

Pharmacogenomic potential of psychiatric medications and CYP2D6

By Kevin F. Foley, PhD, D(ABCC), MT, and Denise I. Quigley, PhD, F(ACMG)

Drugs used for psychiatric applications span a wide range from mood-altering drugs like antidepressants, to anti-psychotics used in schizophrenia. Drugs for anxiety, attention deficit/hyperactivity, and delirium are also included in this class. We also know from first- or second-hand experience that reports of efficacy with these medications can vary widely. Many psychiatric patients are familiar with the notion of “trying” new medications and new treatment regimens under the direction of their physicians to see if the drugs improve their conditions. Pharmacotherapy in psychiatry is almost always performed on a trial-and-error basis; a given drug or treatment’s efficacy is assessed individually and empirically by patients and their physicians. The inter-individual differences in response to treatments as well as the variability in side effects experienced by the psychiatric patient are a well-known phenomenon. Treatment failure in psychiatry is common.

Pharmacogenomics

Psychiatry could turn out to be one of the strongest benefactors of pharmacogenomics (PGx) testing. Pharmacogenomics is the study of how individual variations in the human genome affect disposition and response to medications. Although there are multiple factors which can affect drug response, a predominant factor is the inter-individual differences in the function and/or expression of drug-metabolizing enzymes.

In PGx, polymorphisms can help predict drug response. Polymorphisms are alterations in a gene (allele) affecting at least 1% of the population. Such alterations may or may not affect the function of the resultant protein product. For those variant proteins that do alter drug disposition or response, if they can be uncovered *a priori*, that knowledge should help predict drug response.

Although polymorphisms in a gene’s coding for drug receptors and transporters have been shown to affect drug response, the most well-studied proteins in PGx are the cytochrome P450 enzymes (CYP450), a large group of heme-containing enzymes which are found predominantly in the liver. CYP450 enzymes work on a variety of substrates, altering their molecular structures to facilitate excretion. These enzymes account for much of the liver’s detoxifying action, altering endogenous and foreign compounds so they can be excreted from the body.

There are many different CYP450 enzymes which metabolize psychiatric drugs. CYP1A2, CYP2C9, and CYP2C19 are all associated with genetic polymorphisms which can affect psychiatric-drug performance. The CYP450 enzyme of most interest in psychiatric applications, however, is CYP2D6, as it is thought to be responsible for the metabolism of at least 25% of all drugs.¹ CYP2D6 accounts for only about 1% of all CYP450 enzymes but is important in the metabolism of about 100 drugs, many of

which are used in psychiatric applications.^{2,3} There are dozens of CYP2D6-variant alleles which can arise as the result of mutations and polymorphisms. The normal wild-type allele displays average metabolic activity, whereas some variants have enhanced or diminished activity. Some clinical reference laboratories now offer CYP2D6 genotyping, which will indicate whether a patient is a poor, intermediate, extensive, or ultra-rapid metabolizer.

By knowing a patient’s disposition to drugs, he could be started on appropriate dosing regimens without the extensive trial-and-error period that is common with psychiatric medications.

By measuring a dozen or so of the most common and significant variant sites, a laboratory can detect approximately 98% of known variant CYP2D6 alleles. How common are these variants? The prevalence varies from <1% to as much as 21%. It is estimated, for example, that 8% to 10% of the population has a complete deficiency of CYP2D6.^{4,5} The prevalence of poor metabolizers is thought to be around 6% to 10% for white populations but is lower in other ethnic groups such as Asians and African Americans.^{6,7,8} CYP2D6 activity in the general population of “normal” metabolizers is also known to be highly variable, ranging as much as ten thousandfold between patients.⁹ Clearly, the pharmacogenomics associated with CYP2D6 is relevant to millions of people.

Clinical implications

What are the clinical implications for those who have abnormal CYP2D6 metabolism? Poor metabolizers (PM) are persons who carry two deficient CYP2D6 alleles and, as a result, exhibit decreased metabolism of drugs. These patients require lower dosages to establish therapeutic levels of drug *in vivo*. A PM patient who receives a standard dose is more likely to experience unwanted side effects — or even toxicity — since he will metabolize and clear the drug more slowly. This is important when considering the high rate of unwanted side effects experienced by patients on mood-altering drugs — side effects which often lead to discontinuation of therapy.

Poor metabolizers can also experience diminished effects with drugs that need to be metabolized to active compounds by CYP450s. Using an analgesic example, the prodrug codeine, which is converted to morphine *in vivo*, will not be adequately transformed in PM patients, leading to diminished pain relief or the appearance of tolerance/addiction. Intermediate metabolizers (IM) have one wild-type copy of the gene and one absent, or dysfunctional, copy. The IM group is very heterogeneous.

Persons with normal enzyme activity who carry two functional alleles are referred to as extensive metabolizers (EM). These patients should respond to standard dosages although, as with the IM group, the EM response is also wide ranging. Ultra-rapid metabolizers (UM) have more than two functional alleles due to gene duplication or multiplication. Because of this, they require higher doses than normal, since drug metabolism and clearance is enhanced. These patients may be resistant to treatments, and more time may be required to adjust the dosage before therapy is achieved. In theory, identifying a CYP2D6 UM upfront, would decrease the time needed to adjust a dosage upward, helping to achieve therapeutic success faster.

Other variables besides mutations affect CYP450 enzymes. Many drugs are known to induce the expression of CYP450 enzymes. CYP450 enzyme levels change in the presence of certain chemicals. Smoking, for example, can induce CYP1A2. St. John's wort can induce CYP3A4. Additionally, the drugs carbamazepine, rifampin, and phenobarbital can induce many CYP450s, including CYP2D6. Of course, CYP450s can also be inhibited by substances and substrates. CYP2D6 can be inhibited by many drugs including common medications like cimetidine (Tagamet) and fluoxetine (Prozac). Because most patients are on multiple medications and since dietary and environmental factors can change CYP450 expression levels, the metabolic capacity of patients cannot be solely predicted based on their genotypes. To consider both when ascribing the predictive power of a genotype and when trying to justify the cost of genotyping is important.

Genotype vs. phenotype

Genotyping can give a definitive profile of CYP2D6 alleles. But because there are more than 70 known mutations and polymorphisms that can occur on CYP2D6, even large, well-equipped reference laboratories are not likely to offer complete screening or sequencing. Most genotyping approaches only test for the most common or best characterized alleles. Without complete sequencing of the entire allele, one may not be able to completely rule out a relevant mutation or polymorphism in a patient who shows none of the more common alleles. Yet, complete sequencing methods are currently cost-prohibitive and if less-common variants are uncovered, the significance of these will likely be unknown. Thus, complete sequencing may only confound the interpretation, since the significance of all possible mutations has not yet been ascertained.

When one considers the number of variants, the fact that multiple CYP450s may be involved in a drug's metabolism and the possible presence of inducing/inhibiting substances in the patient, phenotyping for drug metabolism can sound more attractive than genotyping. For CYP2D6, this can be accomplished with the use of probe drugs like dextromethorphan or debrisoquine. Dextromethorphan is a common over-the-counter cough suppressant which is extensively metabolized by CYP2D6. The primary metabolite is the demethylated compound dextrorphan. By measuring the parent drug and the metabolite in urine, the metabolic capacity of CYP2D6 can be estimated. This test is, however, labor intensive, requiring chromatography and/or mass spectrometry techniques; questions remain concerning its sensitivity.

Simple therapeutic drug monitoring of the drug in question can also reveal a good deal about a drug's metabolism and, like probe-drug analysis, would take into account the influence of

external factors like co-medications, diet, smoking, and impaired organ function. But using therapeutic drug monitoring requires that an assay be available for the psychiatric drug in question. Immunoassays for most CYP2D6-metabolized psychiatric medications are not widely available for automated analyzer platforms. When antibody assays are available, they are more often employed as qualitative toxicology assays rather than quantitative drug-monitoring assays. Gas chromatography with mass spectrometry (GC-MS) can be used for nearly all psychiatric drugs, but such equipment is common only in larger reference laboratories and, again, any GC-MS assay must be set up as a quantitative assay rather than a more simple qualitative drug screen if the results are to have value in gauging drug metabolism.

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Also consider the complications surrounding specimen collection. Multiple serum and/or urine specimens are needed to assess a drug's metabolism *in vivo*. This would be a significant pre-analytical challenge compared with genotyping which requires only one blood sample for the entire life of the patient.

It is important to point out that probe-drug analysis is not, in principle, synonymous with therapeutic-drug monitoring. Unlike genotyping and probe-drug testing, therapeutic-drug monitoring is performed during therapy, and, thus, it is not predictive of drug disposition. Instead, it simply reports drug disposition after therapy has started and reached steady state. Given the complexities of probe-drug analysis, genotyping of CYP2D6 is likely to be the method of choice for predicting patient drug response, despite its limitations. Yet, if quantitative therapeutic drug monitoring methods for psychiatric drugs are in place, they can be used alongside genotyping. Ideally, a genotype would first predict response, and then therapeutic-drug monitoring could be used to verify appropriate serum drug levels.

Summary

The ultimate goal in measuring CYP2D6 (or any other CYP450) function or identifying variant alleles is to predict effective therapeutic doses and responses in patients. This is the promise of individualized medicine. By knowing a patient's disposition to drugs, he could be started on appropriate dosing regimens without the extensive trial-and-error period that is common with psychiatric medications. We could also avoid drugs whose metabolism may prove to be problematic, choosing second-line therapies which are metabolized by different, unaffected enzymes. Of course, knowing a genotype is not very useful unless we couple the genotype findings with clinically validated dosing algorithms.

Dosing recommendations for PM, EM, IM, and UM patients are beginning to appear in the literature for various classes of drugs but, at present, there are no well-accepted guidelines available. The Food and Drug Administration does encourage the incorporation of pharmacogenomic testing for investigational compounds in the development process. As the notion of PGx becomes more familiar and more clinical trials are completed, evidence-based dosing adjustments should be forthcoming.

Although the biochemistry and pharmacology of CYP450

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drug metabolism has made huge strides, the application of pharmacogenomics has not yet become commonplace for a number of reasons. Drug metabolism is a complex process, and CYP2D6 may not be the only polymorphic protein involved in a given drug's metabolism. Also, both primary and secondary metabolic pathways exist for drugs, the latter of which may be utilized when other drugs or endogenous compounds occupy the principle pathway. Given the possibility of multiple metabolic pathways, the presence of co-medications, inducers, and inhibitors in the diet and disease changes, predicting drug metabolism in a person remains difficult even when a given CYP450 genotype is obtained.

Also there are multiple variants which can be present and consideration must be given as to which variant allele(s) to look for while, at the same time, always considering the cost/benefit ratio of a possible testing algorithm. Despite the numerous uncontrolled variables involved in drug metabolism and the inability for pharmacogenomics to address them all, there remains some promise for CYP2D6 genotyping to at least help physicians hone in on appropriate dose ranges before therapy is initiated or in identifying individuals at metabolic extremes who are at the highest risk for adverse outcomes. Ultimately, if CYP2D6 characterization is shown to be an evidence-based improvement in the practice of psychiatric medicine, laboratorians will need to be prepared for an influx of requests for these tests. □

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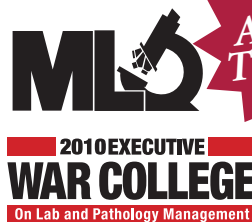
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