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Psychotropic medications: optimal prescribing through the utilization of genetic testing

Abstract

Psychiatric drug treatment is characterized by large interindividual differences in drug response and dosage requirements. Interindividual variability in drug response can be a major clinical problem and may lead to discontinuation of potentially efficacious medications. Research suggests that individual variability in *CYP* enzyme activity is an important reason for drug therapy failure. The most substantial variability in medication metabolism is due to genetic polymorphisms. The polymorphisms present in most *CYP* genes, are responsible for a substantial part of this variability. Research has found that four *CYP* phenotypes can be identified: poor (slow) metabolizers (PM); intermediate metabolizers (IM); extensive metabolizers (EM); and the ultra-rapid metabolizers (UM), who have multiple gene copies. The ultra-rapid metabolizer (UM) phenotype is recognized as a cause of therapeutic inefficacy of antidepressant (due to resulting low serum levels), whereas an increased risk of toxicity and side effects has been reported in poor (slow) metabolizers (PMs) with several psychotropics (desipramine, venlafaxine, amitriptyline, haloperidol). Based on a review of the literature, it is reasonable to assume that some individuals will metabolize relevant drugs too quickly (and perhaps be nonresponders) and others may metabolize medications too slowly and become toxic and symptomatic. These groups perhaps represent individuals who would benefit most from the genetic testing. Despite cost and inconvenience of testing, these individuals may benefit.

Keywords: psychotropic medications, variable efficacy, nonresponders, liver enzymes, cytochrome

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Review

Psychiatric drug treatment is characterized by large interindividual differences in drug response and dosage requirements. For example, only half of the patients will respond to antidepressant treatment and only one-third of patients experience a full remission of symptoms.[1] In terms of antipsychotic medication, approximately 20% to 35% of people affected by schizophrenia, under optimal antipsychotic prescribing fail to respond to antipsychotics.[2] Response and tolerability to medication are highly variable, with some patients responding to one treatment but not another.

Interindividual variability in drug response can be a major clinical problem and may lead to discontinuation of potentially efficacious medications. Additionally, some medications including certain antipsychotic medication have a narrow therapeutic index and significant side effects.[3] The clinical effect of a psychotropic drug depends on several factors influencing the pharmacogenetics and pharmacodynamics of the drug. The majority of drugs are metabolized by drug metabolizing enzymes, of which the cytochrome P450 (*CYP*) enzymes are especially important in metabolizing antipsychotics and antidepressants.[4]

Research suggests that individual variability in *CYP* enzyme activity is an important reason for drug therapy failure.[4] Variability in *CYP* activity may be caused by various factors, including endogenous factors such as age, gender and morbidity as well as exogenous factors such as co-medication, food, and smoking habits. However, the most substantial variability in medication metabolism is due to genetic polymorphisms. The polymorphisms present in most *CYP* genes, are responsible for a substantial part of this variability. Moreover, estimates suggest that 60% to 80% of commercialized drugs are metabolized by polymorphic enzymes.[5] Some research suggests that therapeutic failures and adverse drug reactions may be largely due to variations in drug metabolism. Although *CYP* genotyping has been shown to predict the majority of aberrant phenotypes, it is currently rarely performed in clinical practice, particularly in prescribing psychotropics.

The P450 enzyme with the most variation in different people is the *2D6*. The *2D6* enzyme processes many antidepressants and antipsychotic medications. Specifically, *2D6* is responsible for up to 25% of commonly prescribed antidepressants, antipsychotics, and other medications.[5] The *CYP2D6* PM phenotype may be associated with risperidone ADRs and discontinuation due to adverse drug reactions (ADRs). Venlafaxine, aripiprazole, duloxetine, and atomoxetine are newer drugs metabolized by *CYP2D6* but studies of the clinical relevance of *CYP2D6* genotypes are needed.[6]

Due to *CYP* enzyme variability people speed of metabolism can be classified along a continuum (poor (slow), normal, extensive (fast), ultra-rapid). Research has found that four *CYP* phenotypes can be identified: poor metabolizers (PM); intermediate metabolizers (IM); extensive metabolizers (EM); and the ultra-rapid metabolizers (UM), who have multiple gene copies. The ultra-rapid metabolizer (UM) phenotype is recognized as a cause of therapeutic inefficacy of antidepressant medication, where as an increased risk of toxicity has been reported in poor metabolizers (PMs) with several psychotropics (desipramine, venlafaxine, amitriptyline, haloperidol). The *CYP*2C19 is another enzyme commonly involved in the metabolism of several antidepressants.[5] As a result, there may be an increased risk of adverse effects in *CYP*2C19 poor metabolizers (PM's). Dose reductions have been recommended for some agents to prevent toxicity. IM's represent 10–15 % of Caucasians but are much more frequent in Asians (up to 50 %) because of the high prevalence of the defective allele *10, and up to 30 % of Africans in whom the allele *17 is frequent. The carriers

of gene duplications or multi-duplications are considered the ultra-rapid metabolizer (UMs) phenotype (1–10 % of Caucasians).[7]

Pharmacogenetics is becoming an important component of appropriately prescribing medications. Currently, the US Food and Drug Administration requires drug labels to contain information about pharmacogenetic biomarkers for 26 different psychiatric medications. Determining the appropriate medication dosage involves multiple considerations, including patient age, other perhaps interacting drugs, and genotypic driven *CYP* enzyme activity. The frequency of poor (slow) metabolizers differs among ethnic groups. Less than 1% of Asians, 2-5% of African-Americans, and 6- 10% of Caucasians are poor metabolizers of *CYP2D6*.[8] The most common variant alleles in Caucasians are *CYP2D6**3, *4, *5, and *6, which account for about 98% of poor metabolizers.[9] Genotyping *CYP2D6* has been shown to successfully predict the clearance of fluoxetine, fluvoxamine, desipramine, and some other psychotropic medications.[10] In some instances, the genotype for *CYP2D6* has been useful in predicting adverse effects associated with antidepressants and neuroleptics. A systematic review assessing 46 studies looking at cytochrome polymorphisms in schizophrenics taking antipsychotics found the genotyping helpful in determining who might develop Parkinsonism and Tardive Dyskinesia. Some research[11] suggests pharmacogenetics could at least partially predict antidepressant response. Kato et al.,[11] suggests the personalized pharmacogenetic approach may be helpful in predicting response to depression treatment. Currently, preliminary dosage recommendations based on *CYP2D6* genotypes are available for antidepressants.[12]

Because side effects of many antipsychotics are dose-dependent, and related to serum level, genotyping may be valuable for patients taking agents that are primarily metabolized by *CYP2D6*[13] Clinicians now have access to laboratory resources and FDA-approved methods for assessing *CYP2D6* gene variants.[14] However, it is debatable, whether this testing which can be expensive (≥$400) and may not be covered by health insurance-improves patient outcomes.[15] However, some insurance companies do consider genotyping for *CYP2D6* and *CYP* 2C19 medically necessary for certain medications and conditions.

Several studies and even a systematic review suggest that the evidence for the utility of using genetic polymorphisms in clinical psychopharmacology is weak for treating schizophrenia and perhaps other psychiatric disorders.[16,17] Studies show that tests for determining genotypes appear to be accurate, but research suggest a current absence of convincing evidence of clinical utility.[16] Based on the reviews it is unclear if the absence of evidence for clinical efficacy is due to insufficient empirical research on the topic or if the genotyping only truly benefits few individuals. Based on the limited evidence, and high cost, perhaps universal use is not supported, but it would make clinical sense to use this testing for people who are limited or poor responders or for those who have unusual medication responses such as becoming toxic on standard medication dosages. Another relevant variable in this research is the fact that from a conceptual perspective, this testing may only be clinically relevant to individuals who are either poor metabolizer or ultra-rapid metabolizers.

Conclusion

Medication metabolism is a clinically relevant issue and could potentially account for both nonresponders (in ultra-rapid metabolizer) and also toxicity and side effects (in poor metabolizers). Given the ease and accessibility of genetic testing for *CYP* polymorphisms, some clinicians suggest these tests should be more commonly utilized in clinical practice. However, various factors currently diminish the frequency of use of this testing. Specifically, the tests are expensive, may not be covered by insurance, may delay the prescribing of needed medications and much of the research on these tests suggest that they have not been found to produce clinical benefits to many patients. Based on a review of the literature, it is reasonable to assume that some individuals will metabolize relevant drugs too quickly (and s that perhaps be nonresponders) and others may metabolize medications too slowly and become toxic and symptomatic. These groups perhaps represent individuals who would benefit most from the genetic testing. There is no way to predict, before that fact, who will fall into these groups, unless of course the patient has a history of unusual medication reactions/responses. An unusual medication response history may be an appropriate trigger for genetic testing.

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Conflicts of interest

Author declares there are no conflicts of interest.

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