LITERATURE REVIEW   **Open Access**

Overview of pharmacogenomic testing in clinical practice

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Abstract

Introduction: Pharmacogenomic tests relevant to neuropsychiatric medications have been clinically available for more than a decade, but the utility of regular testing is still unknown. Tests available include both pharmacokinetic and pharmacodynamic targets. The potential practice benefits vary with each target.

Methods: A 10-year literature review was completed utilizing the PubMed database to identify articles relating to the specific pharmacogenomic targets discussed. Further article selection was based on author review for clinical utility.

Results: The clinical dosing guidance available for neuropsychiatric medications such as selective serotonin reuptake inhibitors and tricyclic antidepressants with varying genotypes is useful and has strong evidence to support testing, but it is limited to mainly pharmacokinetic application. Pharmacodynamic targets are gaining additional evidence with increased research, and although the mechanisms behind the potential interactions are scientifically sound, the bridge to clinical practice application is still lacking.

Discussion: Although the benefits of decreasing adverse reactions and improving response time are appealing, clinicians may not utilize pharmacogenomic testing in routine practice due to several barriers. Further clinical guidance and studies are needed to support testing for other neuropsychiatric medications and targets.

Keywords: pharmacogenomics, cytochrome P450, CYP, pharmacokinetic, pharmacodynamic

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Introduction

Psychopharmacology is a dynamic field with new medications, novel targets, and innovative methods of delivering pharmacotherapy developed and approved each year. Practitioners must also adjust to ever-changing regulations that alter the way care is delivered. An increasing area of focus is the utility of pharmacogenomics. Certain aspects of pharmacogenomic testing are familiar. For example, the package insert for carbamazepine recommends testing for HLA-B*1502 in patients with Asian ancestry due to the estimated 10-fold increased risk of Stevens-Johnson syndrome in this population.[1] Mental health clinicians with a high percentage of patients testing positive for human immunodeficiency virus in their practice may recall the warning on abacavir-containing products recommending HLA-B*5701 testing due to an increase in hypersensitivity reactions in patients possessing this allele.[2] Additionally, it is now easier to obtain a pharmacogenomic report as many of these can be obtained in a medical office with a saliva sample. Medical systems and companies who develop these products are capitalizing on these changes and are drawing more public attention. Advances in pharmacogenomic testing are even featured on the nightly news.[3] The majority of tests on the market include both pharmacokinetic (PK) and pharmacodynamic (PD) genomic panels.

TABLE 1: Common pharmacogenomic testing targets

Target	Codes For	Affected Medication Example
CYP1A2	CYP1A2 allele	Clozapine
CYP2B6	CYP2B6 allele	Bupropion
CYP2C9	CYP2C9 allele	Doxepin
CYP2C19	CYP2C19 allele	Citalopram
CYP3A4/5	CYP3A4/5 allele	Lurasidone
CYP2D6	CYP2D6 allele	Fluoxetine
UGT1A4	UGT1A4 allele	Lamotrigine
UGT2B15	UGT1A4 allele	Lorazepam
COMT	Catechol-o-methyltransferase	Methylphenidate
DRD2	Dopamine-2 receptor	Haloperidol
ADRA2A	Alpha-2A receptor	Guanfacine
MTHFR	Methylenetetrahydrofolate reductase gene	Folic acid
SLC6A2	Norepinephrine reuptake transporter	Venlafaxine
SLC6A3	Dopamine reuptake transporter	Bupropion
SLC6A4	Serotonin reuptake transporter	Paroxetine
HTR2A	Serotonin-2A receptor	Quetiapine
HTR2C	Serotonin-2C receptor	Olanzapine
HLA-A*3101	HLA-A*3101 allele	Carbamazepine
HLA-B*1502	HLA-B*1502 allele	Carbamazepine

Pharmacokinetic genes affect the body's absorption, distribution, metabolism, and elimination of medications. The cytochrome P450 (CYP) enzyme family is the major PK mechanism for the biotransformation of medications and can have several variations that affect the way medications are metabolized. Pharmacodynamic genes affect what the medication does to the body and could alter efficacy or adverse-effect profile of the medication. The purpose of this article is to review the components of neuropsychiatric-focused tests, their biological relevance, and potential clinical implications.

Methods

A literature search was conducted using the PubMed database for articles relating to the clinical implications of pharmacogenomic testing. Combinations of the following search terms were used: pharmacogenomic or pharmacogenetic, pharmacodynamic, pharmacokinetic, cytochrome P450, CYP450, specific targets (various CYP450 enzymes, SLC6A4, HTR2A, DRD2, COMT, and HTR2C), and psychiatry. Articles were only included in the initial review by the authors if they were human studies written in English published between June 1, 2007, and June 1, 2017. The authors reviewed the abstracts of the articles returned in the search to determine the level of discussion of clinical practice utility. Articles discussing clinical utility in the abstract were fully reviewed, and author clinical discretion was utilized to determine inclusion within the review. A more robust list of testing targets and their functions commonly found in commercially available tests can be found in Table 1.

Results

Pharmacokinetic Targets

Different polymorphisms of the CYP enzymes can lead to loss of function, decreased function, or increased function of the CYP enzymes. These polymorphisms lead to categories such as poor metabolizer, intermediate metabolizer, extensive/normal metabolizer, and ultrarapid metabolizer. A poor metabolizer is a patient that has little to no enzyme activity, normally from having 2 copies of nonfunctioning alleles, resulting in decreased ability to metabolize medications effectively and increased risk of adverse effects. This can also cause treatment failure of prodrug medications as they will not be converted to the active form. Intermediate metabolizers have impaired metabolism but not to the same degree as poor metabolizers. This is normally caused by at least 1 allele that does not function normally. Extensive metabolizer, as listed in many of the commercially available tests, is considered normal. Guidelines now recommend the term normal metabolizer to describe these individuals. Last, ultrarapid metabolizers have increased enzyme activity compared to normal metabolizers, resulting from at least 1 duplicated allele or alleles with increased function. This leads to an increased capacity to metabolize medications, potentially leading to a lack of efficacy for most medications or increased adverse effects of prodrugs due to faster conversion. A more in-depth review of pharmacogenomics nomenclature can be found in the consensus terms document authored by the Clinical Pharmacogenetics Implementation Consortium (CPIC).[4]

The CYP 1 to 3 families are involved in phase I drug metabolism. A subset of these CYP enzymes has known implications for psychiatric medications, including CYP1A2, CYP2B6, CYP3A4/5, CYP2C9, CYP2C19, and CYP2D6.[5] Of these, only CYP2D6 and CYP2C19 have clinical guidance for psychiatric medications specifically within the CPIC guidelines. The CPIC periodically gathers data from published literature and assembles comprehensive information for clinicians on existing CYP2D6 and CYP2C19 genotypes and resulting guidance on dosing of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs). The SSRIs with guidance include fluvoxamine, paroxetine, citalopram, escitalopram, and sertraline.[6] For the tricyclic antidepressants, there is strong evidence supporting the variation in amitriptyline

and nortriptyline plasma concentrations with different phenotypes of CYP2D6 and/or CYP2C19. The guidelines further state this data for amitriptyline and nortriptyline can be applied to other tertiary and secondary amines, respectively.[7] The CPIC does not currently have guidance for other classes of medications, but the project is currently ongoing. The guideline from the Dutch Pharmacogenetics Working Group is slightly more robust and often cited. However, as a 2017 review article by Bank et al demonstrated, there is "a high rate of concordance"[8(P599)] between the 2 organizations.

There are approximately 200 medications with pharmacogenomic information in the Food and Drug Administration labeling. Of these, there are 40 neuropsychiatric medications listed.[9] As an example, in the aripiprazole package insert, section 2.7 is labeled "Dosage Adjustments for Cytochrome P450 Considerations." This section provides guidance to administer half of the usual dose of aripiprazole for patients who are known CYP2D6 poor metabolizers or are taking strong CYP2D6 or CYP3A4 inhibitors. For CYP2D6 poor metabolizers also taking a strong inhibitor of CYP3A4 or patients taking strong inhibitors of both cytochromes, the recommendation is to administer a quarter of the usual dose.[10] Other medications have varying degrees of recommendations for dose adjustments depending on known metabolizer status and specific testing performed during early phase dose-finding studies. A list of these medications with targets can be found in Table 2.[9]

Pharmacodynamic Targets

The evidence behind PD gene testing is less clear than PK gene testing. Common PD genes related to neuropsychiatric medications include SLC6A4 serotonin transporter, HTR2A serotonin receptor, DRD2 dopamine receptor, COMT, and HTR2C serotonin receptor.

The SLC6A4 gene codes for the serotonin reuptake transporter and has been associated with response to serotonergic antidepressants. Within the gene's promotor region, there are 3 possible genotypes based on a patient having either 2 short (S) alleles, 2 long (L) alleles, or a combination of the 2 (S/L). There is evidence demonstrating that patients with the L/L genotype are more likely to respond to SSRIs and do so more quickly although this has not been consistent with different ethnic backgrounds. Patients with non-Hispanic, white ancestry demonstrated this benefit, and patients with Asian ancestry were less likely to show the same amount of benefit.[11] There also appears to be no difference in escitalopram efficacy with SLC6A4 polymorphisms in the Indian population.[12] With regard to venlafaxine, a serotonin norepinephrine reuptake inhibitor, the L/L genotype was associated with a greater incidence of first episode remission in older patients from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.[13] However, it should be noted that these studies are generally small and contain very specific groups of people, thus external validity in different populations may be lacking.

The HTR2A gene codes for the serotonin 2A receptor and has been associated with antidepressant response. A common variation in this gene is variant rs6313, with which patients are carriers for either cytosine or thymine polymorphisms. Patients with the thymine polymorphism were more likely to respond to antidepressants in 1 study. If the variant contained thymine at all, the odds ratio of response was 1.33 (95% confidence interval [CI] 1.05-1.68). However, if the patient was homozygous for the thymine polymorphism, the odds ratio increased to 1.85 (95% CI 1.18-2.90). Another variant, rs7997012, was associated with increased antidepressant response in patients carrying a guanine polymorphism (odds ratio 1.92, 95% CI 1.02-3.61) although with wider confidence interval the signal is not as strong.[14] Patients carrying the guanine polymorphism also demonstrated better response to and tolerability of venlafaxine in the treatment of generalized anxiety disorder.[15] Better tolerability often leads to increased compliance, which is well known to be a challenge in treating the mental health population.

The DRD2 gene codes for the dopamine 2 receptor and has been associated with antipsychotic response. The gene, located on chromosome 11q22, contains numerous polymorphisms. One example that has been extensively studied is -141C Ins/Del (rs1799732). Patients with the Ins/Ins genotype are more likely to respond to antipsychotic medications than patients with at least 1 copy of the Del allele.[16] With variant rs2514218, patients who carry the homozygous C allele were significantly more likely to respond to antipsychotics in the first 12 weeks of therapy than those patients who were homozygous for the T allele. With regard to medication adverse effects, more akathisia was reported in C homozygotes taking aripiprazole although greater prolactin elevations were demonstrated in T homozygotes taking risperidone.[17] In another smaller study,[18] patients carrying the C polymorphism of variant rs1079597 demonstrated improvement in the negative symptoms of schizophrenia after a short treatment with amisulpride, a second-generation antipsychotic not currently available in the United States. This may be significant as it is well known that antipsychotics tend to have a more profound effect on the positive symptoms of schizophrenia, and the negative symptoms are more difficult to treat. A larger study would be necessary to fully demonstrate this effect.

The COMT gene codes for catechol-o-methyltransferase and has been associated with antipsychotic efficacy in schizophrenia. The COMT plays a major role in dopamine

TABLE 2: Neuropsychiatric medications with pharmacogenomic drug labeling[9]

Medication[a]	Biomarker	Medication[a]	Biomarker
Amitriptyline	CYP2D6	Galantamine	CYP2D6
Aripiprazole	CYP2D6	Iloperidone	CYP2D6
	CYP3A4		
Aripiprazole lauroxil	CYP2D6	Imipramine	CYP2D6
	CYP3A4		
Atomoxetine	CYP2D6	Lacosamide	CYP2C19
Brexpiprazole	CYP2D6	Modafinil	CYP2D6
Brivaracetam	CYP2C19	Nefazodone	CYP2D6
Carbamazepine	HLA-B*1502	Nortriptyline	CYP2D6
	HLA-A*3101		
Citalopram	CYP2D6	Oxcarbazepine	HLA-B*1502
	CYP2C19		
Clobazam	CYP2C19	Paroxetine	CYP2D6
Clomipramine	CYP2D6	Perphenazine	CYP2D6
Clozapine	CYP2D6	Phenytoin	CYP2C9
			CYP2C19
			HLA-B*1502
Desipramine	CYP2D6	Pimozide	CYP2D6
Dextromethorphan/Quinidine	CYP2D6	Protriptyline	CYP2D6
Diazepam	CYP2C19	Risperidone	CYP2D6
Doxepin	CYP2D6	Tetrabenazine	CYP2D6
	CYP2C19		
Duloxetine	CYP2D6	Thioridazine	CYP2D6
Escitalopram	CYP2D6	Trimipramine	CYP2D6
	CYP2C19		
Eteplirsen	DMD	Valproic Acid	POLG
			ABL2, ASL, ASS1, CPS1, NAGS, OTC
Fluoxetine	CYP2D6	Venlafaxine	CYP2D6
Fluvoxamine	CYP2D6	Vortioxetine	CYP2D6

ABL2 = abelson tyrosine-protein kinase 2; ASL = argininosuccinate lyase; ASS1= argininosuccinate synthase 1; CPS1 = carbamoyl-phosphate synthase 1; DMD = dystrophin; HLA = human leukocyte antigen; NAGS = N-acetylglutamate synthase; OTC = ornithine carbamoyltransferase; POLG = DNA polymerase gamma.

[a]Specific recommendations for each listed medication can be found in the table of pharmacogenomic biomarkers in drug labels on the Food and Drug Administration Web site.

clearance in the frontal cortex and, thus, is often linked to stimulant efficacy in many commercially available tests although this data is controversial. Changes in frontal cortex dopamine metabolism may also affect antipsychotic medication action. For COMT, there are three genotypes, met/met, val/val, and met/val, which result in different enzyme activity. The met/met genotype yields lower enzyme functionality, which may help to restore dopamine levels in the prefrontal cortex, ultimately helping with negative symptoms of schizophrenia and improving cognitive function.[19] In a 10-study meta-analysis from 2016, met/met patients were much more likely to respond to antipsychotic treatment (greater reduction in positive symptoms) and showed a greater decrease in negative symptoms with increased cognitive function. Another interesting finding from this study was a post hoc analysis demonstrating this response in patients treated with atypical antipsychotics but no difference in patients treated with typical antipsychotics.[20] However, 1 study included in the meta-analysis featured patients with the val/val genotype, who were more likely to respond to clozapine and have a reduction in their symptoms.[21] The meta-analysis demonstrates the overall positive benefit of the met/met genotype, yet a review of the individual studies highlights some differing directions of effect. This may further complicate the clinical applicability depending on the level of evidence included within the specific commercial test used by a provider.

The HTR2C gene codes for the serotonin 2C receptor and has been associated with adverse effects of antipsychotic treatment. Older studies allude to an increased risk of extrapyramidal side effects (EPS) in patients with certain polymorphisms of HTR2C. One study[22] examining nearly 100 patients demonstrated a statistically significant increase in EPS in patients carrying the Cys23Ser polymorphism compared to those without the polymorphism. It is noted from this study, however, that nearly half of the patients already had a history of EPS, thus limiting the validity of this claim.[22] Further studies do not support this link between HTR2C polymorphisms and EPS risk. A more reliable link is found in the risk of metabolic syndrome. Variant rs3813929 is very well studied for this risk. This variant exists on the X chromosome. In a 2016 meta-analysis,[23] female patients homozygous for the C allele and male patients expressing the C allele on their X chromosome experienced significantly more weight gain than patients expressing the T allele. Differences at the rs1414334 polymorphism also demonstrated a significantly increased risk of developing metabolic syndrome when treated with olanzapine. As the authors of this study also highlight, due to the variant linked to the X chromosome, it is possible the antipsychotic-induced weight gain may be more evident in male patients than female patients because female patients likely require polymorphisms on both X chromosomes for full effect.[24] As with previous PD targets, there is no clear guidance for medication selection of preventative measures to take for patients with these variants. Even though the studies demonstrate a risk of adverse effects or increased/decreased efficacy, there is still no bridge between the science and practice.

Discussion

Pharmacogenomic testing has been around for over a decade but has been slow to catch on in mental health due to multiple barriers. These include the lack of guidelines, unclear clinical validity, variability in available tests, and cost. In 2004, the Food and Drug Administration[25] approved the first pharmacogenomic test for CYP2D6 and CYP2C19. Now there are more than 20 tests available. None of these products is the same as they all have variability in the genes tested. Further complicating clinical practice, not all tests analyze the same variants within a gene, so results have potential for variation and errors. For example, if a test only assesses limited variants within a gene, a possible variant could be missed that could result in decreased or increased function of the gene. In regards to psychiatric gene testing, some tests may have as little as testing the function of CYP2C19 and CYP2D6 or may contain a full panel of more than 20 genes covering more than 300 medications. Specific

studies used to determine the effect may also skew the level of the effect as highlighted in the COMT section. If only small studies were used, the genotype may not be interpreted correctly.

Display of the results may also be a barrier to clinical use. For example, with many commercially available tests, medications are grouped into 3 different colored boxes, similar to those of a stoplight, based on the potential for interactions. The green box normally signifies no change is necessary in prescribing. The yellow box normally implies at least a moderate degree of interaction is possible. The red box normally implies there is a significant drug-gene interaction. Although there are often reasons next to each medication in the yellow and red boxes that describe a clinical consideration, such as "serum level may be too high, lower doses may be required," prescribers may be more likely to choose something out of the green box instead of the other boxes when it may not be the best choice for the patient. A patient may be prescribed a more expensive, branded product that can be dosed according to labeling when a generically available product may cause no adverse effects for the patient if given in smaller doses. In a population with funding concerns, this may lead to increased, unnecessary costs if the provider does not take the extra time to fully interpret the results. Certain other tests without the stoplight method may include a report generated by a specialized pharmacist and take a patient's current medication list into account. This may add not only gene-drug interactions, but also drug-drug and drug-drug-gene interactions to the interpretation algorithm. These types of tests and reports are helpful; however, tests that provide more information will normally come with a higher cost. These tests also require a provider to read a full report rather than a quick printout; thus, a provider may skim the information and miss important pieces that would drive prescribing.

Few studies have reviewed clinicians' perspectives on pharmacogenomic testing. Most of the studies[26-29] that have been conducted were at practice sites already familiar with and utilizing pharmacogenomic testing. A recent study[29] surveying psychiatric pharmacists showed only 36% considered themselves knowledgeable in pharmacogenomics, and 80% worked at sites that did not offer the testing due to lack of funding. Another recent study[30] was conducted in Singapore, which only routinely tests for HLA-B*1502 prior to carbamazepine initiation. Most responders in this study believe pharmacogenomic testing has potential in clinical practice but cost and lack of clear guidelines were identified as barriers (94.3% and 84.5%, respectively).

As seen in practice, some clinicians are particularly hesitant to order preemptive pharmacogenomic testing. Genetic testing is often only done after a patient has

failed multiple treatments secondary to adverse effects or lack of efficacy, which can cause undue harm to the patient and delay time to response. One study,[31] the Mayo RIGHT study, concluded that preemptive pharmacogenomic testing would benefit most patients, especially those taking multiple medications. A total of 1013 patients had five genes tested: SCL01B1 (predicts statin metabolism), CYP2C19, CYP2C9, VKORC1 (predicts deficiencies in vitamin-K–dependent clotting factors and response to warfarin), and CYP2D6. Of the patients in the study, 99% had at least one actionable variant in the genetic panel that was tested. Of these, both CYP2D6 and CYP2C19, which are important with psychiatric medications, had a high percentage of patients with actionable genotype variants, 79% and 60%, respectively. Additional large studies will provide more evidence to support preemptive testing with the goal of avoiding adverse effects and increasing the prescribing of efficacious medications for patients at initiation of treatment.

Cost and insurance coverage of these tests is another barrier; however, this has improved over time. With competing tests on the market, costs have significantly decreased. Cost of different genetic tests will vary based on specific tests included and level of interpretation as well as several other factors. As evidence continues to show benefits of genetic testing, more insurance companies are picking up coverage of these tests although the copay for the patient may still be a barrier in the mental health population.

Although the evidence for PK targets seems to have more clinical utility currently than the PD targets as demonstrated in the results section above, there are still benefits to performing the testing. A couple decades ago, performing a test to study a patient's CYP450 system for potential treatment failures or adverse effects was unheard of. However, practitioners now know how to adjust medications with this information. It is only a matter of time before the PD targets have this level of evidence. Increased testing yields larger databases to further refine the precision of the testing methods. Additionally, when the clinical practice catches up to the science, a patient with existing testing could benefit without having to be retested.

Exactly who is tested is also a clinical controversy. In practice, some providers reserve pharmacogenomic testing for patients with an extensive list of treatment failures. However, in this population, if a careful history is taken to determine why a patient failed each medication and the provider has a working knowledge of the CYP450 metabolic pathway for each agent, it may be easy to deduce a patient's PK profile. For example, if a patient has adverse effects to fluoxetine, paroxetine, and risperidone at low doses but has tolerated escitalopram with no

issues, it may be safe to assume this patient has some level of deficiency in CYP2D6. Other providers may test all first-episode patients to determine if they possess any metabolic differences to decrease risk for preventable dose-related adverse effects and increase patient compliance. However, if the majority of the population has no abnormal polymorphisms, this may be an unnecessary cost when cautious dosing of the agent would decrease this risk. At the current time, it may be best to test those patients with a family history of medication-related adverse effects/treatment failures and a payer source for the test.

Overall, pharmacogenomic testing can be beneficial to optimize treatment outcomes for patients by avoiding adverse effects and maximizing efficacy. There are many targets to test, and only the PK targets have robust evidence with clinical applicability. There are many studies with PD targets although the application to practice is still not fully defined. Therefore, it remains unclear whether and when to obtain these tests. There are many opportunities for further research into the impact of genotypes on other neuropsychiatric medications.

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