

Cytochrome P450 2D6 and 2C19

Managing medication dosing and reducing adverse drug reactions

Cytochrome P450 (CYP) is a major group of drug-metabolizing enzymes (DME) that consists of more than 50 isoforms.¹ The majority of CYP activity takes place in the liver. CYP2D6 is one of the most important DME genes as it metabolizes 25% to 30% of all prescribed drugs.^{1,2} CYP2C19 metabolizes 15% of all prescribed drugs.¹ Common drug categories metabolized by CYP2D6 include (but are not limited to): beta blockers, antiarrhythmics, morphine derivatives, and antidepressants.¹

drug efficacy or adverse drug reactions. Table 1 describes enzyme metabolizer categories (phenotype) and potential consequences.^{1,3,6}

CYP450 2D6 genetic testing can be useful for identifying individuals who may have an adverse drug reaction or a poor response to a medication.¹ Common prescription medications that interact with CYP450 2D6 are listed in Table 3.^{3,4,6-8}

Table 1.—Phenotypes Associated With CYP450 2D6 Variants

Phenotype	CYP2D6 Variant	CYP2C19 Variant	Definition	Active Drug Concerns (Drug administered in active form)	Prodrug Concerns (Drug catabolyzed by DME to active form)
Poor metabolizer (PM)	*3, *4, *4XN, *5, *6, *7, *8, *11, *15, *19, *20, *40 ⁵	*2, *3 ²	Significantly reduced or absent enzyme activity ^{1,5}	Drug metabolized slowly or not at all, increased concentrations of active drug, potential for serious side effects due to increased concentration of active drug ¹	May not respond due to lack of (or reduced amounts of) active metabolite ¹
Intermediate metabolizer (IM)	*10, *10XN, *17, *17XN, *9, *29, *36, *41, *41XN ⁵		Reduced enzyme activity ^{1,5}	May experience some, if any, consequences of poor metabolizers ¹	May experience some (if any) consequences of poor metabolizers ¹
Ultrarapid metabolizer (UM)	*1XN, *2XN, *35XN ⁵		More than two copies of active enzymes ^{1,5}	May not reach therapeutic levels of active drug due to rapid clearance ¹	May reach higher than expected concentrations of active metabolite, which may cause adverse reactions ¹
Normal extensive metabolizer (EM)	*1, *2, *35 ⁵	*1 ⁵	Activity is “normal”—wildtype ^{1,5}	Expected response to standard dose ¹	Expected response to standard dose ¹

*If 2D6 is ordered alone, only 1, 1XN, 2, 2XN, 3, 4, 4XN, 5, 6, 7, 8, *9, *10, and *17 are included.

CYP2C19 is important in the metabolism of antiarrhythmics, proton pump inhibitors, and antidepressants.¹ The package insert of many medications includes information on how that particular drug is metabolized and may indicate when CYP2D6 and/or CYP2C19 genotyping is beneficial.³ Together, CYP2D6 and CYP2C19 are involved most commonly in psychotropic drug metabolism.^{3,4}

Variants (polymorphisms) of CYP2D6 and CYP2C19 are associated with significant phenotypic variations that alter the rate of drug metabolism and may cause increased or decreased

Table 2.—Distributions of Some CYP2D6 Alleles by Race/Ethnicity¹

Variant	Phenotype	Allele Frequency (Percentage)		
		Caucasian	Black/African	Asian
CYP2D6 *3	PM	2	0	0
CYP2D6 *4	PM	12-21	2	1
CYP2D6 *4XN	PM	2-7	4	6
CYP2D6 *10	IM	1-2	6	51
CYP2D6 *17	IM	0	34	0
CYP2C19 *2, *3 ²	PM	1-3	—	13-23

Table 3.—Common Prescription Medications That Interact With CYP2D6*

Drugs	Important Interactions
Beta Blockers S-metoprolol (Toprol®) Timolol (Blocadren®) Propranolol (Inderal®)	If coadministered with a CYP2D6 inhibitor, blood levels and effect of the beta-blocker may increase resulting in bradycardia, hypotension, or heart failure. The risk is highest in extensive metabolizers, which represents 90% of the population. ⁷
Opiates Codeine, dihydrocodeine (Synalgos-DC®) Hydrocodone (Vicodin®/Lortab®)	Poor metabolizers are unable to convert codeine to morphine and may have reduced or lack of pain reduction. Rifampin induces increased metabolism of codeine into morphine in EM, but not PM, individuals. Dihydrocodeine and hydrocodone have a similar structure to codeine and may be subject to the same clinical response in PM. ^{7,8}
Tricyclic Antidepressants (TCA) Amitriptyline (Endep®/Elavil®) Nortriptyline (Aventyl®)	CYP2D6 poor metabolizers may have higher plasma concentration when given usual doses. Coadministration of CYP2D6 inhibitors can increase TCA serum concentrations, possibly leading to toxicity. Other drugs that are substrates for 2D6 such as propafenone, flecainide, and phenothiazines may also have an inhibitory effect when coadministered. Caution must be used when coadministering TCAs and selective serotonin reuptake inhibitors and switching from one class to another. It may be of benefit to monitor TCA plasma levels when coadministering a drug known to inhibit CYP2D6. ^{4,6,7}
Selective Serotonin Reuptake Inhibitors (SSRI) Paroxetine (Paxil®) Fluoxetine (Prozac®) Sertraline (Zoloft®)	Paroxetine and fluoxetine are metabolized by CYP2D6, but like other SSRIs, significantly inhibit CYP2D6 activity. Coadministration of other drugs metabolized by CYP2D6 should be approached with caution. Inhibitors may increase serum concentrations of coadministered drugs which may lead to adverse drug reactions or decreased drug efficacy. Fluoxetine has a very long half-life, so inhibition of CYP2D6 may occur for several weeks after stopping the drug. ^{6,7}
Norepinephrine/Dopamine Reuptake Inhibitor Bupropion (Wellbutrin®)	Bupropion is an inhibitor of CYP2D6. Some research has indicated that bupropion may increase the plasma levels of other drugs metabolized by CYP2D6 when coadministered; therefore caution should be taken when adding bupropion to the treatment regimen of individuals taking drugs metabolized by CYP2D6. ^{6,7}

*Common drugs are those included in the list of the top 300 drugs prescribed in 2004.⁹

Table 4.—Common Prescription Medications That Interact With CYP2C19*

Proton Pump Inhibitors Omeprazole (Prilosec®) ¹	Omeprazole treatment success for <i>Helicobacter pylori</i> infections in those with peptic ulcer may be dependent on CYP2C19 status. Data show that the cure rate with double therapy for PM is 100% and for EM, 29%. With triple therapy, the cure rates are 100% for PM and 86% for EM. ¹
Antiepileptics/Anticonvulsants Diazepam, Phenytoin ¹	The half-life of diazepam is significantly prolonged in PM individuals. Prolonged sedation is possible, particularly if coadministered with CYP2C19 inhibitors. ¹
Tricyclic Antidepressants (TCA) Amitriptyline (Endep®/Elavil®) ¹⁰	Further data are needed, but studies suggest that PM individuals should have a lower starting dose than recommended as average by the manufacturer for TCAs such as amitriptyline and imipramine. ¹⁰
Selective Serotonin Reuptake Inhibitors (SSRI) Citalopram (Celexa®) ¹⁰ Fluoxetine (Prozac®) ¹⁰ Paroxetine (Paxil®) ¹⁰ Sertraline (Zoloft®) ^{1,10}	Sertraline, fluoxetine, and paroxetine clearance may be affected by CYP2C19, ¹ but no dosage adjustments for these drugs have been suggested based on CYP2C19 genotyping. ^{1,10} Similar findings have been reported for citalopram ¹ ; however, studies suggest a lower starting dose for PM for citalopram. ¹⁰ Studies suggest that PMs may be at risk for cardiotoxicity related to SSRIs. ¹

*Common drugs are those included in the list of the top 300 drugs prescribed in 2004.⁹

Drug response is multifactorial. In addition to DME genotypes, other variables should be considered, including race, medications being used (including over-the-counter medications), smoking, illegal drug use, mode of drug delivery (oral, injected, or intravenous), foods and food supplements (herbs, vitamins, etc), age, weight, environment, diseases in the patient, and exercise.^{2,7,8,11,12}

Cytochrome AmpliChip™ P450 2D6/2C19 Genotyping and Phenotyping 511316

CPT 83891; 83894; 83900; 83896(x29); 83892(x29); 83903; 83912

Related Information Cytochrome P450 2D6, 2C9, 2C19 genotyping

Synonyms AmpliChip™, DME Genotyping

Specimen Whole blood

Volume 7 mL

Minimum Volume 3 mL

Container Lavender-top (EDTA) tube

Storage Instructions Maintain specimen at room temperature or refrigerate.

Causes for Rejection Hemolyzed specimen; quantity not sufficient for analysis

Limitations The metabolism of drugs is also influenced by ethnicity, diet, and other medications. All factors should be considered prior to initiating new therapy. This test may be considered by Medicare and other carriers as investigational and, therefore, may not be payable as a covered benefit for patients.

Methodology Polymerase chain reaction (PCR), gel electrophoresis, microarray (hybridization)

Cytochrome P450 2D6 Genotyping 511160

CPT 83891; 83894; 83908(x25); 83900; 83901(x2); 83896(x25); 83892(x25); 83903(x2); 83912

Synonyms DME Genotyping

Specimen Whole blood

Volume 7 mL

Minimum Volume 3 mL

Container Lavender-top (EDTA) tube

Storage Instructions Maintain specimen at room temperature or refrigerate.

Causes for Rejection Hemolyzed specimen; quantity not sufficient for analysis

Limitations The metabolism of drugs is also influenced by race, ethnicity, diet and other medications and all factors should be considered prior to initiating new therapy. This test may be considered by Medicare and other carriers as investigational and, therefore, may not be payable as a covered benefit for patients.

Methodology Isothermal amplification strategy (Invader Assay)

Cytochrome P450 2C19 Genotyping 511320

CPT 83891; 83898; 83900; 83892; 83894(x2); 83912

Related Information Cytochrome P450 2D6, 2C9 genotyping

Synonyms DME Genotyping

Specimen Whole blood

Volume 7 mL

Minimum Volume 3 mL

Container Lavender-top (EDTA) tube or yellow-top (ACD) tube

Storage Instructions Maintain specimen at room temperature or refrigerate.

Causes for Rejection Hemolyzed specimen; quantity not sufficient for analysis; improper container

Limitations The metabolism of drugs is also influenced by ethnicity, diet, and other medications. All factors should be considered prior to initiating new therapy. This test may be considered by Medicare and other carriers as investigational and, therefore, may not be payable as a covered benefit for patients.

Methodology Polymerase chain reaction (PCR), gel electrophoresis

References

1. Blue Cross Blue Shield Association. Special report: Genotyping for cytochrome P450 polymorphisms to determine drug-metabolizer status. *Technology Assessment Program*. 2004; 19(9):1-34.
2. American College of Clinical Pharmacology. *Pharmacogenomics: Applications to Patient Care*. AACP, Kansas City, Mo: ACCP; 2004:262,263,290.
3. *Cytochrome P450 Drug Interaction Table*. medicine.iupui.edu/flockhart/ Cited: February 22, 2005.
4. Fishbain DA, Fishbain D, Lewis J, et al. Genetic testing for enzymes of drug metabolism: Does it have clinical utility for pain medicine at the present time? A structural review. *Pain Med*. 2005; 5(1):81-93.
5. Human Cytochrome P450 (CYP) Allele Nomenclature Committee. www.imm.ki.se/CYPalleles. Cited: January 10, 2005.
6. RxList Drug Monographs. *Nortriptyline*. www.rxlist.com. Cited July 22, 2005.
7. Hansten PD, Horn JR. *The Top 100 Drug Interactions*. Edmonds, Wash: H&H Publications; 2005:11-13,26-27,47-48,65.
8. Wilkinson GR. Drug metabolism and variability among patients in drug response. *N Engl J Med*. 2005 May 26; 352(21):2211-2221.
9. RxList. *Top 300 Drugs Prescribed in 2004*. www.rxlist.com.
10. Kirchheiner J, Brosen K, Dahl ML, et al. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: A first step towards subpopulation-specific dosages. *Acta Psychiatr Scand*. 2001 Sep; 104(3):173-192.
11. Khazaieina T, Ramsey AA, Tam YK. The effects of exercise on the pharmacokinetics of drugs. *J Pharm Pharmaceut Sci*. 2000; 3(3):292-302.
12. Pollack BG. The pharmacokinetic imperative in late-life depression. *J Clin Psychopharmacol*. 2005 Aug; 25(4 Suppl 1):S19-S23.



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