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

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 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 CYP2C19 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 CYP2C19 poor metabolizers (PMs). 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 multiplications 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 schizophrenia 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 researchers 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 others 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.

**References**

1. Narasimhan S, Lohoff FW (2012) Pharmacogenetics of antidepressant drugs: current clinical practice and future directions. Pharmacogenomics 13(4): 441-464.
2. Conley RR, Kelly DL (2001) Management of treatment resistance in schizophrenia. Biol Psychiatry 50(11): 898-911.
3. Mitchell PB (2001) Therapeutic drug monitoring of psychotropic medications. Br J Clin Pharmacol 52(Suppl 1): 45S-54S.
4. Van der Weide J, Hinrichs JW (2006) The influence of cytochrome P450 pharmacogenetics on disposition of common antidepressant and antipsychotic medications. Clin Biochem Rev 27(1): 17-25.
5. Samer CF, Lorenzini KL, Rollason V, Daali Y, Desmeules JA (2013) Applications of CYP450 testing in clinical setting. Mol Diagn Ther 17(3): 165-184.
6. Zhou SF (2009) Polymorphism of human cytochrome P450 2D6 and its clinical significance: part II. Clin Pharmacokinet 48(12): 761-804.
7. Ingelman-Sundberg M, Oscarson M, McLellan RA (1999) Polymorphic human cytochrome P450 enzymes: an opportunity for individualized drug treatment. Trends Pharmacol Sci 20(8): 342-349.

8. Kalow W, Otton SV, Kadar D, Endrenyi L, Inaba T (1980) Ethnic difference in drug metabolism: debrisoquine 4-hydroxylation in Caucasians and Orientals. Can J Physiol Pharmacol 158(9): 1142-1144.

9. Gaedigk A, Gotschall RR, Forbes NS, Simon SD, Kearns GL, et al. (1999) Optimization of cytochrome P4502D6 (CYP2D6) phenotype assignment using a genotyping algorithm based on allele frequency data. Pharmacogenetics 9(6): 669-682.

10. Spina E, Gitto C, Avenoso A, Campo GM, Caputi AP, et al. (1997) Relationship between plasma desipramine levels, CYP2D6 phenotype and clinical response to desipramine: a prospective study. Eur J Clin Pharmacol 51(5): 395-398.

11. Sharif ZA (2003) Pharmacokinetics metabolism, and drug-drug interactions of antipsychotics in special populations. Primary Care Companion J Clin Psychiatry 5(Suppl 6): 22-25.

12. Kirchheiner J, Brosen K, Dahl ML, Gram LF, Kasper S, et al. (2001) CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. Acta Psychiatr Scand 104(3): 173-192.

13. Kirchheiner J, Rodriguez-Antona C (2009) Cytochrome P450 2D6 genotyping: potential role in improving treatment outcomes in psychiatric disorders. CNS Drugs 23(3): 181-191.

14. de Leon J, Susce MT, Murray-Carmichael E (2006) The AmpliChip CYP450 genotyping test: integrating a new clinical tool. Mol Diagn Ther 10(3): 135-151.

15. Bishop JR, Chae S (2010) Should you order genetic testing to identify how patients metabolize antipsychotics? Current Psychiatry 9(9): 32-34.

16. Freeman N, McLeod C, Bagust A, Beale S, Boland A, et al. (2010) The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics: A systematic review and economic evaluation. Health Technol Assess 14(3): 1-157.

17. Singh AB, Bousan CA, Ng C, Berk M (2014) Antidepressant pharmacogenetics. Curr Opin Psychiatry 27(1): 43-51.

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