

Med-Psych Drug-Drug Interactions Update

Clinical Guidelines for Psychiatrists for the Use of Pharmacogenetic Testing for CYP450 2D6 and CYP450 2C19

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Pharmacogenetics has arrived in clinical psychiatric practice with the FDA approval of the AmpliChip CYP450 Test that genotypes for two cytochrome P450 2D6 (CYP2D6) and 2C19 (CYP2C19) genes. Other pharmacogenetic tests, including those focused on pharmacodynamic genes, are far from ready for clinical application. CYP2D6 is important for the metabolism of many antidepressants and antipsychotics, and CYP2C19 is important for some antidepressant metabolism. Poor metabolizers (PMs), lacking the enzyme, account for up to 7% of Caucasians for CYP2D6 and up to 25% of East Asians for CYP2C19. Patients having three or more active CYP2D6 alleles (up to 29% in North Africa and the Middle East), are called CYP2D6 ultra-rapid metabolizers (UMs). CYP2D6 phenotypes (particularly PMs) are probably important in patients taking tricyclic antidepressants (TCAs), venlafaxine, typical antipsychotics, and risperidone. The CYP2C19 PM phenotype is probably important in patients taking TCAs and perhaps citalopram, escitalopram, and sertraline. On the basis of the literature and the authors' clinical experience, the authors provide provisional recommendations for identifying and treating CYP2D6 PMs, CYP2C19 PMs, and CYP2D6 UMs. The next few years will determine whether CYP2D6 genotyping is beneficial for patients taking the new drugs aripiprazole, duloxetine, and atomoxetine. Practical recommendations for dealing with laboratories offering CYP2D6 and CYP2C19 genotyping are provided.

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The genetic revolution has been the result of two intertwined processes: human genome sequencing and the development of new technologies permitting genetic testing in an automated and efficient way. Although the development of genomic medicine and genetic testing has helped in diagnosing some relatively rare and unusual disorders, this progress has had limited impact in medicine.¹ Pharmacogenetics is usually defined as the study of variability in drug response due to heredity.² More recently, the term “pharmacogenomics” is being used, a broader term encompassing all genes in the genome that may determine drug response. The distinction is arbitrary, given that the terms are often used interchangeably.²

The FDA completed the approval of the first phar-

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macogenetic test, the AmpliChip CYP450 Test, in January 2005.^{3,4} This test performs massive parallel genotyping, using one of the major technological advances in genetic testing, the so-called DNA microarray, DNA chip, or GeneChip. The latter name was given by Fodor,⁵ the Affymetrix CEO who first developed this technology for massive parallel genotyping based on the hybridization process (the patient's DNA strand recognizes the uniquely complementary sequence in a computer chip through base pairing). The AmpliChip CYP450 Test assesses two polymorphic genes, the Cytochrome P450 2D6 (CYP2D6) and the Cytochrome P450 2C19 (CYP2C19).³

In 1997, the journal *Science*⁶ described “personalized prescription” or “tailoring drugs to a patient's genetic make-up” in their “six research horizons for 1998” and predicted that it will “soon” reach clinical practice. More precise estimations for the generalized use of personalized prescription have been provided: the year 2015, according to the lay journal *Time*⁷ and 2020, by *JAMA*.⁸ Because CYP2D6 metabolizes many of the psychiatric drugs, psychiatry has become the first area of medicine for the practical clinical use of pharmacogenetic testing. A recent article⁹ in a mainstream economic journal focused on “personalized medicine,” presenting an example of a bipolar patient who had a complicated pharmacological treatment history. Although many psychiatrists may not be ready for “personalized prescription,” their patients may be reading this article⁹ or listening to government officials promoting “personalized prescription” in the media.¹⁰

PHARMACOGENETIC APPROACHES IN PSYCHIATRY

To appreciate the context of these initial and limited practical pharmacogenetic recommendations for clinicians, one has to understand the different ways that pharmacogenetics may be used in the future in psychiatry. The first and most obvious distinction is between using single-gene and multiple-gene testing (Table 1).^{11–13} Single-gene testing can include pharmacodynamic genes, such as the serotonin transporter or the dopamine receptors,¹¹ but these gene tests are not ready for clinical use (Table 1) and may require many years until they are useful and available. As an example, the dopamine₂ receptor (DRD₂) gene¹⁴ appears a reasonable choice to explore for antipsychotic response, but many of its known single-nucleotide polymorphisms (SNPs) have no functional influence; there are a couple of SNPs believed to be functional, but the studies on association with treatment response have not been encouraging.

The DRD₂ gene-status research can be compared with more than 30 years of CYP2D6 knowledge that has allowed the identification of more than 50 SNPs that have functional consequences relatively well established.

The two pharmacokinetic genes, CYP2D6 and CYP2C19, have reached clinical practice by means of the FDA's approval of the AmpliChip CYP450 Test. No other technology using massive parallel CYP genetic testing has yet been completely developed or approved by the FDA. The authors are aware¹⁵ that other companies developing CYP testing, include General Electric Health Care (CodeLink™ P450 SNP Bioarray); Tm Bioscience (Tag-It™ Mutation Detection Kit), which uses the microsphere-based universal array genotyping platform developed by Luminex; Third Wave Molecular Diagnostics (Invader® Technology); and Jurilab Ltd (DrugMet™ Genotyping Test). Finally, the authors know that two U.S. academic laboratories and several commercial pharmacogenetic companies offer physicians the opportunity to genotype their patients for CYP genes (costs for an individual sample range from \$250 to \$500, depending on the number of genes tested).

Current genetic microarray systems could easily test hundreds of SNPs from many genes to identify a complex pattern predicting drug response.^{16,17} However, considering how difficult taking a well-understood polymorphic gene such as CYP2D6 to the clinical environment has been, it is unlikely that such an approach, using multiple SNPs of multiple genes, may reach the market in the next 5 to 10 years. The currently available technology simply helps clinicians and selected patients to decide if they should “not take that drug” or “take this low or high dose,” an application called “safety pharmacogenetics.”¹⁸ The future may lead to recommendations that would determine the best drug for a particular patient, which determination is called “efficacy pharmacogenetics.”¹⁸

Testing for a limited number of genetic variations of multiple pharmacokinetic genes (Table 1) can be done easily, from a technical point of view. Several commercial laboratories provide batteries of genotype testing that include pharmacokinetic genes besides CYP2D6 and CYP2C19. The tested genes vary from laboratory to laboratory and include other CYP and other Phase I enzymes, but most of these genetic variations have little relevance for psychiatric patients; therefore there are no clear reasons to consider genotyping other genes besides CYP2D6 and CYP2C19 in a typical psychiatric patient at this time.

In spite of the obstacles that psychiatric pharmacogenetics may overcome in becoming standard clinical prac-

tice, it is encouraging that a recent paper indicated that current antipsychotics may be the ideal place for implementing pharmacogenetic techniques, since they are efficacious in only 30% of patients and tend to have a narrow therapeutic window. The report stressed that the cost-effectiveness of pharmacogenetics may be influenced by the therapeutic window and interindividual variability.¹⁹

BRIEF REVIEW OF CYP2D6 AND CYP2C19 GENOTYPING

CYP2D6 is a metabolic liver-enzyme that biotransforms approximately 25% of known drugs metabolized by CYPs.²⁰ Many of these drugs are antipsychotic or antidepressant drugs, making it an important metabolic enzyme for psychiatry. The gene encoding this enzyme is located on Chromosome 22. The CYP2D6 enzyme is expressed constitutively in several tissues, in particular, the liver.

The activity of the CYP2D6 enzyme is extremely variable because of more than 50 genetic variations, and it can be expressed as having four main levels of activity (phenotypes).²¹ In the traditional view, the ultra-rapid meta-

bolizer (UM) has three or more copies of the active CYP2D6 gene and exhibits extremely high CYP2D6 activity. There is increasing data that only some UMs have additional copies.²² A recent study has suggested that current genotyping methods only identified approximately 20% of CYP2D6 UMs; therefore, approximately 80% are currently missed by genetic testing.²³ Currently, we do not know which other polymorphic variations may be associated with unusually high activity in individuals without known allele duplication or multiplication. In summary, psychiatrists need to be very aware that our current status of knowledge does not allow us to identify many of the CYP2D6 UMs.

The normal subject, or extensive metabolizer (EM), has one or two functional copies of the CYP2D6 gene and displays typical CYP2D6 activity. The term “intermediate metabolizer” (IM) usually refers to a subject with one non-functional CYP2D6 allele and an allele that is expressed as an enzyme with low activity. Other groups consider subjects with one functional copy of CYP2D6 as IM instead of EM.¹¹ In reality, with our current limited knowledge, this distinction between IMs and EMs is more important

TABLE 1. Recommendations for Psychiatrists Regarding the Type of Pharmacogenetic Approach

Approach	Recommendation	
Single gene (pharmacogenetics)	Pharmacokinetic Genes	Pharmacodynamic Genes
Examples		
Antidepressants	CYP2D6 and CYP2C19 ¹¹	5-HT transporter and receptors ¹¹
Antipsychotics	CYP2D6 ¹¹	Dopamine receptors ¹¹
Gene validation	Phenotyping methods and therapeutic drug-monitoring	Face validity (known mechanism of action)
Functional significance		
Study by	Phenotyping methods	In-vitro and brain imaging
Tested SNPs	Functional	Many are not functional
Most functional SNPs	Known	Probably unknown
Racial variations	Understood	Not understood
Statistics		
Univariate	Some had moderate OR: 3–10	OR of 1.1–1.6 are modest ¹¹
Multivariate	Confounders tend to be ignored	Confounders usually ignored
Evidence-based level	Meta-analysis encouraging ¹¹	Lack of replication ¹¹
Recommendation	See Appendix 1 and Appendix 2	Unsure of clinical value
Combinations of genes (pharmacogenomics)	Several pharmacokinetic genes	Multiple genes
Examples	Packages offered by some commercial labs	Research microarrays with multiple SNPs and genes
Validation	Almost no data in clinical environment (one study combining CYP2D6 and CYP2C19); ¹² many offered genes are not well studied	Initial research studies
Statistics	Statistics for gene-gene interactions starting to be developed	New approaches are needed ¹³
Evidence-based level	No data on commercial packages	Very limited data; replication may be a problem
Recommendation	Not ready for clinical use	Not ready for clinical use

Note: SNPs: single-nucleotide polymorphisms; OR: odds ratio.

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for researchers than for clinicians, since the clinical relevance of the terms needs to be demonstrated. Without doubt, the most important phenotype is the “poor metabolizer” (PM). PMs are subjects with two nonfunctional CYP2D6 alleles and no CYP2D6 in their liver. Table 2 provides a summary of the CYP2D6 phenotypes in different racial groups.^{24–27} Quinidine, paroxetine, bupropion, and fluoxetine are powerful CYP2D6 inhibitors, and the use of potent inhibitors can render a patient that is a CYP2D6 EM (a normal individual with one or two functional alleles) into a phenotypic PM. CYP2D6 induction is controversial, but appears likely not to be clinically relevant.

The CYP2C19 phenotypes include some PMs and a majority of normal (EM) subjects.²⁸ Table 2 provides the estimated frequency, by race, for subjects who may lack both enzymes CYP2D6 and CYP2C19. These subjects may be rather rare, and the first author has found only 1 case among 1,500 patients genotyped in an ongoing study that will genotype up to 4,000 patients.

CLINICAL GUIDELINES FOR USING CYP2D6 AND CYP2C19 GENOTYPING IN ANTIDEPRESSANT THERAPY

Appendix 1^{11,29–39} and Appendix 2^{11,40–50} provide guidelines for the use of genetic testing with antidepressants and antipsychotics, respectively. We hope to explain that CYP2D6 and CYP2C19 testing may help some patients

taking some antidepressants, and CYP2D6 testing may help some patients taking some antipsychotics. Extensive footnotes are included in case additional readings are needed. Extreme CYP2D6 and/or CYP2C19 genetic profiles should encourage clinicians to explore different treatment options. It is crucial to have a detailed pharmacological history. Clinical diagnosis is a Bayesian process of progressive accumulation of data, in which each piece makes the diagnosis “somewhat more or less suggestive.”⁵¹ Therapeutic drug monitoring (TDM) of drug levels may be particularly helpful when one suspects unusual genetic profiles of CYP2D6 and CYP2C19.

Known polymorphisms in other CYPs may have less relevance in psychiatry. CYP1A2 genetic variations associated with PM or UM profiles appear to be very rare.⁵² More frequent CYP1A2 polymorphisms may influence the response to CYP1A2-inducers such as smoking.⁵²

In general, CYP2D6 PMs are likely to have poor tolerance of tricyclic antidepressants (TCAs) and perhaps of venlafaxine, with average tolerance of the majority of other antidepressants. TCA levels will surely help to identify CYP2D6 PMs and may be less costly than genetic testing. In spite of our limited knowledge and the lack of studies supporting this strategy, it appears safer to recommend prescribing antidepressants not dependent on CYP2D6, such as bupropion, citalopram, escitalopram, mirtazapine, or sertraline to CYP2D6 PMs. (The “BCEMS” mnemonic may be helpful.) CYP2D6 UMs are likely to have low plasma levels of TCAs and perhaps of venlafaxine. Al-

TABLE 2. Variations of CYP2D6 and CYP2C19 Phenotypes According to Race (approximated frequencies, %)^{24–28}

Phenotypes	Caucasians	East Asians	African Americans	North Africa and Middle East	Mexican Americans ^b
CYP2D6 PM	5–10	1	1–2 ^a	2	3
UM	1–10 ^c	0–2	2	10–29	1
Other	80–94	>90 ^d	96–97 ^e	69–88	96
CYP2C19 ^f PM	2–4	10–25	1–5	2	4
PM for both ^g	0.1–0.4	0.1–0.25	0.01–0.1	0.04	0.12

Note: UM: ultra-metabolizer; PM: poor metabolizer.

^aOne study found 1% PMs, but in another, 6% appeared to have low activity in a phenotyping test, suggestive of their being CYP2D6 PM.²⁵ African Americans appear to have rates of 0%–20%.²⁵ In an unpublished study of 222 African Americans in Kentucky genotyped with Roche AmpliChip CY450, we found 1.4% CYP2D6 PMs and 4.5% CYP2D6 UMs.

^bNot homogeneous; they have a mix of European and Asian genes.^{26, 27}

^cThis is based on patients having at least three active alleles. This means they have at least one normal allele and one duplicated allele that is also active. Current genotyping methods are suspected of underdiagnosing CYP2D6 UMs.

^dMany Asians have a *10 allele that has low activity for many drugs, although this may have population significance (on average, Asians tend to be prescribed a lower average of typical antipsychotics), but the clinical significance for individuals is not clear.

^eThe allele *17 is frequent in African Blacks and African Americans, but the clinical significance for individuals is not clear. For some drugs, patients with *17 may have an enzyme with lower activity, but, for other drugs, it may have higher activity.

^fThe rest of people are CYP2C19 EMs (extraordinary metabolizer).

^gThese are independent probabilities of being both a CYP2D6 PM and a CYP2C19 PM. To calculate, a multiplication is needed (e.g., for Mexican Americans, $0.03 \times 0.04 = 0.0012$, or 0.12%, or 1.2 per 1,000, or 12 per 10,000).

though not all CYP2D6 UMs may be identified by current genotyping, it appears safer to recommend prescribing antidepressants not dependent on CYP2D6 (BCEMS) to patients identified as CYP2D6 UMs. Other more complex alternatives^{37–39} are described in Appendix 1.

CYP2C19 PMs are likely to have poor tolerance of several TCAs that are demethylated by CYP2C19 and may also have poor tolerance to citalopram, escitalopram, and sertraline (“CES”). In spite of our limited knowledge and the lack of studies supporting this strategy, it appears safer to recommend prescribing CYP2C19 PMs antidepressants not dependent on CYP2C19, such as bupropion, fluvoxamine, mirtazapine, or paroxetine (“BFMP”). TCA levels may help to identify PMs of 2C19 and may be less costly.

PMs for both CYP2D6 and CYP2C19 are rare, but recommending antidepressants not dependent on CYP2D6 or CYP2C19, such as bupropion or mirtazapine, would seem prudent.

The tables do not have any reference to duloxetine, since we do not have enough information and cannot easily predict its profile. According to the marketer, duloxetine is metabolized by CYP2D6 and CYP1A2.⁵³ Thus, it is likely that CYP2D6 phenotypes may influence duloxetine response.

CLINICAL GUIDELINES FOR USING CYP2D6 GENOTYPING IN ANTIPSYCHOTIC THERAPY

Appendix 2 summarizes our current limited knowledge of metabolism of antipsychotics.^{11,40–50} CYP2D6 PMs are likely to have poor tolerance of many typical antipsychotics and risperidone, with average tolerance for other antipsychotics. TDM of drug levels may be particularly helpful when one suspects unusual CYP2D6 genetic profiles.

In spite of our limited knowledge and the limited studies supporting this strategy, it appears safer to recommend prescribing CYP2D6 PMs antipsychotics not dependent on CYP2D6, such as clozapine, olanzapine, quetiapine, or ziprasidone (“COQZ”), or, at least, very low doses of CYP2D6-dependent antipsychotics. CYP2D6 UMs are likely not to respond to usual doses of typical antipsychotics and risperidone, although they may respond normally to other antipsychotics. In spite of our limited knowledge and the lack of studies supporting this strategy, it appears safer to recommend prescribing CYP2D6 UMs antipsychotics not dependent on CYP2D6 (“COQZ”).

According to its marketer, aripiprazole (not included in Appendix 2) is metabolized, like risperidone, by CYP2D6 and CYP3A; thus it may behave very similarly

to risperidone, although it may have a wider therapeutic window.⁵² The company studies are very limited,⁵⁴ and independent studies are needed.

CASE EXAMPLES FOR USING PHARMACOGENETIC TESTING

Pharmacogenetic testing may be a new addition to psychiatric treatment, but, to use it properly, one needs to take into account basic pharmacological knowledge and common sense. Drug response is controlled by pharmacokinetic and pharmacodynamic factors,⁵⁵ which can be both genetic and environmental. Thus, CYP2D6 and CYP2C19 testing provides information only on one aspect: genetic pharmacokinetic factors. To understand and use these data, clinicians may want to read recent reviews on antipsychotic⁵² and antidepressant^{56,57} metabolism, psychiatric pharmacogenetics,¹¹ and the AmpliChip CYP 450 Test.⁴ Because many psychiatric patients undergo polypharmacy and are at risk for drug–drug interactions (DDIs), clinicians need to be very familiar with the basic concepts of DDI, such as inhibition and induction.⁵⁸ Pharmacogenetic testing of CYP2D6 and CYP2C19 adds a new level of complexity in assessing drug efficacy and/or adverse drug reactions (ADRs). Even with this new technology, the principle of Occam’s Razor still holds true. For example, the most likely cause of very-low or nondetectable plasma drug levels would be nonadherence to a drug regimen, and not a polymorphic UM at CYP2D6.

Four real-world examples regarding CYP2D6 and CYP2C19 testing are described here to demonstrate a common-sense approach.

1. A fellow-psychiatrist calls the psychiatric consultant, describing one of her complex patients with bipolar disorder. The patient’s history is long and complicated. In brief, he did not respond to mood stabilizers, antidepressants, or antipsychotics. This led the treating psychiatrist to believe that the patient must be a UM, and she wanted to know how he could be tested.

It was important to note with the consultee that mood stabilizers are not metabolized by CYP2D6 or CYP2C19. Also, several of the antipsychotics and antidepressants that were presented were also not dependent on these enzymes. The cause for this patient’s lack of response to medications cannot be explained by his being a UM for CYP2D6; therefore, testing would probably be unproductive.

2. A 72-year-old female patient with long-lasting panic disorder calls the psychiatric consultant and explains that she cannot tolerate any antidepressant. The patient believes

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she must be “a universal PM” for antidepressants. She has tried seven or eight antidepressants and had problems with all of them. She has been genotyped in an academic lab. She reads the report that describes her as an IM and explains that she has one normal allele. The consultant explains to her that she has CYP2D6 in her liver and is “relatively normal.” The patient tells the consultant that the academic lab’s report lists 30–40 medications that she cannot take. The consultant explains that several of the antidepressants that she has tried are not metabolized by CYP2D6 and/or CYP2C19 and that there are likely other reasons for the lack of tolerance she has with antidepressants. Also, the lab’s list of medications was one for PMs, and was overstated in her case. She is not a CYP2D6 PM. She is an IM, essentially the same as a normal EM.

3. A mother calls the psychiatric consultant, asking how she can get her daughter genotyped, because medications do not help her, and she may be a “universal UM.” Her daughter has seizures and does not respond to any anticonvulsants. The consultant explains that anticonvulsants are not metabolized by CYP2D6, and, thus, testing would not likely be helpful. Phenytoin is only metabolized in part by CYP2C19. Further history reveals that the daughter is autistic; she has gained significant weight when on risperidone and has been tried on paroxetine. Nothing clinically appears to suggest that her daughter is a CYP2D6 PM, CYP2D6 UM, or a CYP2C19 PM. However, the mother appears overwhelmed by the complexity of her daughter’s clinical situation. The psychiatrist helps the mother to contact a laboratory and recommends she discuss the need for testing with her daughter’s psychiatrists, since she appears to feel that she needs to try all possible alternatives in helping her daughter.

4. A 23-year-old patient with borderline intelligence and borderline personality traits was admitted to the hospital. After we spoke with the patient’s brother, it was obvious that, since his father died 3 years ago, the patient has had a pattern of utilizing multiple emergency rooms, with false allegations of symptoms. Problems have included use of drugs or alcohol, psychotic symptoms, and suicidal and homicidal ideation. During this admission, he complained of “voices,” was treated with perphenazine, 4 mg/day, and developed a severe case of stiffness. More worrisome, several years ago he received a high dose of parenteral haloperidol and developed a serious case of neuroleptic malignant syndrome, from which he almost died. There are also some indications that the patient may have developed priapism on trazadone, but complete ADR documentation was lacking. His genotyping revealed that he was a CYP2D6

PM. All medications were stopped, and the psychiatrist explained to the patient and the family the high risk of serious ADRs on some antidepressants and antipsychotics (a list was provided), since his psychiatrists appeared particularly prone to using high doses of medications to control some of his acting out.

These first three cases suggest that CYP2D6 and CYP2C19 cannot and will not resolve all psychopharmacologically difficult cases. In other instances, such as the fourth case, genotyping provides very helpful information that may be even life-saving.

CLINICAL GUIDELINES FOR SELECTING A LABORATORY

Appendix 3^{3,22,23,28,59} presents information on how to select a laboratory and how to interpret AmpliChip CYP 450 Test results. Current available information and testing reliability appears reasonable for CYP2D6 PMs and CYP2C19 PMs. A CYP2D6 PM or a CYP2C19 PM genotype needs to be taken seriously in order to avoid side effects. It is more difficult to be sure about other genotypes. Remember that normal alleles are frequently diagnosed by defect, so the fewer alleles that the laboratory tests, the more likely it is to classify subjects as EMs. It is much more likely that the lab reports a false negative in the case of an EM with one active copy than in an EM with two copies. If the pharmacological profile strongly suggests a PM, and the test result is an EM, you may need to discuss with them their estimations of their false negatives for CYP2D6 PMs. For example, if a patient has repeated high nortriptyline levels after a low dose, and a lab labels him a CYP2D6 EM, clinicians definitively need to discuss with the lab the possibility of rechecking the genotyping and considering the possibility of a false negative.

Assuming that the laboratory classifies the subject as a CYP2D6 PM, what is the clinical relevance? According to the first author’s experience, CYP2D6 PM explains only 10%–20% of risperidone ADRs or discontinuations because of ADRs (public health perspective),⁷ but CYP2D6 PMs (individual perspective)⁴ have 3–6 times more risk of having risperidone ADRs or discontinuations because of ADRs. In the context of predicting risperidone ADRs, the CYP2D6 PM genotype has low sensitivity (10%–20%), but very high specificity (>90%). Risperidone TDM had a little higher sensitivity (25%), but, clearly, lower specificity (72%) of predicting risperidone ADRs.⁴

CONCLUSION

“Personalized medicine” has reached psychiatry with FDA approval of the first pharmacogenetic test, the AmpliChip CYP450. CYP2D6 and CYP2C19 testing may help patients with a history of excessive difficulties with antidepressants; CYP2D6 testing may help patients with a history of problems with antipsychotics. Current available information and testing reliability appears reasonable for CYP2D6 PMs and CYP2C19 PMs. Other CYP2D6 phenotypes, such as UMs, may be important, but both the literature and our ability to detect them are quite deficient. CYP2D6 phenotypes (particularly PM) are probably important for patients taking TCAs, venlafaxine, typical antipsychotics, and risperidone. The CYP2C19 PM phenotype is probably important for patients taking TCAs and, perhaps, citalopram, escitalopram, and sertraline. The next few years will determine whether CYP2D6 genotyping is beneficial for patients taking the new drugs aripiprazole, duloxetine, and atomoxetine.^{60,61} The availability of laboratories offering CYP2D6 and CYP2C19 genotyping is currently limited but will expand significantly in the next several years. Time and clinical experience will be required to develop appropriate and practical laboratory guidelines for pharmacogenetic testing.

Finally, the recently published CATIE study⁶² suggests that the first antipsychotic a psychiatrist prescribes to a patient may not be the best choice for an individual patient. Therefore, the future of “personalized medicine,” with better pharmacokinetic and pharmacodynamic genetic testing, could ultimately lead to better clinical outcomes. Studies such as CATIE may help clinical researchers to change their focus from simply trying to find the best antipsychotic or antidepressant for the average patient. The “average” patient may, indeed, be uncommon.

Roche Molecular Systems, Inc. markets the AmpliChip CYP450 Test detecting the CYP2D6 and CYP2C19 gene variations. Jose de Leon, M.D., has received support for his laboratory and research-initiated grants from Roche-Molecular Systems, Inc. and has lectured once supported by Roche-Molecular Systems, Inc., but he has not received any consultant payments. He has no other financial arrangements with Roche Molecular Systems, Inc. He has no stocks in Roche, Affymetrix, or any other companies developing pharmacogenetic tests. In the past 2 years, Dr. de Leon has 1) been on the advisory board of Bristol-Myers Squibb; 2) received researcher-initiated grants from Eli Lilly; and 3) delivered a lecture supported by Eli Lilly (once).

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APPENDIX 1. Clinical Guidelines for Using CYP2D6 and CYP2C19 Genotypes in Patients Taking Antidepressants^{11,29-39}**A. CYP2D6 PM**

1. Suspecting a CYP2D6 PM
 - a. Clinical information
 - i) Poor tolerance of typical TCA doses (and perhaps to venlafaxine)^a
 - ii) Normal tolerance of antidepressants not dependent on CYP2D6 is expected
 - iii) Other (see Appendix 2 for response to antipsychotics)
 - b. Laboratory evidence
 - i) TCA C/D: 4-6^b in absence of CYP inhibitors
 - ii) Some limited information on venlafaxine TDM^c
 - iii) See Appendix 2 if antipsychotic TDM is available
2. Treating a CYP2D6 PM
 - a. Use antidepressants not dependent on CYP2D6 (bupropion, citalopram, escitalopram, mirtazapine, or sertraline)
 - b. If using TCAs, use half of TCA dose;¹¹ if using venlafaxine, use lower venlafaxine dose^d
 - c. If using paroxetine and fluoxetine, be careful and consider low doses^e

B. CYP2C19 PM

1. Suspecting a CYP2C19 PM
 - a. Clinical information
 - i) Poor tolerance of usual doses of some TCAs^f
 - ii) Possible poor tolerance of usual doses of citalopram, escitalopram, or sertraline^g
 - iii) Poor tolerance of antidepressants not dependent on CYP2C19 is not expected^h
 - iv) Otherⁱ (low tolerance of usual diazepam doses and no problems with other benzodiazepines)
2. Treating a CYP2C19 PM
 - a. Use antidepressants not dependent on CYP2C19 (bupropion, fluvoxamine, mirtazapine, or paroxetine)
 - b. If using TCAs,^f use half of TCA dose;¹¹ if using citalopram, use half of citalopram dose;¹¹ if using escitalopram or sertraline, it may be safer to use lower dose

C. PM for both CYP2D6 and CYP2C19

1. Suspecting a PM for both CYP2D6 and CYP2C19
 - a. Remember these are extraordinarily rare cases (Table 2).
 - b. They may have had problems with antidepressants dependent on CYP2D6 and/or CYP2C19. Although there is no published experience with these subjects, they should have problems with many but not all antidepressants (and some antipsychotics).
2. Treating a PM for both CYP2D6 and CYP2C19
 - a. Avoid antidepressants dependent on CYP2D6 or CYP2C19. Bupropion or mirtazapine may be good choices

D. CYP2D6 UM

1. Suspecting a CYP2D6 UM
 - a. Clinical information^j
 - i) Lack of response to usual doses of TCAs¹¹
 - ii) See Appendix 2 for response to antipsychotics
 - b. Laboratory evidence^k
 - i) TCA C/D <0.5^k in absence of CYP inducers
 - ii) See Appendix 2 if antipsychotic TDM is available
2. Treating a CYP2D6 UM
 - a. Use antidepressants not dependent on CYP2D6 (bupropion, mirtazapine, citalopram, escitalopram, or sertraline)
 - b. If using TCAs, you may need to use high doses^{m,n,11} and TDM. Dosing may depend on the number of active alleles.
 - c. There are not enough data on venlafaxine, paroxetine, and fluoxetine (possibly, high doses are needed).

Note: PM: poor metabolizer; UM: ultra-metabolizer; TCA: tricyclic antidepressant; TDM: therapeutic drug-monitoring; ADRs: adverse drug reactions.

^aFluoxetine and paroxetine are mainly metabolized by CYP2D6, but the effects of being a CYP2D6 PM are not easy to see because of their inhibition of their own metabolism. One-half to 2/3 of CYP2D6 EMs taking fluoxetine or paroxetine may look phenotypically like CYP2D6 PMs.²⁹

^bTCA C/D is measured by dividing the concentration (ng/ml) by the dose (mg/day). In the absence of CYP inducers or inhibitors, CYP2D6 PMs have C/D: 4-6, and CYP2D6 EMs have C/D: 0.5-1.5.³⁰

^cAn article on venlafaxine TDM³¹ suggested that in the absence of CYP inducers or inhibitors, a ratio of O-desmethylvenlafaxine/venlafaxine <0.5 indicates a CYP2D6 PM. CYP2D6 EMs had ratios of 1-10.

^dOne venlafaxine article described four patients with cardiovascular problems: two were CYP2D6 PMs, and two were taking CYP2D6 inhibitors.³²

^eTDM studies and case reports suggested higher potential for CYP2D6 PMs to develop ADRs on paroxetine or fluoxetine, but a fluoxetine study did not agree.³³

^fSeveral TCAs: amitriptyline, clomipramine, imipramine, and trimipramine, are dependent on CYP2C19.

^gPharmacokinetic studies suggest that CYP2C19 PMs have lower citalopram³⁴ and sertraline³⁵ clearance, but there are no large studies of ADRs in the clinical environment, and cases of ADRs on CYP2C19 PMs are few and come from the same pharmacokinetic articles. There are no escitalopram studies.

^hAccording to the literature, CYP2C19 partly metabolizes fluoxetine and venlafaxine.

Med-Psych Drug-Drug Interactions

ⁱCYP2C19 PMs have longer diazepam half-life and may have a higher risk of diazepam-induced sedation, but Asian physicians have empirically prescribed lower doses in Asian populations than those recommended for Caucasians.³⁶

^jAlthough it has not been well studied, it is likely that CYP2D6 UMs may not respond to usual doses of venlafaxine.

^kAn article on venlafaxine TDM³¹ suggested that in the absence of CYP inducers or inhibitors, a ratio of O-desmethylvenlafaxine/venlafaxine >10 indicates a CYP2D6 UM. CYP2D6 EMs had ratios of 1–10.

^lTCA C/D is measured by dividing the concentration (ng/ml) by the dose (mg/day). In the absence of CYP inducers or inhibitors, CYP2D6 UMs have C/D<0.5, and CYP2D6 EMs have C/D: 0.5–1.5.³⁰

^mThere are no studies on appropriate doses of venlafaxine, paroxetine, or fluoxetine in CYP2D6 UMs.

ⁿKraus et al.,³⁷ Leuch et al.,³⁸ and Laine et al.³⁹ studied adding fluoxetine or paroxetine to TCAs in CYP2D6 UMs.

APPENDIX 2. Clinical Guidelines for Using CYP2D6 Genotypes in Patients Taking Antipsychotics^{11,40–50}

A. CYP2D6 PM

1. Suspecting a CYP2D6 PM

a. Clinical information

- i) Poor tolerance of typical antipsychotics^a or risperidone^b
- ii) Normal tolerance of other atypical APs (not dependent on CYP2D6) is expected
- iii) Other (see Table 3 for response to antidepressants)

b. Laboratory evidence

- i) Risperidone/9-hydroxyrisperidone >1.0^c in absence of CYP2D6 inhibitor/drugs
- ii) Limited information on haloperidol TDM^d
- iii) See Appendix 2 if antidepressant TDM is available

2. Treating a CYP2D6 PM

- a. Use antipsychotic not dependent on CYP2D6 (clozapine, olanzapine, quetiapine, or ziprasidone)
- b. If using risperidone, use no more than half dose used in normal circumstances^{e,43}
- c. It appears to be safer to avoid phenothiazines and haloperidol

B. CYP2D6 UM

1. Suspecting a CYP2D6 UM

a. Clinical information

- i) Possible lack of response to usual doses of risperidone^f
- ii) Possible lack of response to typical antipsychotics^g
- iii) See Appendix 2 for TCA

b. Laboratory evidence

- i) Risperidone/9-hydroxyrisperidone ≤0.10 is highly sensitive but not specific^h
- ii) Limited information on haloperidol TDMⁱ
- iii) See Appendix 2 for TCA TDM

2. Treating a CYP2D6 UM

- a. Use antipsychotic not dependent on CYP2D6 (clozapine, olanzapine, quetiapine, or ziprasidone)
- b. If using risperidone, use higher doses of what you would normally use.
- c. It appears to be easier and safer to avoid phenothiazines and haloperidol.

Note: PM: poor metabolizer; UM: ultra-metabolizer; TCA: tricyclic antidepressant; TDM: therapeutic drug-monitoring; ADRs: adverse drug reactions

^aPhenothiazines (well studied for perphenazine and thioridazine) clearly appear to depend on CYP2D6. The limited information on haloperidol and CYP2D6 PM appears to conflict. One study found 4/5 CYP2D6 PMs have high scores for extrapyramidal side effects.⁴⁰ The first author had conflicting results in two different studies using different designs. In a study with a 4-week haloperidol baseline phase, all five genotyped patients with a history of haloperidol intolerance and refusing haloperidol were CYP2D6 EMs, whereas two CYP2D6 PMs completed the haloperidol phase (one with mild arm stiffness on 10 mg/day and one with akathisia on 20 mg/day).⁴¹ A retrospective survey found a CYP2D6 PM on 5 mg/day of haloperidol had akathisia, and another had a history of neuroleptic malignant syndrome with intensive-care-unit treatment after receiving high doses of haloperidol.⁴²

^bAfter adjusting for confounders, a large risperidone study found that the odds ratio (OR) of the CYP2D6 PM patients and 95% confidence intervals (CI) of having clinically relevant side effects on risperidone was 3.4 (CI: 1.5–8.0) and of discontinuing risperidone because of side effects was 5.6 (CI: 1.3–23.9). The CYP2D6 PMs appear protected from risperidone side effects when taking low doses, approximately less than half of the usually recommended dose.⁴³

^cInverted ratios, risperidone/9-hydroxyrisperidone >1 were considered a sign of CYP2D6 PM in absence of CYP2D6 inhibitors.⁴⁴ In 281 risperidone subjects treated in a naturalistic way,⁴³ 53 (or 19%) had inverted ratios (risperidone/9-hydroxyrisperidone >1). Of the 53, 36% (19/53) were CYP2D6 PMs, 43% (23/53) were taking powerful CYP2D6 inhibitors (paroxetine, fluoxetine, or bupropion), and most of the remaining 21% (11/53) were CYP2D6 EMs or IMs taking other CYP inhibitors or CYP2D6 medications.

^dCYP2D6 PMs may have high average C/D haloperidol of 0.8 but these high C/D ratios do not appear specific. One article described a CYP2D6 PM with a high C/D of 0.8;⁴⁵ the CYP2D6 EMs averaged 0.37, but ranged as high as 0.93. In another study,⁴¹ in patients taking doses >20 mg/day, the C/D was approximately 0.84 in CYP2D6 PMs and 0.65 in EMs. Two CYP2D6 PMs had average C/D ratios after repeated measures of 0.26 and 0.60, but the patient with slower haloperidol metabolism was a CYP2D6 EM with a very high C/D of 1.1, suggesting that other enzymes may be important in explaining cases of poor haloperidol metabolism.⁴¹

^eWilliams⁴⁶ described recommended risperidone doses for usual patients according to age, previous use of antipsychotics, and the presence of dementia. On the basis of the first author's experience with a larger risperidone naturalistic study,⁴³ it is recommended that CYP2D6 PMs take half or less of the upper range Williams⁴⁴ recommended.

^fSome case reports support the idea that CYP2D6 UMs may not respond to the usual doses of risperidone treatment.^{47,48} In a large, naturalistic study of 212 patients who discontinued risperidone, there were 5 CYP2D6 UMs. The reasons for discontinuation were assessed retrospectively and blind to genotyping. None of the 5 UMs was discontinued because of lack of response, although 14% of the 212 patients were discontinued because of lack of response.⁴³

^gA study of 5 CYP2D6 UMs suggested that UMs have poor response, with less decrease in psychotic symptoms, and more side effects when they are treated with haloperidol.⁴⁰ Some case studies suggest that UMs may not respond to usual phenothiazine doses,⁴⁹ but one study found no overrepresentations in 235 treatment-refractory patients.⁵⁰

^hAll 9 genotyped CYP2D6 UMs in the first author's study⁴³ had very low risperidone/9hydroxyrisperidone: ≤ 0.10 . In CYP2D6 EMs, the mean for risperidone/9hydroxyrisperidone was 0.19, and a good number had ≤ 0.10 . In fact, 111 subjects (10 UMs, 100 EMs, and 1 IM) had risperidone/9hydroxyrisperidone ≤ 0.1 . This finding suggests that a risperidone/9hydroxyrisperidone of ≤ 0.10 is very sensitive but nonspecific for UMs. Another interpretation is that some subjects classified by our genotyping as EMs are really UMs in which the genetic variation associated with high activity has not been yet identified.

ⁱCYP2D6 UMs may have low average C/D haloperidol of 0.2. One study found that the C/D was approximately 0.65 in EMs and 0.2 in UMs in patients taking doses >20 mg/day.⁴⁰ In one CYP2D6 UM, the C/D ratio was 0.27.⁴²

APPENDIX 3. Clinical Guidelines for Selecting a Laboratory to Send Samples for CYP Genotyping

- A. Become familiar with a laboratory. Obviously if you have previous experience with a laboratory for other tests, the previous experience may help you in making the selection.
- B. Consider benefits and problems of comprehensive laboratories (academic or commercial) versus commercial laboratories specializing in genotyping.
- C. Remember that the clinical applications of pharmacogenetics are very limited, and many of the gene tests have very limited evidence supporting their use.
- D. Be aware that laboratory standards for pharmacogenetic testing have not been developed yet, and there are going to be false positives and false negatives. The only equipment approved by the FDA is the Roche AmpliChip CYP450, which genotypes for CYP2D6 and CYP2C19.³ The false negatives and false positives will be influenced by the specific laboratory, technique, equipment (ask which one is used) and, importantly, by the number of alleles tested and by the patient's race.
 1. CYP2D6 UM
 - a. Most laboratories will only tell you that the patient has 3 or more active copies
 - b. Knowing the number of active copies is important (more copies leads to more activity), but the number is not offered by clinical laboratories.
 - c. Current genetic testing may have false negatives. According to some studies, 70%–90% of CYP2D6 UMs are not identified by current genotyping methods.^{22,23}
 2. CYP2D6 PM
 - a. Remember that traditional methods diagnose normal alleles (*1) by the absence of tested alleles,^a and testing too few alleles will underdiagnose CYP2D6 PMs and will overdiagnose CYP2D6 EMs.
 - b. Misclassification of a CYP2D6 PM as EM by the laboratory is much more likely when the subject is classified by the laboratory as heterozygous EM (one normal allele) than when the patient is classified as homozygous EM (two normal alleles).
 - i) In Caucasians: CYP2D6 PMs are much more frequent (Table 2); four alleles *3, *4, *5, and *6 account for most (98%) inactive alleles⁵⁹; false negatives (CYP2D6 PMs mislabeled as CYP2D6 EMs) are probably rare in most laboratories, but check that they are at least testing these 4 alleles.
 - ii) In other races: CYP2D6 PMs are less frequent (Table 2); if clinical data is strongly suggestive of CYP2D6 PM, but the laboratory classifies the subject as CYP2D6 EM, discuss with the laboratory the risk of a false negative.
 3. OTHER CYP2D6 PHENOTYPES: current knowledge of the CYP2D6 IM clinical meaning is limited. Some alleles (*10, which is frequent in Asians and *17, which is frequent in Blacks) may have different activity for different drugs.
 4. CYP2C19 PM
 - a. Remember that traditional methods diagnose normal alleles (*1) by the absence of tested alleles^a; two defective alleles, *2 and *3, should be tested (other defective alleles are rare).
 - i) In Asians: CYP2D6 PMs are much more frequent (Table 2); two alleles, *2 and *3, account for almost all inactive alleles.²⁸
 - ii) In other races: CYP2D6 PMs are less frequent (Table 2); defective alleles besides *2 are rare.²⁸

Note: ^aThe traditional genotyping systems call the allele *1 by default when the rest of the tested alleles are not detected. The AmpliChip CYP450 Test does not really call the allele *1 by default, since it has a wild-type probe and mutant probe. It queries directly for either the wild-type or mutant sequence.