele.

[c]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 (fully function) or 0 (non-functional). It should be noted that the CYP2D6 activity score is a nominal scale. For example, 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. The score of 0.5 indicates the allele has decreased metabolic activity compared to the wild-type allele when activity is measured towards probe substrates.

[d]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 may confer loss-of-function in an individual, and thus lead to the rare possibility of a non-functional allele being erroneously called as wild-type.

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

[f]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 (reduced function).

Supplemental Table S5. Commonly tested polymorphisms defining *CYP2C19* variant alleles and their effect on CYP2C19 protein

Allele[a]	Major Nucleotide Variation[b]	dbSNP Number[c]	Effect on CYP2C19 Protein
1	-	-	-
2	c.681G>A	rs4244285	Splicing defect
3	c.636G>A	rs4986893	W212X
4[d]	c.1A>G	rs28399504	M1V
5	c.1297C>T	rs56337013	R433W
6	c.395G>A	rs72552267	R132Q
7	c.819+2T>A	rs72558186	Splicing defect
8	c.358T>C	rs41291556	W120R
17[e]	c.-806C>T	rs12248560	Increased expression

[a]See Human Cytochrome P450 Allele Nomenclature Committee (*http://www.cypalleles.ki.se*) for comprehensive haplotype definitions of *CYP2C19* variant alleles and updated allele information.

[b]All coordinates refer to GenBank *CYP2C19* mRNA sequence M61854.1 as detailed at http://www.cypalleles.ki.se/cyp2c19.htm. All variants are annotated to the positive DNA strand.

[c]RefSNP accession ID number (*http://www.ncbi.nlm.nih.gov/snp/*).

[d]The *CYP2C19*4* loss-of-function allele has been identified in linkage disequilibrium with **17* (c.-806C>T) in certain ethnic subpopulations and this haplotype is designated *CYP2C19*4B*.[7,41]

[e]There is linkage disequilibrium between *CYP2C19*2* (c.681G) and *CYP2C19*17* (c.-806T). For instance, D'=1.0 and r^2=0.064 in CEU HapMap sample; D'=1.0 and r^2=0.065 in YRI HapMap sample; and D'=1.0 and r^2=0.074 in CHB HapMap sample.[7]

Supplemental Table S6. Association between allelic variants and CYP2C19 enzyme activity

Functional Status	Alleles	References
Functional / normal activity / wild-type[a]	**1*	57
Loss-of-function / no or decreased activity	**2, *3, *4, *5, *6, *7, *8*	58-64
Gain-of-function / increased activity	**17*	65-67

[a]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 may confer loss-of-function in an individual, and thus lead to the rare possibility of a non-functional allele being erroneously called as wild-type.

Supplemental Table S7. 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	EM
**1*	**17*	**1/*17*	1.5	EM
**2*	**3*	**2/*3*	1.0	EM
**1*	**4x2*[d]	**1/*4x2*	1.0	EM
**10*	**10*	**10/*10*[e]	1.0	EM[e]
**4*[d]	**10*	**4/*10*	0.5	IM
**5*	**6*	**5/*6*[f]	0	PM

Abbreviations are as follows: EM = extensive metabolizer, IM = intermediate metabolizer, PM = poor metabolizer, UM = ultrarapid metabolizer. Extensive 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 value for allele 1 and allele 2. The allele activity value is presented in Supplementary Table S4.

[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 non-functional 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 PM phenotype. The same may occur in the presence of *CYP2D7/2D6* hybrid genes.

Supplemental Table S8. Predicted metabolizer phenotypes based on *CYP2D6* diplotypes

Predicted Metabolizer Phenotype (Range Multi-Ethnic Frequency[a])											
Allele	***1***	***2***	***1xN or *2xN***	***3***	***4 or *4xN***	***5***	***6***	***9***	***10***	***17***	***41***
1	EM	EM	UM	EM	EM	EM	EM	EM	EM	EM	EM
2		EM	UM	EM	EM	EM	EM	EM	EM	EM	EM
1xN or *2xN			UM	EM or UM	EM or UM	EM or UM	EM or UM	UM	UM	UM	UM
3				PM	PM	PM	PM	IM	IM	IM	IM
4					PM	PM	PM	IM	IM	IM	IM
5						PM	PM	IM	IM	IM	IM
6							PM	IM	IM	IM	IM
9								EM[b]	EM[b]	EM[b]	EM[b]
10									EM[b]	EM[b]	EM[b]
17										EM[b]	EM[b]
41											EM[b]

Abbreviations are as follows: EM = extensive metabolizer, IM = intermediate metabolizer, PM = poor metabolizer, UM = ultrarapid metabolizer

[a]Frequencies of predicted metabolizer phenotypes can be estimated based on the frequencies provided in Supplementary Table S1.

[b]Note that some investigators may define patients with these diplotypes as intermediate metabolizers.

Supplemental Table S9. Predicted metabolizer phenotypes based on *CYP2C19* diplotypes

Predicted Metabolizer Phenotype (Range Multi-Ethnic Frequency[a])									
Allele	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***17*[b]**
1	EM	IM	IM	IM	IM	IM	IM	IM	UM
2		PM	PM	PM	PM	PM	PM	PM	IM[c]
3			PM	PM	PM	PM	PM	PM	IM[c]
4				PM	PM	PM	PM	PM	IM[c]
5					PM	PM	PM	PM	IM[c]
6						PM	PM	PM	IM[c]
7							PM	PM	IM[c]
8								PM	IM[c]
17									UM

Abbreviations are as follows: EM = extensive metabolizer, IM = intermediate metabolizer, PM = poor metabolizer, UM = ultrarapid metabolizer

[a]Frequencies of predicted metabolizer phenotypes can be estimated based on the frequencies provided in Supplementary Table S2.

[b]Due to conflicting data, the clinical importance of the *CYP2C19*17* allele is debated.[7,65-67,69-74] For patients carrying the *CYP2C19*17* allele (e.g., patients with a *CYP2C19*17/*17*, *CYP2C19*1/*17*, or *CYP2C19*2/*17* diplotype), strong clinical data is lacking to suggest that these patients should receive different tricyclic doses than wild-type (*CYP2C19*1/*1*) patients.

[c]The predicted phenotype is based on limited data; therefore, this is a provisional classification.[68,69]

Supplemental Table S10. Tricyclic antidepressant metabolism by CYP2D6 and CYP2C19

Parent drug	CYP2C19 metabolite[a]	CYP2D6 metabolite[b]	Therapeutic drug monitoring[c]
Amitriptyline[d]	**Nortriptyline[e,d]**	**hydroxy-amitriptyline**	**amitriptyline + nortriptyline**
Clomipramine[d]	**desmethyl-clomipramine[d]**	**hydroxy-clomipramine**	**clomipramine + desmethyl-clomipramine**
Desipramine[e,d]	--------	**hydroxy-desipramine**	**desipramine**
Doxepin[d]	**desmethyl-doxepin[d]**	**hydroxy-doxepin**	**doxepin + desmethyl-doxepin**
Imipramine[d]	**Desipramine[e,d]**	**hydroxy-imipramine**	**imipramine + desmethyl-imipramine**
Nortriptyline[e,d]	--------	**hydroxy-nortriptyline**	**nortriptyline**
Trimipramine[d]	**desmethyl-trimipramine[d]**	**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.[11]

[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.[75-77]

[d]Tricyclics are mixed serotonin and norepinephrine reuptake inhibitors. The tertiary amines amitriptyline, clomipramine, doxepin, imipramine, and trimipramine have a more pronounced serotonin reuptake inhibitor effect.[78-80] The secondary amines desmethyl-clomipramine, desmethyl-doxepin, desmethyl-trimipramine, desipramine, and nortriptyline have a more pronounced norepinephrine reuptake inhibitor effect.[78-80] *CYP2C19* or *CYP2D6* genetic variants may alter the ratio of tertiary to secondary amine plasma concentrations, thereby modulating antidepressant activity and side effects.[78]

[e]Desipramine and nortriptyline are the CYP2C19 metabolites of imipramine and amitriptyline respectively. It should be noted that desipramine and nortriptyline are antidepressant drugs themselves.

Supplemental Table S11. Tricyclic antidepressant side effects[a]

Amitriptyline	CYP2C19 metabolite (Nortriptyline)	CYP2D6 metabolites (hydroxy-amitriptyline, hydroxy-nortriptyline)
Anticholinergic Affects Blurred vision Constipation Dizziness Urinary retention Xerostomia Cardiotoxicity Arrhythmias Heart Block Orthostatic hypotension Tachycardia Central nervous system toxicity Delirium Seizures Dementia Headache Sedation	Anticholinergic Affects 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.[79]

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.[11] Tricyclics also bind α-adrenergic, serotonin and histamine receptors resulting in orthostatic hypotension and sedation.[81] 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.[75] Amitriptyline plus nortriptyline plasma concentrations above the recommended therapeutic range are also associated with central nervous system and cardiac toxicity.[82] Therefore, a CYP2D6 or CYP2C19 phenotype (e.g., a CYP2D6 or CYP2C19 poor metabolizer) that may result in increased plasma concentrations of tertiary or secondary amines could 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.[83-86] In elderly depressed patients, plasma concentrations of hydroxy-nortriptyline metabolites were associated with increases in QRS duration and QTc intervals.[87] Stern *et al.* found that desipramine and hydroxy-desipramine plasma concentrations may predict prolongation of cardiac conduction in young adults.[88] Because CYP2D6 metabolizes tricyclics to hydroxy-metabolites, CYP2D6 ultrarapid

metabolizers may have elevated hydroxy-metabolite plasma concentrations resulting in an increased risk for cardiotoxicity.[89] 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 CYP P450 genetic polymorphisms, CYP P450 inhibitors can influence 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.[90-93] 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.[8,94] 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.[11,82,95-100] 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.[11,81,82,95,101-108] 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 extensive (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 S12. Evidence linking CYP2D6 and/or CYP2C19 phenotype or genotype with amitriptyline metabolism or response

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major findings	References	Level of evidence[a]
Evidence linking CYP2D6 and/or CYP2C19 phenotype/genotype with amitriptyline metabolism or response			
Clinical	Seven healthy volunteers were administered a single dose of 75 mg amitriptyline. Poor CYP2D6 metabolizers determined by debrisoquine phenotyping had higher amitriptyline plasma concentrations.	Balant-Gorgia *et al*. 1982[109]	High
Clinical	Twelve adult males were administered 50 mg amitriptyline to determine the role of CYP2C19 in demethylation of amitriptyline. The 6 CYP2C19 poor metabolizers had a significantly higher amitriptyline AUC than the 6 extensive metabolizers. The poor metabolizers had a significantly lower nortriptyline AUC than the extensive metabolizers. CYP2C19 polymorphisms had a significant effect on amitriptyline demethylation, but not on drug clearance or half-life.	Jiang *et al*. 2002[110]	High
Clinical	In a Faroese patient group (n=23), no significant differences in the [(amitriptyline + nortriptyline plasma concentration)/dose] or median daily dose were found between extensive and poor CYP2D6 metabolizers. One poor metabolizer was found to exceed the recommended plasma concentration of amitriptyline + nortriptyline (130-325nM) with a concentration of 454nM. The median amitriptyline dose for all patients was 25 mg/day; therefore, one possible conclusion is that poor metabolizers taking lower doses of amitriptyline are not as likely to have plasma concentrations above the recommended therapeutic range.	Halling *et al*. 2008[111]	High
Clinical	The effect of *CYP2D6*4* was studied in 1198 elderly Dutch patients. Antidepressant dose, antidepressant switching, and discontinuation of therapy were the primary end points. A total of 807 patients were taking a tricyclic antidepressant, and for these patients the risk of switching to another antidepressant was significantly higher in CYP2D6 poor metabolizers than extensive metabolizers (OR = 5.77; 95% CI 1.59, 21.03; p=0.01). There was also an increased risk of poor metabolizers discontinuing therapy when compared to extensive metabolizers, but the difference was not significant (OR = 1.45; 95% CI 0.91, 2.32; p=0.12). Although the starting dose of tricyclics was initially similar, the maintenance dose for poor metabolizers was lower than extensive metabolizers. The majority of patients were taking amitriptyline (n=551), though other tricyclics included clomipramine (n=79), nortriptyline (n=35), imipramine (n=29), and doxepin (n=4).	Bijl *et al*. 2008[112]	High
Clinical	Sixteen depressed patients were treated with 150 mg/day amitriptyline for 3 weeks. Four patients were determined to be poor CYP2D6 metabolizers based on debrisoquine phenotyping, and 1 patient was determined to be a poor CYP2C19 metabolizer based on mephenytoin metabolism. Three of the 5 poor metabolizers were found to have the highest amitriptyline + nortriptyline plasma concentrations on day 22. The other 2 poor metabolizers were analyzed on day 15 and found to have higher amitriptyline +	Baumann *et al*. 1986[104]	High

	nortriptyline plasma concentrations than the non-poor metabolizers.		
Clinical	A total of 69 patients were investigated to determine the effect of *CYP2C19* genetic variants on the metabolic ratio (MR) of amitriptyline to nortriptyline. There was a significant difference in the logMR between patients with 2, 1 or no functional *CYP2C19* alleles.	van der Weide *et al*. 2005[113]	High
Clinical	Fifty Caucasian patients receiving 75 mg twice daily amitriptyline were investigated to determine if *CYP2C19* and *CYP2D6* genetic variants affect outcomes. Patients with two functional *CYP2D6* alleles (*CYP2D6*1, *2, *10, *41*) were found to be at a low or medium low risk of side effects, and patients with at least one non-functional *CYP2D6* allele (*CYP2D6*4*) were found to be at a medium high to high risk of side effects. Additionally, particular combinations of *CYP2D6* and *CYP2C19* genetic variants had an effect upon side effect risk.	Steimer *et al*. 2005[114]	High
Clinical	Prospective, blinded two-center study investigating the effect of *CYP2C19* and *CYP2D6* genetic variants on drug concentrations in 50 patients receiving amitriptyline 75 mg twice daily. *CYP2C19* heterozygotes (*CYP2C19*1/*2*) had higher amitriptyline and lower nortriptyline plasma concentrations than wild-types, but there was no change between groups in the total plasma concentrations for amitriptyline + nortriptyline. *CYP2D6*41*, **10* and **4* were associated with a 1.95, 2.67 and 3.83 fold increase respectively in the metabolic ratio of nortriptyline to hydroxy-nortriptyline. Based on the pharmacokinetic data, a semiquantitative gene dose of 1 was assigned to functional alleles, 0.5 for *CYP2D6*10* and **41*, and 0 for *CYP2D6 *4*. This gene dose is comparable to the allele activity values in Supplementary Table S4.	Steimer *et al*. 2004[115]	High
Clinical	A total of 678 Dutch patients were investigated to determine the effect of *CYP2D6* and *CYP2C19*, in particular *CYP2C19*17*, on drug metabolism. One hundred and fifty patients were taking amitriptyline. Patients carrying a *CYP2C19*2* allele had significantly higher amitriptyline plasma concentrations, but *CYP2C19* genetic variants did not alter amitriptyline + nortriptyline plasma concentrations. *CYP2C19*17* and *CYP2D6* non-functional alleles were significantly associated with patients having an elevated nortriptyline plasma concentration above the recommended range (50-150 ug/L)	de Vos *et al*. 2011[69]	High
Clinical	Fifty Japanese psychiatric patients were administered an average of 101.1 $\pm$ 53.7 mg/day of amitriptyline. Significantly higher plasma concentrations of amitriptyline were observed in patients with two variant *CYP2C19* alleles versus patients with no variant *CYP2C19* alleles. There was a trend towards a higher ratio of nortriptyline to its metabolite in patients with two variant *CYP2D6* alleles. However, no poor CYP2D6 metabolizers as defined by this guideline were included in the patients carrying two variant *CYP2D6* alleles, which may explain why the results were not significant.	Shimoda *et al*. 2002[105]	High
Clinical	A case report of a patient determined to have a low debrisoquine metabolic ratio (indicates rapid CYP2D6 metabolism) and a *CYP2D6* gene duplication. The patient had a low plasma concentration of	Bertilsson *et al*. 1993[116]	Moderate

	amitriptyline + nortriptyline during amitriptyline therapy. Another study demonstrated a relationship between the number of functional *CYP2D6* genes and debrisoquine metabolism.	Bertilsson *et al.* 1985[89] Johansson *et al*. 1993[117]	
Clinical	A total of 136 depressed patients treated with antidepressants were genotyped for *CYP2D6*, *CYP2C19*, and *CYP2C9*. A CYP2D6 ultrarapid metabolizer was reported to have a 6% increased plasma concentration of amitriptyline + nortriptyline. A CYP2C19 poor metabolizer had a 133% increased amitriptyline + nortriptyline plasma concentration.	Grasmader *et al*. 2004[118]	Moderate
Clinical	Eleven healthy non-smokers were administered a single dose of 50 mg amitriptyline. Individuals with a higher debrisoquine to 4-OH-debrisoquin metabolic ratio (poor CYP2D6 metabolism) had slower clearance of amitriptyline.	Mellstrom *et al*. 1986[119]	Moderate
Clinical	A 55 year old Caucasian woman determined to be a CYP2D6 poor metabolizer (*CYP2D6*4/*4*) demonstrated slow clearance of amitriptyline following an intentional overdose.	Smith *et al*. 2011[120]	Moderate
Clinical	A series of 202 postmortem toxicology cases were examined to investigate the role of *CYP2D6* and *CYP2C19* genetic variants in amitriptyline metabolism. The number of functional *CYP2D6* alleles was correlated to the plasma concentrations of nortriptyline and its hydroxy-metabolites, and the number of *CYP2C19* alleles was correlated to the plasma concentrations of amitriptyline and its metabolite nortriptyline. The presence of functional *CYP2D6* or *CYP2C19* alleles resulted in lower amitriptyline or nortriptyline plasma concentrations, respectively.	Koski *et al*. 2006[121]	Moderate
Clinical	In 26 hospitalized depressed patients there was a positive correlation between nortriptyline plasma concentrations and the logMR (metabolic ratio) of dextromethorphan, and a positive correlation between amitriptyline plasma concentrations and the logMR of mephenytoin.	Breyer-Pfaff *et al*. 1992[122]	Moderate

[a]The grading system for evidence is explained in the section *level of evidence* located in the introduction.

Supplemental Table S13. Evidence linking CYP2D6 phenotype or genotype with nortriptyline metabolism or response

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major findings	References	Level of evidence[a]
Evidence linking CYP2D6 phenotype/genotype with nortriptyline metabolism or response			

Clinical	*CYP2D6* genotypes and nortriptyline plasma concentrations were obtained from 16 healthy Korean individuals. Subjects carrying at least one reduced function or non-functional *CYP2D6* allele had a longer nortriptyline half-life along with a larger maximum plasma concentration and AUC than subjects carrying only functional alleles or duplicated functional alleles.	Lee *et al*. 2006[123]	High
Clinical	Fifteen healthy Chinese volunteers were administered 25 mg nortriptyline and then analyzed for the effect of *CYP2D6*10* on plasma concentrations. *CYP2D6*10*10* subjects had a significantly higher half-life and AUC of nortriptyline and a significantly lower oral clearance when compared to *CYP2D6*1/*1* or *CYP*1/*10* individuals. No significant differences in nortriptyline half-life, AUC, or oral clearance were noted between *CYP2D6*1/*1* and *CYP2D6*1/*10* individuals.	Yue *et al*. 1998[124]	High
Clinical	Ten healthy Korean volunteers were given a single dose of 20 mg debrisoquine and 25 mg nortriptyline on separate occasions to study the influence of *CYP2D6*10* on disposition of these drugs. The AUC of 4-hydroxydebrisoquine was significantly lower in *CYP2D6*1/*10* individuals than *CYP2D6*1/*1* individuals. However no significant differences in nortriptyline plasma concentrations were noted between *CYP2D6*1/*10* and *CYP2D6*1/*1* individuals.	Dalen *et al*. 2003[125]	High
Clinical	Twenty-one healthy Caucasian subjects were given a single dose of 25 mg nortriptyline. Nortriptyline clearance was positively correlated with the number of functional *CYP2D6* genes present.	Dalen *et al*. 1998[126] Kvist *et al*. 2001[127]	High
Clinical	Twenty-three healthy Ghanaian (n=11) and Swedish (n=12) subjects were administered a single dose of 28.5 mg nortriptyline to investigate the correlation between nortriptyline and debrisoquine metabolism. Individuals with a higher metabolic ratio of debrisoquine (indicator of slow CYP2D6 metabolism) had slower clearance of nortriptyline.	Woolhouse *et al*. 1984[128]	High
Clinical	Thirty-six geriatric patients taking concurrent medications were investigated to determine if nortriptyline plasma concentrations can be predicted by *CYP2D6* genotyping. Patients were divided into extensive metabolizers (*CYP2D6*1/*2, *1/*10B, *1/*1*) or impaired metabolizers (*CYP2D6*1/*4A, *2/*4A, *2/*10B, *1/*3, *2/*2, *10B/*5, *3/*4A, *4A/*4A*). Although the impaired metabolizers were taking a significantly lower nortriptyline dosage than extensive metabolizers, the impaired metabolizers had significantly higher nortriptyline plasma concentrations.	Murphy *et al*. 2001[129]	High
Clinical	Among 21 depressed patients taking 100-150 mg/day nortriptyline, a CYP2D6 poor metabolizer was found to have the highest nortriptyline plasma concentration. There was not a significant difference in nortriptyline plasma concentrations between patients with two function *CYP2D6* genes or one functional and one non-functional *CYP2D6* gene. However, patients with one functional and one non-functional *CYP2D6* gene had significantly lower plasma concentrations of 10-OH-nortritpyline.	Dahl *et al*. 1996[107] Kvist *et al*. 2001[127]	High
Clinical	Side effects were analyzed in patients taking tricyclic antidepressants including nortriptyline along with amitriptyline, desipramine, clomipramine and imipramine. High dextromethorphan metabolic ratios (indicates poor CYP2D6 metabolism) were associated with the reporting of adverse effects. Patients carrying a deficient *CYP2D6* gene had a significantly higher rate of reporting side effects.	Chen *et al*. 1996[130]	High
Clinical	The impact of *CYP2D6* genotypes on nortriptyline steady-state plasma concentrations were studied in	Morita *et al*.	High

	41 Japanese psychiatric patients. The patients were divided into three groups as follows: patients carrying 0, 1, or 2 *CYP2D6* variant alleles. Nortriptyline plasma concentrations corrected for weight and dose were significantly higher in patients with 1 or 2 variant *CYP2D6* alleles when compared to patients with 0 variant alleles.	2000[131]	
Clinical	Twenty depressed patients were treated with nortriptyline for at least 3 weeks. The nortriptyline plasma concentrations correlated with debrisoquine metabolic ratio, with higher nortriptyline plasma concentrations observed in slower debrisoquine metabolizers (indicates slow CYP2D6 metabolism).	Nordin *et al*. 1985[132] Kvist *et al*. 2001[127]	High
Clinical	In 8 healthy volunteers the clearance of nortriptyline was positively related to debrisoquine metabolism. The slowest metabolizers of debrisoquine (indicates slow CYP2D6 metabolism) had lower total clearance of nortriptyline.	Bertilsson *et al*. 1980[133]	Moderate
Clinical	The correlation of nortriptyline metabolism to debrisoquine metabolism was studied in 8 healthy subjects administered a single dose of 28.5 mg nortriptyline. Individuals with a higher metabolic ratio of debrisoquine (indicator of slow CYP2D6 metabolism) had a higher nortriptyline AUC.	Mellstrom *et al.* 1981[134]	Moderate
Clinical	A 54 year old patient received 150 mg/day nortriptyline. The patient experienced side effects and had a higher plasma concentration than expected (470.6 ng/ml). A genotype test demonstrated that the patient had one deleted *CYP2D6* gene and one reduced function *CYP2D6* allele (*CYP2D6*5/*10B*).	Lee *et al*. 2004[135]	Moderate
Clinical	A patient determined to have a low debrisoquine metabolic ratio (indicates rapid CYP2D6 metabolism) required 500 mg/day nortriptyline to achieve a therapeutic plasma concentration. The patient was found to have a *CYP2D6* gene duplication. Another study demonstrated a relationship between the number of functional *CYP2D6* genes and debrisoquine metabolism.	Bertilsson *et al*. 1993[116] Bertilsson *et al.* 1985[89] Johansson *et al*. 1993[117]	Moderate
Clinical	A 69 year old female was prescribed 25 mg nortriptyline administered three times daily. The patient experienced side effects and the nortriptyline plasma concentration was found to be 1300 nmol/L (usual range 200-600 nmol/L). The patient was phenotyped using the probe drug debrisoquine and found to be a CYP2D6 poor metabolizer.	Bertilsson *et al*. 1981[18]	Moderate

[a]The grading system for evidence is explained in the section *level of evidence* located in the introduction.

Supplemental Table S14. Evidence linking CYP2D6 and/or CYP2C19 phenotype or genotype with clomipramine metabolism or response

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major findings	References	Level of evidence[a]
Evidence linking CYP2D6 and/or CYP2C19 phenotype/genotype with clomipramine metabolism or response			
Clinical	A total of 25 healthy subjects were phenotyped using the probe drugs sparteine and mephenytoin. Nine	Nielsen *et al*.	High

	subjects were poor CYP2D6 metabolizers, 5 subjects were poor CYP2C19 metabolizers, and 1 subject was both a poor CYP2D6 and CYP2C19 metabolizer. When compared to the extensive metabolizers, CYP2D6 or CYP2C19 poor metabolizers had a significantly lower clearance of clomipramine.	1994[136]	
Clinical	A total of 678 Dutch patients were investigated to determine the effect of *CYP2D6* and *CYP2C19*, in particular *CYP2C19*17*, on drug metabolism. Two hundred and forty-four patients were taking clomipramine. Over all there was no clear trend between *CYP2C19* genetic variants and clomipramine or desmethyl-clomipramine plasma concentrations. However, *CYP2C19*2/*2* patients had a significantly higher metabolic ratio of clomipramine to desmethyl-clomipramine than *CYP2C19*1/*1* patients. *CYP2C19*17/*17* patients had a significant association with subtherapeutic clomipramine plasma concentrations. No statistically significant effects were observed between *CYP2D6* genetic variants and clomipramine or desmethyl-clomipramine plasma concentrations.	de Vos *et al*. 2011[69]	High
Clinical	A total of 45 depressed Caucasian patients treated with clomipramine were genotyped for *CYP2D6* and phenotyped with dextromethorphan. There was a significant correlation between reported side effects and slower dextromethorphan metabolism (indicates slow CYP2D6 metabolism). There was a trend for higher reported side effects with patients carrying a non-functional *CYP2D6* gene.	Vandel *et al*. 2004[137]	High
Clinical	The effect of *CYP2D6* and *CYP2C19* genetic variants on the metabolism of clomipramine was studied in 51 Japanese psychiatric patients administered 10 to 250 mg/day clomipramine. There was a significant correlation with increasing clomipramine plasma concentrations and the number of variant *CYP2C19* alleles. No significant correlation was found between desmethyl-clomipramine plasma concentrations and the number of variant *CYP2D6* alleles. However, as defined by phenotype assignment in this CPIC guideline all patients in this study would have been CYP2D6 extensive metabolizers.	Yokono *et al*. 2001[138]	High
Clinical	One hundred and nine depressed patients enrolled on a clomipramine dose-effect study were phenotyped with sparteine (probe drug used to determine CYP2D6 metabolizer status). When compared to extensive metabolizers, poor metabolizers had a significantly higher desmethyl-clomipramine plasma concentration and a significantly higher clomipramine + desmethyl-clomipramine plasma concentration.	DUAG 1999[139]	High
Clinical	A total of 36 depressed patients were treated with 75 mg clomipramine twice daily. The patients were phenotyped using the probe drug sparteine (used to determine CYP2D6 metabolizer status). When compared to extensive metabolizers, CYP2D6 poor metabolizers had a significantly higher desmethyl-clomipramine plasma concentration.	Nielsen *et al*. 1992[140]	High
Clinical	A patient prescribed 150-225 mg/day clomipramine had low plasma concentrations of clomipramine and desmethyl-clomipramine. The patient was found to have a duplication of a functional *CYP2D6* gene.	Baumann *et al*. 1998[141]	Moderate
Clinical	A psychiatric patient was initiated with 150 mg clomipramine daily, but no response to the drug was observed and the dose was increased to 225 mg/day. The plasma concentrations of the drug were much	Bertilsson *et al*. 1993[116]	Moderate

	lower than expected and the dose was further increased to 300 mg/day. The patient was found to have a *CYP2D6* gene duplication.	Traskman *et al*. 1979[142]	
Clinical	A 47-year-old male patient experienced multiple adverse drug reactions during therapy with clomipramine 225-300 mg/day and quetiapine 700 mg/day. Plasma concentrations were elevated (clomipramine + desmethyl-clomipramine 1228 ng/ml), and the patient was found to be a CYP2D6 poor metabolizer (*CYP2D6*4/*6*). After reduction of the clomipramine dose to 75 mg/day and discontinuation of quetiapine, all adverse drug reactions resolved except for increased liver enzymes. The plasma concentration after dose reduction was 374 ng/ml clomipramine + desmethyl-clomipramine.	Stephan *et al*. 2006[143]	Moderate
Clinical	A patient taking 100 mg/day clomipramine was noted to have elevated plasma concentrations of the drug as follows: 148 ng/ml clomipramine and 450 ng/ml desmethyl-clomipramine. Although the dose was decreased, plasma concentrations continued to increase. The patient was found to be a CYP2D6 poor metabolizer by debrisoquine phenotyping.	Balant-Gorgia *et al*. 1987[144]	Moderate
Clinical	A depressed patient was prescribed clomipramine 150 mg/day. After three weeks no clinical improvement was noted. The plasma concentration of clomipramine was 235 ng/ml and the desmethyl-clomipramine plasma concentration was 980 ng/ml. The patient was found to be a CYP2D6 poor metabolizer by debrisoquine phenotyping. A dose of 50 mg/day lead to improvement of depressive symptoms and resulted in plasma concentrations of 60 ng/ml clomipramine and 165 ng/ml desmethyl-clomipramine. A second patient was prescribed clomipramine 225 mg/day. The patient had no improvement in depressive symptoms and experienced side effects. The plasma concentration of clomipramine was 160 ng/ml and the desmethyl-clomipramine plasma was 960 ng/ml. The patient was found to be a CYP2D6 poor metabolizer by debrisoquine phenotyping.	Balant-Gorgia *et al*. 1989[93]	Moderate

[a]The grading system for evidence is explained in the section *level of evidence* located in the introduction.

Supplemental Table S15. Evidence linking CYP2D6 phenotype or genotype with desipramine metabolism or response

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major findings	References	Level of evidence[a]
Evidence linking CYP2D6 phenotype/genotype with desipramine metabolism or response			
In Vitro and Clinical	A single oral dose of 25 mg desipramine was given to 18 healthy subjects phenotyped by the probe drug debrisoquine. Individuals with a higher debrisoquine metabolic ratio, indicative of CYP2D6 poor metabolism, had a higher desipramine to hydroxy-desipramine ratio. There was a statistically significant correlation between debrisoquine metabolism and desipramine metabolism in human liver microsomes. Competitive inhibition studies demonstrated desipramine	Spina *et al*. 1984[145]	High

	metabolism was dependent on CYP2D6 enzyme activity.		
Clinical	The impact of CYP2D6 phenotype, determined by the probe drug sparteine, on desipramine hydroxylation was studied in patients administered 100 mg desipramine orally. Poor metabolizers had a significantly higher half-life and lower clearance of desipramine when compared to extensive metabolizers.	Brosen *et al*. 1986[146]	High
Clinical	The impact of CYP2D6 phenotype, determined by the probe drug sparteine, on first pass metabolism was studied in patients administered 50 mg desipramine intravenously. Poor metabolizers had a significantly higher half-life and lower clearance of desipramine when compared to extensive metabolizers.	Brosen *et al*. 1988[147]	High
Clinical	The effect of *CYP2D6* genetic variants on desipramine hydroxylation was studied in 223 Swedish subjects administered a single dose of 10 mg desipramine. Individuals were genotyped and phenotyped using the probe drugs debrisoquine and desipramine. The accuracy was 99% between predicted phenotype based on genotyping and the metabolic ratio of debrisoquine. There was a significant correlation between the metabolic ratios of debrisoquine and desipramine.	Dahl *et al*. 1992[148]	High
Clinical	Fourteen healthy volunteers were divided into rapid (n=8) or slow (n=6) metabolizer groups based on debrisoquine phenotyping. Desipramine AUC and half-life were significantly higher in poor metabolizers when compared to rapid metabolizers. The clearance of desipramine was also significantly lower in poor metabolizers.	Spina *et al*. 1987[149]	High
Clinical	The effect of CYP2D6 inhibition, using the moderate inhibitor cimetidine, on desipramine metabolism was studied in 9 subjects administered a single dose of 25 mg desipramine. The individuals were phenotyped using the probe drug debrisoquine and divided into two groups, rapid (n=5) and slow (n=4) metabolizers. Desipramine AUC and half-life were significantly greater in slow metabolizers than rapid metabolizers. The co-administration of 1200 mg cimetidine did not alter the pharmacokinetics of slow metabolizers, but the AUC and half-life of desipramine did increase in rapid metabolizers.	Steiner *et al*. 1987[92]	High
Clinical	The impact of *CYP2D6* reduced function alleles on desipramine pharmacokinetics was studied in 16 subjects administered a single dose of 100 mg desipramine. The pharmacokinetic properties (half-life, Cmax, AUC, and metabolic ratio) were similar between subjects carrying two functional alleles, a functional and reduced function allele, a functional and non-functional allele, or two reduced functional alleles. An individual with one reduced function and one non-functional allele had a higher AUC, half-life and metabolic ratio.	Furman *et al*. 2004[150]	High
Clinical	The impact of *CYP2D6* genetic variants on the metabolism of desipramine was studied in 18 Japanese psychiatric patients administered 50-250 mg/day desipramine. There was a significant correlation between the metabolic ratio of desipramine and the number of *CYP2D6* variant alleles, with a higher metabolic ratio (slower metabolism) observed in patients with two variant alleles. Patients with two variant alleles also had a significantly higher plasma concentration of desipramine.	Shimoda *et al*. 2000[151]	High
Clinical	The relationship between CYP2D6 phenotype, desipramine plasma concentrations, and clinical	Spina *et al*. 1997[101]	High

	response were studied in 31 patients treated with 100 mg/day desipramine for three weeks. The patients were phenotyped using the probe drug dextromethorphan. There was a significant correlation between desipramine plasma concentrations and dextromethorphan metabolic ratio, with slower dextromethorphan metabolizers (CYP2D6 poor metabolizers) having higher desipramine plasma concentrations. The two patients classified as CYP2D6 poor metabolizers experienced side effects and required a dose reduction to 50 mg/day.		
Clinical	Among 35 depressed patients treated with 75 mg twice daily desipramine, 10 were selected for debrisoquine phenotyping and determination of desipramine plasma concentrations. There was a strong correlation between steady-state desipramine plasma concentrations and the debrisoquine metabolic ratio, with higher desipramine concentrations correlating with higher debrisoquine metabolic ratios (indicates slower metabolism).	Bertilsson *et al*. 1983[152]	Moderate
Clinical	The effect of *CYP2D6* duplications was studied in 12 subjects (6 with duplications) after a single dose of 100 mg desipramine. Although not statistically significant, the individuals with *CYP2D6* duplications had a higher clearance (373 L/hr) of desipramine than the individuals with no duplications (196 L/hr).	Bergmann *et al*. 2001[153]	Moderate
Clinical	A 46 year old Caucasian male with chronic major depression was prescribed 250 mg/day desipramine. The patient experienced cardiotoxicity and was found to have a desipramine plasma concentration of 764 ng/ml (usual range 50-250). Based on debrisoquine phenotyping the patient was found to be a CYP2D6 poor metabolizer.	Bluhm *et al*. 1993[154]	Moderate

[a]The grading system for evidence is explained in the section *level of evidence* located in the introduction.

Supplemental Table S16. Evidence linking CYP2D6 and/or CYP2C19 phenotype or genotype with doxepin metabolism or response

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major findings	References	Level of evidence[a]
Evidence linking CYP2D6 and/or CYP2C19 phenotype/genotype with doxepin metabolism or response			
In Vitro	CYP2C19 was demonstrated to substantially contribute to the metabolism of doxepin to desmethyl-doxepin. Inhibition experiments showed that the formation of desmethyl-doxepin was correlated to CYP2C19 enzymatic activity.	Hartter *et al*. 2002[155]	High
In Vitro	CYP2D6 was demonstrated to be the major enzyme of doxepin hydroxylation. Inhibition experiments showed that metabolism of doxepin, particularly the E-isomer, was correlated to CYP2D6 enzymatic activity.	Haritos *et al*. 2000[156]	High
Clinical	The contribution of CYP2D6 and CYP2C19 to the metabolism of doxepin was studied in 42 healthy volunteers administered a single dose of 75 mg doxepin. The volunteers were divided into poor,	Kirchheiner *et al*.	High

	intermediate or extensive metabolizers. There was a significant correlation between the number of *CYP2D6* non-functional alleles and oral clearance, plasma concentration, and half-life of doxepin and its desmethyl-metabolite. There was a significant correlation between the number of *CYP2C19* non-functional alleles and oral clearance of doxepin.	2002[157]	
Clinical	The impact of CYP2D6 ultrarapid metabolism on doxepin was studied in a total of 25 healthy volunteers administered a single dose of 75 mg doxepin. Ultrarapid CYP2D6 metabolizers were found to have a significantly lower maximum plasma concentration (Cmax) and AUC of the active compounds of the drug [(E,Z)-doxepin and (E,Z)-desmethyldoxepin] when compared to extensive metabolizers. Although the study was designed to determine the effects of CYP2D6 ultrarapid metabolism on doxepin, poor metabolizers were noted to have a higher Cmax and AUC of the active compounds when compared to extensive metabolizers.	Kirchheiner *et al*. 2005[158]	High
Clinical	A post mortem toxicology report showed a fatal doxepin poisoning. The blood concentration of doxepin was 2.4 mg/L, which is 16-80 times higher than therapeutic concentrations (0.03-0.15 mg/L). The individual was found to be a CYP2D6 poor metabolizer (*CYP2D6*3/*4*).	Koski *et al*. 2007[159]	Moderate
Clinical	The debrisoquine metabolic ratio of four patients with elevated doxepin plasma concentrations was compared to 4 patients with normal doxepin plasma concentrations that were matched for sex, age and dose. No CYP2D6 poor metabolizers were in the group with normal doxepin levels, but 50% of the patients with elevated doxepin levels were determined to be CYP2D6 poor metabolizers.	Tacke *et al*. 1992[160]	Moderate

[a]The grading system for evidence is explained in the section *level of evidence* located in the introduction.

Supplemental Table S17. Evidence linking CYP2D6 and/or CYP2C19 phenotype or genotype with imipramine metabolism or response

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major findings	References	Level of evidence[a]
Evidence linking CYP2D6 and/or CYP2C19 phenotype/genotype with imipramine metabolism or response			
In Vitro	The metabolism of imipramine was studied in human liver microsomes. The formation of 2-hydroxyimipramine was dependent on CYP2D6 enzyme activity.	Brosen *et al*. 1991[161]	High
Clinical	The relationship between CYP2D6 phenotype, determined by sparteine phenotyping, and imipramine metabolism was investigated in families of 18 Danish poor metabolizers. The hydroxylation ratios (measurement of imipramine metabolism) were lower in poor metabolizers when compared to extensive metabolizers.	Madsen *et al*. 1996[162]	High
Clinical	Imipramine metabolism was studied in 327 healthy subjects following a single dose of 25 mg imipramine. The subjects were phenotyped using the probe drugs sparteine and mephenytoin. Hydroxylation ratios were higher in the CYP2D6 extensive metabolizers when compared to the poor	Madsen *et al*. 1995[163]	High

	metabolizers. There was a significant correlation with mephenytoin metabolism and demethylation ratios.		
Clinical	The impact of CYP2D6 phenotype, determined by the probe drug sparteine, on imipramine metabolism was studied in patients administered 100 mg imipramine orally. Poor metabolizers had significantly lower clearance of imipramine, but no statistically significant differences were observed in imipramine demethylation. The ratio of AUC desmethyl-imipramine to AUC imipramine was significantly higher in poor metabolizers.	Brosen *et al*. 1986[146]	High
Clinical	Imipramine metabolism was studied in 16 healthy subjects following a single dose of 25 mg imipramine. The subjects were phenotyped using the probe drugs metoprolol and mephenytoin and classified into three groups as follows: CYP2D6 extensive/CYP2C19 poor metabolizer, CYP2D6 poor/CYP2C19 extensive metabolizer, and CYP2D6/CYP2C19 extensive metabolizer. The clearance of imipramine was significantly lower in CYP2D6 extensive/CYP2C19 poor metabolizers when compared to CYP2D6/CYP2C19 extensive metabolizers. The AUC of desipramine was significantly greater in CYP2D6 poor/CYP2C19 extensive metabolizes than CYP2D6/CYP2C19 extensive metabolizers.	Koyama *et al*. 1994[164]	High
Clinical	The effect of *CYP2C19*17* on the metabolism of imipramine was studied in 178 depressed patients. The mean dose-corrected imipramine plasma concentration was significantly lower in *CYP2C19*17/*17* patients when compared to *CYP2C19*1/*1* patients. However, the mean dose-corrected imipramine + desipramine plasma concentrations were not significantly different between *CYP2C19* genotypes.	Schenk *et al*. 2010[74]	High
Clinical	The relationship between CYP2D6 phenotype, determined using the probe drug sparteine, and steady-state concentrations of imipramine was investigated in 35 patients treated with 100 mg/day imipramine. Poor metabolizers had a higher imipramine + desipramine plasma concentration than extensive metabolizers.	Brosen *et al*. 1986[165]	High
Clinical	The ability to predict drug dose using *CYP2D6* genotypes was investigated in 181 depressed patients treated with imipramine. Patient carrying only non-functional *CYP2D6* alleles had the lowest dose requirement (131 $\pm$ 109 mg/day) while patients with *CYP2D6* duplications had the highest dose requirement (509 $\pm$ 292 mg/day). There was a significant correlation between required imipramine dose and the number of variant *CYP2D6* alleles present.	Schenk *et al*. 2008[166]	High
Clinical	The effect of *CYP2C19* genetic variants on imipramine metabolism was studied in 10 depressed Japanese patients. Demethylation of imipramine was significantly lower in patients carrying *CYP2C19* variants, and plasma concentrations of imipramine + 2-hydroxyimiprmaine were significantly higher.	Morinobu *et al*. 1997[167]	High
Clinical	Imipramine steady-state concentrations were studied in 28 Japanese patients with major depression. Five of the patients were CYP2C19 poor metabolizers determined by mephenytoin phenotyping. All patients were CYP2D6 extensive metabolizers determined by metoprolol phenotyping. The CYP2C19 poor metabolizers had a 2.4 times greater imipramine plasma concentration and a 1.8 times greater imipramine + desipramine plasma concentration.	Koyama *et al*. 1996[168]	High

Clinical	Nineteen diabetic patients treated with imipramine for peripheral neuropathy were phenotyped with sparteine. Imipramine doses required to achieve therapeutic plasma concentrations were 20-25 mg/day in two poor metabolizers, 50 mg in extensive metabolizers, and 350 mg in a rapid metabolizer. In the extensive metabolizers, the concentration/dose ratio increased for imipramine and desipramine with increasing dose.	Sindrup *et al*. 1990[169]	High
Clinical	One hundred and six healthy subjects all CYP2D6 extensive metabolizers were phenotyped with mephenytoin and given a single dose of 25 mg imipramine. The desipramine/imipramine ratio and the 2-hydroxy desipramine/2-hydroxy imipramine ratios showed significant negative correlations with the mephenytoin S/R ratio.	Skjelbo *et al*. 1993[170]	High
Clinical	Twenty-two healthy subjects all CYP2D6 extensive metabolizers, except for 1 CYP2D6 poor metabolizer, received 100 mg imipramine (50 mg CYP2D6 poor metabolizer) and were phenotyped with mephenytoin. The 6 CYP2C19 poor metabolizers showed significant lower oral clearance, demethylation, and a reduced desipramine/imipramine ratio.	Skjelbo *et al*. 1991[171]	High
Clinical	CYP2C19 was demonstrated to have a dominant role in demethylation of imipramine when compared to CYP1A2 or CYP3A4.	Madsen *et al*. 1997[172]	Moderate
Clinical	A depressed patient was prescribed imipramine up to 150 mg/day. The patient did not improve and side effects were noted. The plasma concentration of imipramine was 125 ng/ml and the plasma concentration of desmethyl-imipramine was 1730 ng/ml. The patient was found to be a CYP2D6 poor metabolizer by debrisoquine phenotyping. Three other patients taking imipramine in combination with CYP2D6 inhibitors were found to have elevated plasma concentrations of imipramine and desmethyl-imipramine.	Balant-Gorgia *et al*. 1989[93]	Moderate

[a]The grading system for evidence is explained in the section *level of evidence* located in the introduction.

Supplemental Table S18. Evidence linking CYP2D6 and/or CYP2C19 phenotype or genotype with trimipramine metabolism or response

Type of experimental model (in vitro, in vivo preclinical, or clinical)	Major findings	References	Level of evidence[a]
Evidence linking CYP2D6 and/or CYP2C19 phenotype/genotype with trimipramine metabolism or response			
Clinical	The contribution of CYP2D6 and CYP2C19 to the metabolism of trimipramine was studied in 42 healthy volunteers administered a single dose of 75 mg trimipramine. The individuals were divided into poor, intermediate or extensive metabolizers. There was a significant decrease in clearance and increased half-life of trimipramine in intermediate and poor CYP2D6 metabolizers when compared to extensive metabolizers, and there was a significant increase in the AUC of both trimipramine and desmethyl-trimipramine observed in intermediate and poor CYP2D6 metabolizers. There was a significant decrease in clearance and increased half-life of trimipramine in intermediate and poor CYP2C19 metabolizers when compared to extensive metabolizers, and there was a significant increase in the AUC of trimipramine observed in intermediate and poor CYP2C19 metabolizers. CYP2C19 poor metabolizers had a significantly lower desmethyl-trimipramine AUC than extensive metabolizers.	Kirchheiner *et al*. 2003[173]	High
Clinical	Trimipramine pharmacokinetics was studied in poor (n=5), extensive (n=7), and ultrarapid (n=3) metabolizers of CYP2D6. The oral bioavailability was significantly higher in poor metabolizers and the clearance significantly lower. In ultrarapid metabolizers, the oral bioavailability was significantly lower and the clearance significantly higher.	Kirchheiner *et al*. 2003[174]	High
Clinical	The pharmacokinetics and pharmacodynamics of trimipramine were studied in 2 healthy subjects following a single dose of 75 mg trimipramine on two separate occasions. Quinidine, an inhibitor of CYP2D6, was given with the second administration to mimic poor CYP2D6 metabolism. In the presence of quinidine, the half-life of trimipramine increased and the clearance of the drug decreased. EEG changes were noted as well when quinidine was administered in combination with trimipramine.	Eap *et al*. 1992[91]	Moderate
Clinical	Twenty-seven schizophrenic patients received 300-400 mg/day trimipramine. One patient was found to be a CYP2D6 poor metabolizer based on dextromethorphan phenotyping and one patient was found to be a CYP2C19 poor metabolizer based on mephenytoin phenotyping. The CYP2D6 poor metabolizer had higher plasma concentrations of desmethyl-trimipramine and undetectable concentrations of hydroxylated metabolites. The CYP2C19 poor metabolizer had higher plasma concentrations of trimipramine and lower plasma concentrations of the desmethyl-metabolite.	Eap *et al*. 2000[175]	Moderate

[a]The grading system for evidence is explained in the section *level of evidence* located in the introduction.

Supplemental Table S19. Dosing recommendations for amitriptyline based on both CYP2D6 and CYP2C19 phenotype[a,b,c,d]

Phenotype	CYP2D6 Ultrarapid metabolizer	CYP2D6 Extensive metabolizer	CYP2D6 Intermediate metabolizer	CYP2D6 Poor metabolizer
CYP2C19 Ultrarapid metabolizer	Avoid tricyclic use. If a tricyclic is warranted utilize therapeutic drug monitoring to guide dose adjustment.	Consider alternative drug not metabolized by CYP2C19. If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustments.	Consider alternative drug not metabolized by CYP2C19. If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustments.	Avoid tricyclic use. If a tricyclic is warranted utilize therapeutic drug monitoring to guide dose adjustment.
CYP2C19 Extensive metabolizer	Avoid tricyclic use. If a tricyclic is warranted consider increasing the starting dose.[a] Utilize therapeutic drug monitoring to guide dose adjustments.	Initiate therapy with recommended starting dose.[a]	Consider 25% reduction of recommended starting dose.[a] Utilize therapeutic drug monitoring to guide dose adjustments.	Avoid tricyclic use. If a tricyclic is warranted consider 50% reduction of recommended starting dose.[a] Utilize therapeutic drug monitoring to guide dose adjustment.
CYP2C19 Intermediate metabolizer	Avoid tricyclic use. If a tricyclic is warranted utilize therapeutic drug monitoring to guide dose adjustments.	Initiate therapy with recommended starting dose.[a]	Consider 25% reduction of recommended starting dose.[a] Utilize therapeutic drug monitoring to guide dose adjustments.	Avoid tricyclic use. If a tricyclic is warranted consider 50% reduction of recommended starting dose.[a] Utilize therapeutic drug monitoring to guide dose adjustment.
CYP2C19 Poor metabolizer	Avoid tricyclic use. If a tricyclic is warranted utilize therapeutic drug monitoring to guide dose adjustments.	Consider 50% reduction of recommended starting dose.[a] Utilize therapeutic drug monitoring to guide dose adjustments.	Avoid tricyclic use. If a tricyclic is warranted utilize therapeutic drug monitoring to guide dose adjustments.	Avoid tricyclic use. If a tricyclic is warranted utilize therapeutic drug monitoring to guide dose adjustments.

[a]Patients may receive an initial low dose of tricyclics, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose. [b]The classification for all of the dosing recommendations in this table is optional. The rating scheme for the recommendation classification is described in the introduction of the Supplementary Data. [c]Dosing recommendations only apply to higher initial doses of amitriptyline for treatment of conditions such as depression. See *other considerations* in the main document for dosing recommendations for conditions where lower initial doses are used, such as neuropathic pain. [d]The dosing recommendations are based on studies focusing on amitriptyline. Because tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply these guidelines to other tricyclic antidepressants including clomipramine, doxepin, imipramine and trimipramine. [d]Therapeutic drug monitoring of tricyclic antidepressants is well described in the literature.[75-77,176,177] Because certain phenotype combinations are rare (e.g., CYP2C19 ultrarapid metabolizer also having CYP2D6 ultrarapid metabolism) sparse data are available to develop dosing recommendations. Therefore, we strongly recommend utilizing therapeutic drug monitoring if a tricyclic is prescribed to a patient with CYP2D6 ultrarapid, intermediate or poor metabolism in combination with CYP2C19 ultrarapid, intermediate or poor metabolism.

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.[10,35,178] Although dosing recommendations have been established for the genes-drug pair *VKORC1*/*CYP2C9*-warfarin[52], 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.[114,136,157,164] 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.[114] However, further studies are needed to develop moderate or strong dosing recommendations for tricyclics when considering combined CYP2D6/CYP2C19 phenotypes. The optional dosing recommendations provided above were developed by assessment of the supporting data in Supplemental Table S12, and by combining the dosing recommendations from Tables 2 and 3 in the main document.

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