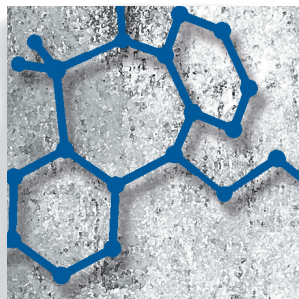


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Pharmacogenetic tests for antipsychotic medications: clinical implications and considerations

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Optimizing antipsychotic pharmacotherapy is often challenging due to significant variability in effectiveness and tolerability. Genetic factors influencing pharmacokinetics and pharmacodynamics may contribute to some of this variability. Research studies have characterized these pharmacogenetic relationships, and some genetic markers are now available as clinical tests. These advances in pharmacogenetics research and test availability have great potential to improve clinical outcomes and quality of life in psychiatric patients. For clinicians considering using pharmacogenetics, it is important to understand the clinical implications and also the limitations of markers included in currently available tests. This review focuses on pharmacokinetic and pharmacodynamic gene variants that are currently available in commercial genetic testing panels. Associations of these variants with clinical efficacy and adverse effects, as well as other clinical implications, in antipsychotic pharmacotherapy are discussed.

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Introduction

Antipsychotics were first introduced in the 1950s to treat psychotic disorders and are now also used in the treatment of other psychiatric conditions. Although antipsychotic medications often need to be used long-term, 1-year discontinuation rates are 32% to 74%, which illustrates a need to improve these treatments.^{1,2} Treatment discontinuation can be partially explained by inadequate response and intolerability. For many patients, treatment selection remains a “trial-and-error” process, requiring multiple medication changes and dose adjustments to achieve a safe and effective balance between therapeutic response and tolerability. The widely observed variability among patients with identical treatment regimens results from multiple factors that can alter both drug metabolism (pharmacokinetics) and drug action (pharmacodynamics). A wide range of clinical and demographic factors (eg, age, sex, ethnicity, disease severity, diet, tobacco/alcohol use, and concurrent medications) can influence variability in both therapeutic and adverse event outcomes. Additionally, genetic variability can contribute to inherited

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Selected abbreviations and acronyms

ABCBI	<i>ATP binding cassette subfamily D member 1</i>
AUC	<i>area under the concentration-time curve</i>
CPATP	<i>clinically available pharmacogenetic test panel</i>
CPIC	<i>Clinical Pharmacogenetics Implementation Consortium</i>
CYP	<i>cytochrome P450</i>
DPWG	<i>Dutch Pharmacogenetics Working Group</i>
DRD2	<i>dopamine D₂ receptor gene</i>
EM	<i>extensive metabolizer</i>
P-gp	<i>P-glycoprotein</i>
PM	<i>poor metabolizer</i>
SNP	<i>single-nucleotide polymorphism</i>
TD	<i>tardive dyskinesia</i>

differences in drug action and metabolism, and there is a growing need to understand how to consider this information in clinical settings. To date, pharmacogenetic research related to antipsychotic treatment has identified numerous polymorphisms across multiple genes involved in both antipsychotic pharmacokinetics and pharmacodynamics, culminating in the availability of commercially available pharmacogenetic tests within the United States and other countries.³ Some antipsychotic agents (eg, aripiprazole, brexpiprazole, iloperidone, and pimozide) have “actionable” pharmacogenetic language listed on their product labels, but guidelines of how best to interpret and apply this information are lacking. The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) are working on guidelines for applying or interpreting pharmacogenetic information in clinical practice. The European Pharmacogenetics Implementation Consortium (Eu-PIC) is also working to integrate pharmacogenetic information into clinical care; however, presently no CPIC and Eu-PIC guidelines and only a few DPWG guidelines (for aripiprazole, risperidone, and haloperidol) exist for antipsychotic medications.⁴ It is therefore important to understand the clinical implications and limitations of pharmacogenes that are now accessible for clinical use.

Pharmacogenetic testing in psychiatry is not yet a standard of practice, but its utilization is increasing and may play a role in advancing a precision-medicine approach through optimizing antipsychotic treatment and dosing strategies. However, its clinical utility remains an ongoing area of investigation. Understanding the

clinical implications of these tests requires clinicians to understand of the underlying biology of pharmacogenetic variants, as well as their associations with treatment outcomes. This review focuses on genetic markers relevant to antipsychotic therapy known to be currently available on pharmacogenetic test panels. We identified clinically available pharmacogenetic test panels (CAPTPs) from the Genetic Test Registry⁵ as well as more broadly through Internet search queries for “pharmacogenetic test” or “pharmacogenomic test.” Testing labs or panels identifying either specific antipsychotic drugs or, more broadly, psychiatric conditions, were examined for genes and variants therein. Whereas our paper elaborates more detailed information on commercially available pharmacogenetic tests, the paper by Eap in this issue (p 313) has a stronger focus on their clinical application.

Pharmacogenetic factors influencing antipsychotic pharmacokinetics

Pharmacogenetic research has traditionally focused on genetic markers involved in the metabolism of antipsychotic medications through hepatic enzyme pathways, primarily by cytochrome P450 (CYP) enzymes. Genetic variation within drug-metabolizing enzymes may result in altered metabolic activity, which may affect pharmacokinetic parameters of antipsychotics. Among the multiple CYP enzymes in the liver, the CYP1, CYP2, and CYP3 families are the most relevant for the biotransformation of antipsychotic drugs and were identified as central to many psychiatric-focused pharmacogenetic test panels.

Genetic variants in metabolism enzymes often result in functional activity changes used to define or predict drug metabolizer phenotypes. Polymorphisms in drug metabolism genes that may affect function include single-nucleotide polymorphisms (SNPs), as well as gene duplications or deletions, small insertions/deletions, or larger copy number variants that affect gene expression or protein conformation. The National Center for Biotechnology Information (NCBI) Single-Nucleotide Polymorphism Database (dbSNP), a public repository for SNP data, assigns unique reference SNP identifiers (rs number) for each variant. For drug-metabolizing enzyme genes, combinations of these polymorphisms are used to define alleles, which historically have a star “*” designation. Diplotypes (star allele combinations,

eg, *CYP2D6* *1/*4) are then used for assignment of genetically defined metabolizer groups, which are generally classified into four main categories. “Extensive/normal metabolizers (EMs/NMs)” display normal enzyme activity, characterized by usually either two normal functional alleles or one normal and one partly reduced-function allele. “Intermediate metabolizers (IMs)” display partly reduced enzyme activity, characterized by one decreased-function and one no-function allele or one normal-function allele and a decreased- or no-function allele.⁶ “Poor metabolizers (PMs)” display little or no enzyme activity, characterized by two non-functional alleles. Lastly, “rapid and ultrarapid metabolizers (UMs)” display increased enzyme activity, characterized by multiple copies of functional alleles or alleles with greater-than-normal activity. The allele combinations for the classification of IMs are gene-specific. The following section reviews some of the clinically relevant aspects of pharmacogenetics related to antipsychotic drug metabolism (*Table I*).

CYP2D6

CYP2D6 is an important hepatic enzyme that serves as the primary metabolic pathway for many antipsychotics (*Table II*).^{4,7,8-19} *CYP2D6* activity greatly affects the bio-transformation of its substrates; therefore, increases or

decreases in *CYP2D6* function influence pharmacokinetics and potentially impact dose-related outcomes.¹⁷

More than 1400 variants have been identified in *CYP2D6* to date.²⁰ *CYP2D6**1, *2, *33, and *35 are classified as active alleles. *CYP2D6* alleles *9, *10, *17, *29, *36, and *41 cause decreased enzyme activity as a result of decreased gene expression (*9, *41) or altered protein conformation (*10, *17, *36).^{18,19} The most common inactive allele in European populations, *CYP2D6**4, has been identified with frequencies ranging from 0% in East Asian to 19% in white European populations. Other loss-of-function alleles include *CYP2D6**3, *5-8, *11-16, *19-21, *38, *40, and *42. The *CYP2D6* PM phenotype has been observed in approximately 7% to 10% of whites, 6% of Asians, and 3% to 8% of African-Americans.²¹ One unique structural characteristic of *CYP2D6* is the presence of duplications or deletions of the whole gene. Deletion of the *CYP2D6* gene results in the aforementioned *5 allele, whereas duplication of the gene results in an UM phenotype (*2XN), provided that functional versions of *CYP2D6* are duplicated. The frequency of the UM phenotype was found to be 0% to 2% in East Asian, 1% to 10% in white, and up to 29% in some Eastern African populations.^{22,23}

Fifteen currently approved antipsychotics are major or minor substrates of *CYP2D6*, with seven medications mentioning the effects of metabolizer status on pharma-

Gene	Alleles commonly tested	Enzyme activity	Predicted phenotype
<i>CYP2D6</i>	*1, *2, *2A, *35	Active	EM/NM: (1) Two active alleles (2) One active and one partially active allele IM: (1) One active and one inactive allele (2) One inactive and one partially active allele (3) Two partially active alleles PM: Two inactive alleles UM: Three or more active alleles (active allele duplication)
	*9, *10, *17, *29 *36, *41	Partially active	
	*3, *4, *5, *6, *7, *8, *11, *12, *14, *15	Inactive	
	Gene duplications		
<i>CYP1A2</i>	*1A	Active	Not uniformly/globally established
	*1E, *1J, *1K, *4, *6, *7, *8, *11, *15, *16	Partially active or inactive	
	*1F	Higher inducibility	
<i>CYP3A4</i>	*1	Active	Not uniformly/globally established
	*13, *15A, *17, *22	Inactive	
<i>CYP3A5</i>	*1	Active	Not uniformly/globally established
	*3	Inactive	

Table I. Common pharmacokinetic gene variants included in clinical testing panels for antipsychotic therapy. *Designation for allele; CYP, cytochrome P450; EM, extensive metabolizer; NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer

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Drug	Metabolism pathway	PGx information included in FDA label?	CPIC guideline?	DPWG guideline?	Percent change in AUC for poor metabolizers
Atypical antipsychotics (second-generation [SGA])					
Aripiprazole	CYP2D6	YES (PM: half of usual dose)	NO	YES (PM: reduce maximum dose to 10 mg/day)	↑76.9% ⁸
	CYP3A4	NO	NO	NO	N/A
Asenapine	CYP1A2	NO	NO	NO	N/A
	UGT1A4	NO	NO	NO	N/A
	CYP2D6	NO	NO	NO	N/A
	CYP3A4	NO	NO	NO	N/A
Brexpiprazole	CYP2D6	YES (PM: half of usual dose)	NO	NO	↑47% ⁸
	CYP3A4	NO	NO	NO	N/A
Cariprazine	CYP3A4	NO	NO	NO	N/A
	CYP2D6	YES (PM: no clinically relevant effects)	NO	NO	NS ⁸
Clozapine	CYP1A2	NO	NO	NO	N/A
	CYP2D6	YES (PM: dose reduction may be necessary)	NO	YES (No dose recommendations)	↓16.8% ⁹
	CYP3A4	NO	NO	NO	N/A
Iloperidone	CYP2D6	YES (PM: half of usual dose)	NO	NO	↑57.5% ⁸
	CYP3A4	NO	NO	NO	N/A
Lurasidone	CYP3A4	NO	NO	NO	N/A
Olanzapine	CYP1A2	NO	NO	NO	N/A
	CYP2D6	NO	NO	YES (No dose recommendations)	↓24.6% ¹⁰
Quetiapine	CYP3A4	NO	NO	NO	N/A
	CYP3A5	NO	NO	NO	↑66.6% ¹¹
Risperidone	CYP2D6	YES (PM: the PKs of active moiety are similar to EM)	NO	YES (PM: select alternative drug or be extra alert)	↑641% ⁸
	CYP3A4	NO	NO	NO	N/A
Ziprasidone	CYP3A4	NO	NO	NO	N/A
	CYP1A2	NO	NO	NO	N/A
Typical antipsychotics (first-generation [FGA])					
Chlorpromazine	CYP2D6	NO	NO	NO	↑65% ¹²
	CYP1A2	NO	NO	NO	N/A
	CYP3A4	NO	NO	NO	N/A
Fluphenazine	CYP2D6	NO	NO	NO	N/A

cokinetic parameters in the product labeling (Table II). The drug-labeling language referencing the relevance of metabolizer status for antipsychotics is broad, ranging from general comments to specific implications on dosing, particularly for newer medications. Aripiprazole, brexpiprazole, iloperidone, and pimozide labeling all mention specific dose adjustments for known CYP2D6 PMs (see Table II). DPWG guidelines also recommend dose changes for aripiprazole, risperidone, and haloperidol in CYP2D6 PMs,⁴ but no CPIC guidelines, at the time of writing, exist for antipsychotics.

CYP2D6 metabolizer status strongly influences the metabolism of antipsychotics, leading to changes in pharmacokinetic parameters, including overall exposure as defined by the area under the concentration-time curve (AUC), half-life, clearance, and steady-state

concentration. Pharmacokinetic effects of CYP2D6 metabolizer phenotypes are described in Table II. Of note, the magnitude of influence is different in each medication that is a CYP2D6 substrate, with AUC increases ranging from 47% to 641% for the PMs. Half-life displayed an approximate twofold increase in PMs for aripiprazole, iloperidone, pimozide, and thioridazine, and a sevenfold increase for risperidone (see Figure 1).^{8-10,15,16}

Many researchers have also investigated the relationship between CYP2D6 genotype and plasma concentration of antipsychotic agents and found concentration levels to be 1.1-4.5 times higher for PMs than for EMs for aripiprazole, risperidone, haloperidol, perphenazine, and thioridazine.¹⁷ Interestingly, the product labeling for clozapine indicates that dose reduction

Drug	Metabolism pathway	PGx information included in FDA label?	CPIC guideline?	DPWG guideline?	Percent change in AUC for poor metabolizers
Haloperidol	CYP2D6	NO	NO	YES* (PM: use half of usual dose or select alternative drug)	N/A
	CYP1A2	NO	NO	NO	N/A
	CYP3A4	NO	NO	NO	N/A
Loxapine	CYP1A2	NO	NO	NO	N/A
	CYP2D6	NO	NO	NO	N/A
	CYP3A4	NO	NO	NO	N/A
Perphenazine	CYP2D6	YES (PM: will metabolize more slowly)	NO	NO	↑190%-311% ^{13,14}
Pimozide	CYP1A2	NO	NO	NO	N/A
	CYP2D6	YES (PM: maximum dose of 0.05 mg/kg/day for children and 4 mg/day for adults)	NO	NO	↑153% ¹⁵
	CYP3A4	NO	NO	NO	N/A
Thioridazine	CYP2D6	NO	NO	NO	↑348% ¹⁶
	CYP2C19	NO	NO	NO	N/A
Thiothixene	CYP1A2	NO	NO	NO	N/A
Trifluoperazine	CYP1A2	NO	NO	NO	N/A

Table II. Drug metabolism pathways, labeling, and guideline information, and drug exposure (AUC) implications of pharmacogenetic information in antipsychotic medications. **Bold font**, major metabolism pathway; *Recommendation is based on haloperidol plasma levels studies.^{4,17} Percent Change in AUC: $\frac{AUC \text{ in PM} - AUC \text{ in EM}}{AUC \text{ in EM}} \times 100$

AUC, area under the concentration-time curve; CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Royal Dutch Association for the Advancement of Pharmacy-Pharmacogenetics Working Group; EM, extensive metabolizer; FDA, US Food and Drug Administration; N/A, not available; NS, nonsignificant; PGx, pharmacogenetic; PK, pharmacokinetic; PM, poor metabolizer

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may be necessary in CYP2D6 PMs. However, studies have shown no differences in clozapine AUC, half-life, and dose-corrected plasma concentration between CYP2D6 PMs and EMs,¹⁷ suggesting that patients treated with clozapine would not benefit from CYP2D6 pharmacogenetic testing.

There are important considerations related to pharmacokinetic implications of drug metabolism pharmacogenetics. Firstly, some antipsychotics have active metabolites (eg, aripiprazole, risperidone) and, therefore, the disposition of both parent drug and active metabolite(s) may need to be taken into account when considering clinical implications. For example, risperidone is metabolized to an equally active metabolite (9-hydroxy-risperidone) by CYP2D6. Risperidone appears to be metabolized to the active metabolite much slower in PMs than in EMs; thus, whereas the AUC of the parent drug was 169 ng·h/mL in PMs and 22.8 ng·h/mL in EMs, the AUC of its active metabolite was, respectively, 57.5 ng·h/mL and 139 ng·h/mL.⁸ Therefore, when considering its total active moiety (risperidone + 9-hydroxy-risperidone), the increase in AUC was only 30%, compared with a 641% increase when considering the risperidone parent drug only (Table II). Given the complexity, DPWG guidelines recommend the use of alternative drugs or that extra caution be exercised for use of risperidone in patients who are PMs.⁴ A second consideration is that the impact of altered metabolizer status needs to be assessed on a drug-by-drug basis, as

secondary drug metabolism pathways may impact the magnitude of effect of PM status.

Associations between CYP2D6 polymorphisms and clinical efficacy or safety have yielded conflicting results. Most clinical studies failed to show a significant relationship between CYP2D6 genotype and symptom response.²⁴⁻²⁶ Numerous study limitations present challenges in interpreting these outcomes (limitations include nonprospective study design, small numbers of patients, heterogeneous methods of phenotype assignment, heterogeneous population groups across the studies, and confounding factors, such as interaction with concomitant drugs). On the other hand, some studies have demonstrated associations with adverse effects, especially extrapyramidal symptoms.^{26,27} When confined to prospective studies, a meta-analysis found a significant association between tardive dyskinesia (TD) and CYP2D6 polymorphisms.²⁶

It is premature to unequivocally conclude that CYP2D6 pharmacogenetic testing is highly predictive of clinical response in patients taking antipsychotics. However, well-established links between CYP2D6 PM status and pharmacokinetic parameters in some antipsychotic agents indicate that this information may be helpful for dosing and titration decisions.

CYP1A2

CYP1A2 represents another important enzyme responsible for the biotransformation of some antipsychotics (Table II). Many pharmacogenetic testing laboratories now offer tests for CYP1A2 polymorphisms, although pharmacogenetic information regarding CYP1A2 remains absent from product labels and guideline statements for antipsychotic medications.

Compared with genes encoding other CYP enzymes (eg, CYP2D6), the effects of CYP1A2 genetic polymorphisms on enzyme activity are not as well understood. Additionally, there is currently no universally accepted method for defining CYP1A2 metabolizer groups by genotype. Commercial pharmacogenetic testing companies estimate CYP1A2 metabolizer status based on general effects that single-nucleotide variants have on expression or activity. CYP1A2 activity can be strongly influenced by environmental factors (tobacco and diet), which makes understanding the effect of CYP1A2 genotype more difficult.²⁸

The most commonly tested variants in CAPTPs are CYP1A2*1F, *1K, *4, *5, *6, *7, *8, *11, *15, and *16.

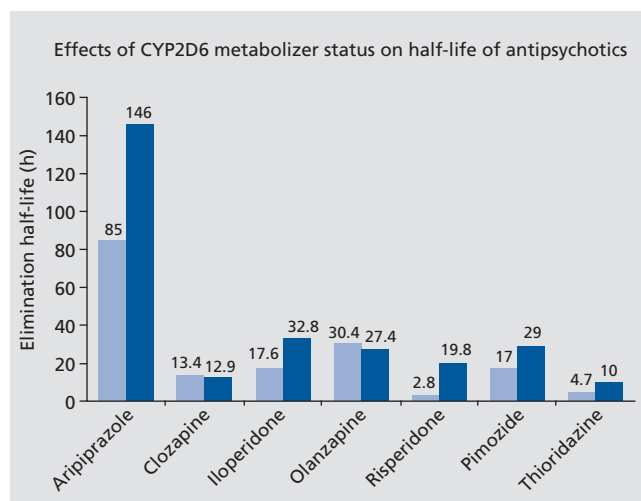


Figure 1. Pharmacokinetic effects of CYP2D6 metabolizer phenotypes on elimination half-life.^{8-10, 15, 16} light blue, extensive metabolizer; dark blue, poor metabolizer

Some of these variants increase gene function by induction of expression (*CYP1A2**1F), and others decrease (*CYP1A2**1K, *4, *7, *8, *11, *15, and *16) or abolish (*CYP1A2**6) enzyme activity.²⁹

The clinical utility of *CYP1A2* genotypes is unclear. One rather unique consideration for the interpretation of *CYP1A2* pharmacogenetics is the significant impact of smoking on enzyme activity. Smoking rates in patients with psychosis are twice that of the general population.³⁰ The hydrocarbons in cigarette smoke are responsible for the induction of *CYP1A2* in the body, increasing the clearance of substrates such as olanzapine, clozapine, chlorpromazine, and haloperidol up to 1.6-fold.³¹ In fact, smoking status has a more profound effect on clozapine metabolism than any known and currently tested *CYP1A2* genetic variant (*CYP1A2**1C and *CYP1A2**1F).^{32,33} Thus, parsing the environmental and genetic effects on *CYP1A2* metabolism is difficult, and conflicting studies highlight the complexity and uncertainties of interpreting antipsychotic-*CYP1A2* relationships.³⁴⁻³⁸

CYP3A subfamily

The CYP3A subfamily includes CYP3A4, CYP3A5, CYP3A7, and CYP3A43. These enzymes are involved in the metabolism of approximately 37% of 200 top-selling prescription drugs,³⁹ and many antipsychotics are substrates for the CYP3A4 enzyme (Table II).⁷ CYP3A4 and CYP3A5 have some overlap in substrate metabolism and are the most prevalent CYP3A enzymes in adults, and thus genetic variation influencing their activity may play a role in antipsychotic pharmacokinetics.

CYP3A5 is located at chromosome 7q22.1 and contains 13 coding exons, with over 2000 variants reported to date.²⁰ Although CYP3A4 and CYP3A5 enzyme activity is highly variable across the general population, most *CYP3A4* alleles identified are either very rare or have minimal effects on CYP3A4 activity.⁴⁰ *CYP3A4* alleles tested for on currently available commercial pharmacogenetic panels include *1, *13, *15A, and *22. Although some structural or general enzyme activity changes have been ascribed to these variants,⁴¹ uniformly accepted metabolizer groupings for CYP3A4 are lacking.

CYP3A5 arguably has more defined data on the effects of genetic variants on enzyme expression or function. The most common loss-of-function allele in white populations, *CYP3A5**3, has been identified with frequencies ranging from 94% in Europeans to 18% in Af-

rican populations. Other loss-of-function alleles include *CYP3A5**6 and *7. *CYP3A5**2 is considered to be a reduced-function allele.⁴² Currently available pharmacogenetic tests assay *1 and *3 for *CYP3A5*.

Presently, there are no established guidelines or product labeling recommendations that address CYP3A pharmacogenetics related to antipsychotics. Although some evidence exists that decreased-function alleles increase exposure to some antipsychotics,^{11,43} other studies have not found such effects,^{44,45} making recommendations related to clinical utility premature at the present time.

ABCB1

The P-glycoprotein (P-gp) drug transporter, encoded by *ABCB1*, is a transmembrane transporter located throughout the body, including intestine, liver, and the blood-brain barrier.⁴⁶ P-gp may affect drug absorption and distribution of substrates.^{47,48} Many antipsychotics, such as aripiprazole, olanzapine, risperidone, and paliperidone, are substrates of P-gp⁴⁸; therefore, it may play a significant role in their disposition.

Among the over 12 000 variants identified in the *ABCB1* gene region,²⁰ three SNPs (rs1128503 [1236C>T], rs2032582 [2677G>T], and rs1045642 [3435C>T]) are the most commonly studied variants, and results are inconclusive regarding SNP-phenotype associations. Some studies suggested that the phenotype of these silent polymorphisms may result from protein folding and stability rather than from changes in gene expression, and the effect of the structural alterations is expected to be more substrate-specific.^{49,50} In this regard, true relationships between *ABCB1* genotype and pharmacokinetics of antipsychotic agents, as well as clinical outcomes, are unclear. Moreover, the high overlap in specificity of substrates for P-gp with CYP3A4 makes understanding the effect of the P-gp genotype more difficult.⁵¹ Preliminary evidence suggests that patients who have the rare allele of those three polymorphisms may have better symptom response outcomes, higher risks of adverse events (olanzapine, risperidone), and higher plasma levels or AUCs of antipsychotic agents (olanzapine, risperidone, and clozapine). However, as results across studies are mixed, the clinical utility of examining these variants is still uncertain.⁴⁸ A few pharmacogenetic testing laboratories now offer *ABCB1*-polymorphism testing of those three common SNPs for some other medical conditions, includ-

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ing epilepsy, cardiovascular diseases, and inflammatory bowel disease, and also with regard to antidepressant treatment. But to date there are no established guidelines or product labels that provide recommendations for *ABCBI* pharmacogenetics related to antipsychotic use.

Pharmacodynamic genes and antipsychotic response

In addition to drug metabolizing enzymes and drug transporters, pharmacogenetic research has also focused on genes encoding therapeutic targets of antipsychotic pharmacotherapies, with an emphasis on dopamine and serotonin neurotransmitter systems thought to be dysregulated in psychotic disorders.^{52,53}

Some of these markers are now included in CAPTPs (*Table III*),⁵⁴⁻⁶⁰ although they have yet to be included in drug labels or guidelines. Variants in pharmacodynamic genes have been important for understanding underlying mechanisms related to both disease presentation and treatment response. Some pharmacodynamic gene variants may be related to clinical response or tolerability to antipsychotic drugs and have also been investigated for relationships with disease risk, disease phenotypes, and risk for other nonpsychiatric conditions. The following sections review genes and variants associated with antipsychotic treatment outcomes and for which clinical tests are currently available. Putative mechanisms, summaries of association data, and other considerations will be discussed.

Gene	Variant description	Variant classification	Frequency 1000 genomes populations						Association data
			AFR	AMR	EAS	EUR	SAS	All	
<i>COMT</i>	c.472 G>A, V158M rs4680	missense	0.28 A	0.38 A	0.28 A	0.50 A	0.44 A	0.37 A	Homozygous Met allele increased clinical response [OR=1.37, 95% CI: 1.02-1.85] ⁸¹
<i>DRD2/ ANKK1</i>	c.2137G>A, E713K Taq1A; rs1800497	missense	0.33 A	0.39 A	0.41 A	0.19 A	0.31 A	0.33 A	Taq1A_A2 allele increased risk of tardive dyskinesia [OR=1.30, 95% CI: 1.09-1.55] ^{57,58}
<i>DRD2</i>	c.-486_-485 insC -141C ins/del rs1799732	5'-US promoter region	0.57 C Del	0.16 C Del	0.14 C Del	0.08 C Del	0.13 C Del	0.24 C Del	-141 Del_C decreased treatment response [OR=0.65, 95% CI: 0.43-0.97] ⁵⁶
<i>DRD3</i>	c.25A>G, S9G rs6280	missense	0.82 G	0.43 G	0.31 G	0.34 G	0.42 G	0.49 G	Gly allele increased risk of tardive dyskinesia [OR=1.17, 95%CI: 1.01-1.37] ⁷²
<i>HTR2A</i>	c.102C>T, S34S rs6313	synonymous	0.39 T	0.35 T	0.59 T	0.44 T	0.42 T	0.44 T	C allele increased risk of tardive dyskinesia [OR=1.64, 95%CI: 1.17-2.23] ⁸⁶
<i>HTR2C</i>	-759 C>T rs3813929	5'-US promoter region	0.01 T	0.12 T	0.15 T	0.16 T	0.28 T	0.13 T	C allele increased risk of weight gain [OR: 2.70; 95%CI: 1.46-5.01] ¹⁰⁰

Table III. Common pharmacodynamic gene variants included in clinical testing panels for antipsychotic treatment response. 1000 genomes superpopulations are as follows: African (AFR; n=661), Mixed American (AMR; n=347), East Asian (EAS; n=504), European (EUR; n=503), and South Asian (SAS; n=489). Association data for each variant is summarized from the most recently published meta-analysis. US, upstream

Dopamine system: *DRD2*

All currently approved antipsychotics have varying degrees of antagonistic action at dopamine D₂ receptors in the brain. Dopamine receptor genes have therefore received much attention as strong candidates in antipsychotic pharmacogenetic association studies. The D₂ receptor is expressed in the brain,⁶¹ and D₂ antagonism by antipsychotics in the mesolimbic dopamine pathway is thought to be responsible for the reduction in positive symptoms of schizophrenia, and antagonism in the nigrostriatal pathway is related to movement disorder side effects.

Over over 4000 variants in *DRD2* have been identified²⁰; however, at present only two: the Taq1A polymorphism (rs1800497) and -141 Ins/Del (c.-486_-485insC; rs1799732) are available on CAPTPs. It is important to be aware that *DRD2* has also been associated with several nonpharmacogenetic phenotypes, including risk for attention-deficit/hyperactivity disorder (ADHD), alcohol dependence, schizophrenia, Tourette syndrome, and others.⁶²⁻⁶⁵

Taq1A nomenclature is derived from the restriction endonuclease enzyme originally used to identify this SNP. The “A1” allele of Taq1A—now known to be located 10 kb downstream of *DRD2* within the coding region of the ankyrin repeat and kinase domain-containing 1 (*ANKK1*) gene (c.2137G>A, Glu713Lys)—is associated with D₂ expression and reduced striatal receptor density.⁶⁶⁻⁶⁸ The A1 allele is in linkage disequilibrium with two other *DRD2* intronic variants (rs2283265 and rs1076560), which influence *DRD2* splicing.⁶⁹ Associations between the Taq1A_A1 allele and increased symptom response have been reported, but meta-analysis of this relationship showed no significant association.⁵⁷ With respect to side effects, meta-analyses indicate an approximately 30% increase in the odds of developing TD in Taq1A_A2 allele carriers (predominantly first-generation antipsychotics).^{55,56} Additionally, studies have also shown correlations between other side effects, including hyperprolactinemia and weight gain, and Taq1A genotype.⁷⁰⁻⁷²

The *DRD2* -141 Ins/Del polymorphism is located in the promoter region approximately 485 nucleotides upstream of the coding start site and consists of a deletion or insertion of a cytosine base. The -141 Del_C allele is correlated with altered D₂ expression^{58,73} and decreased antipsychotic treatment response.⁷⁴⁻⁷⁶ Though

conflicting results exist, meta-analysis suggests that -141 Del_C carriers are approximately 35% less likely to respond than insertion homozygotes.⁵⁷ There are other *DRD2* variants, (A-241G [c.-585A>G; rs1799978]; Ser-311Cys [c.932 C>G; rs1801028]; and Taq1B [-882 G>A; rs1079597]) that have been examined, with mixed results, in association studies, but they are not currently available as clinical tests.^{52,53}

Dopamine system: *DRD3*

In addition to the dopamine D₂ receptors, antipsychotics show similar affinity for the dopamine D₃ receptor. D₃-receptor expression increases in the striatum after antipsychotic treatment,⁷⁷⁻⁷⁹ suggesting that the gene encoding the D₃ receptor (*DRD3*) may be important for pharmacogenetic investigation. Over 4000 *DRD3* variants have been identified.²⁰ Pharmacogenetic research related to antipsychotic treatment has focused on a missense variant that results in a serine-to-glycine amino acid substitution (Ser9Gly, c.25A>G, rs6280). Multiple studies have investigated the relationship between the Ser9Gly polymorphism and antipsychotic response; however, they have produced conflicting results, with a meta-analysis observing a nonsignificant trend between the Ser9 allele and decreased antipsychotic response (odds ratio=0.82; 95% confidence interval, 0.65-1.04).⁸⁰ Additionally, multiple studies have reported a significant association between Ser9Gly and TD⁵²; however, three separate meta-analyses provide inconsistent findings with only a modest to non-existent effect for the Gly9 allele with increased TD risk.^{58,81,82}

Dopamine system: *COMT*

Catechol-*O*-methyltransferase (COMT) is a key enzyme for dopamine clearance and metabolic termination of dopamine activity and has been investigated in antipsychotic association studies.

Over 1900 variants have been identified in *COMT*.²⁰ Most studies have focused on a common missense variant, Val158Met (c.472 G>A, rs4680), which is now included on some CAPTPs. The Met allele confers thermostability of the COMT enzyme, decreasing dopamine catabolism, and thereby increasing dopamine in areas of the brain, such as the prefrontal cortex.⁸³ Correlations have been observed between the Met allele

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allele and increased clinical response to antipsychotics, greater improvement in negative symptoms, and cognitive function.⁸⁴⁻⁸⁹ Conflicting results exist, but two recently published meta-analyses confirmed significant associations between homozygous Met allele carriers and a 37% increase in the odds of clinical response, which may be driven by effects on positive symptoms and atypical antipsychotic treatment.^{54,90} Early studies suggested that the Met allele may be protective against TD; however, meta-analyses have presented conflicting or nonsignificant results.^{55,91}

Serotonin system genes

Second-generation or “atypical” antipsychotics (SGAs) have higher affinities for serotonin 2A receptors (5-HT_{2A}) than for D₂ receptors, a pharmacodynamic characteristic thought to have implications for both the efficacy and tolerability profiles of these medications.^{92,93} As a result, many pharmacogenetic studies have investigated genes governing or influencing serotonin transmission. Of the serotonin receptors, the 5-HT_{2A} and 5-HT_{2C} subtypes have been the primary targets of investigations into antipsychotic response and tolerability and are now included on some clinically available test panels.

Serotonin system: *HTR2A*

The serotonin 2A receptor, encoded by *HTR2A*, is the most extensively studied serotonin-receptor target of SGAs. Currently, two polymorphisms of *HTR2A* are represented on commercially available pharmacogenetic test platforms. The first, T102C (c.102C>T, S34S; rs6313), has shown weak associations with SGA response, with the T allele resulting in a modest (36%) increase in the odds of response.⁹⁴ Additionally, studies have also suggested a relationship between the 102C allele and a modestly increased TD risk.⁵⁹ The functional consequence of this synonymous polymorphism remains unknown, but the C allele has been associated with lower *HTR2A* expression resulting either from suspected epigenetic mechanisms⁹⁵ or due to a second polymorphism in tight linkage disequilibrium. The G allele of this linked SNP, A-1438G (rs6311), is associated with decreased promoter activity,^{96,97} as well as with antipsychotic response; however, results are inconsistent.⁹⁸ Other SNPs in *HTR2A* including His452Tyr (c.1354C>T, H452Y; rs6314) and c.614-2211 G>A (rs7997012) have also been correlated with

antipsychotic treatment response and side effects,^{94,99-103} but with inconsistent results and uncertain clinical implications.^{59,104}

Serotonin system: *HTR2C*

The serotonin 2C receptor, encoded by *HTR2C*, has also been extensively studied because of its critical involvement in mediating the effect of antipsychotics on weight gain, negative symptoms, and possibly cognitive function.¹⁰⁵ Although there are other nonsynonymous SNPs potentially relevant to treatment outcomes that reside in *HTR2C*,¹⁰⁶ the variant that appears on some CAPTPs is -759 T/C (rs3813929), which has been extensively investigated for associations with antipsychotic-induced weight gain. It is well known that the 5-HT_{2C} receptor is involved in regulation of food intake, and 5-HT_{2C} antagonists cause increases in food intake and weight gain.¹⁰⁵ In regard to the C-759T polymorphism, the C allele has been consistently associated with a 240% to 270% increased odds in the risk of weight gain when meta-analyses examine findings across multiple studies.^{60,107} Studies indicate that the C-759T polymorphism may affect transcription factor binding, with the T allele associated with greater expression and less weight gain.^{108,109} Knockout rodent studies indicate that an absence of 5-HT_{2C} receptors is related to greater feeding activity and adipose disposition.¹¹⁰ Antipsychotics with the greatest affinities for 5-HT_{2C} receptors (ie, clozapine and olanzapine) are also associated with the greatest weight gain, a risk that seems to be modestly lower in persons carrying the higher-expressing form of the gene. Owing to the strength and replicability of this association, the C-759T polymorphism has been informative for understanding one mechanistic piece underlying antipsychotic weight gain. Although it appears on some CAPTPs, the clinical utility of this SNP requires further study. Specifically, whether selecting antipsychotic therapy based on this SNP results in a more favorable weight gain profile than usual care is not known.

Other development and regulatory system genes

Despite the evidence for the relationships between specific variants within dopamine and serotonin genes, antipsychotic treatment response, and tolerability, there may arguably be other pharmacodynamics genes that contribute to these outcomes. This evident need has led to numerous investigations in other genes that influ-

ence neuronal function, neurotransmitter signaling, and neurotransmitter disposition. Currently, these genes are not included in clinically available pharmacogenetic tests and thus not included for detailed discussion in this review. Nonetheless, genetic variations in *BDNF*, *GRM3*, *HSPG2*, *HTR1A*, *LEP*, *LEPR*, *MC4R*, *MTHFR*, *SULT4A1*, and *ZNF804A* (and others) have shown some promising associations with aspects of antipsychotic symptom improvement and side effects.^{52,53,98}

Clinical implementation of pharmacogenetics in psychiatry

Progress in the field of antipsychotic pharmacogenetics has been substantial over the past 20 years, resulting in the identification of numerous associations between antipsychotic drug efficacy and tolerability with various genetic markers in both pharmacokinetic and pharmacodynamic pathways. This has led to excitement about using this knowledge in the clinic where there is a dire need to improve treatment outcomes. Commercial pharmacogenetic testing companies have now made this technology accessible by selectively including genetic variants into antipsychotic-related genetic testing panels. However, decisions about which variants to include in commercial panels are made by the testing companies. Although the selection of variants is often based on an evaluation of scientific literature, there are currently no standards to guide this process.

Governmental agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) now emphasize that drug manufacturers should include pharmacogenetic information in product labeling when appropriate. Additionally, groups including CPIC, DPWG, and Eu-PIC have worked to establish guidelines about how to use available genetic information to guide treatment. Currently, DPWG guidelines provide actionable recommendations for aripiprazole, risperidone, and haloperidol (see *Table II*).⁴ CPIC and Eu-PIC have not yet published pharmacogenetic recommendations for antipsychotics. Moreover, clinical validity and utility of these pharmacogenetic testing panels are not well evaluated for antipsychotics. Clinical use thus remains limited by the knowledge gap between laboratory and translational research and clinical practice. In order to decrease this gap, additional work is in progress to determine how and when testing might be useful, as well as whether

pharmacogenetics-guided dosing or drug selection strategies are better than usual care.

Currently, testing laboratories report the results with varying degrees of interpretation, decision support, and even therapeutic recommendations. However, it is challenging to integrate pharmacogenetic testing data into clinical records because of the complexity and heterogeneity of the information. In order to address this issue, a number of groups, including the Institute of Medicine Roundtable on Translating Genomic-Based Research for Health and CPIC have worked to standardize the terminology of pharmacogenetic testing. In spite of this, standardized terms and languages are still lacking; thus, each clinician still needs to navigate the testing results and enter them into medical records without standardized guides for this process.

Another important consideration affecting the clinical utility of antipsychotic-related pharmacogenetics has to do with the differences in genomic coverage across pharmacogenetic testing methodologies. Initially, pharmacogenetic testing was conducted by the single-gene approach. Multigene panels, analyzing multiple genes or genetic variants in a single assay, have now become available and are offered by numerous clinical laboratories.³ Testing multiple pharmacogenetic variants relevant to a specific treatment or therapeutic area in a single assay is more cost-effective and can provide valuable preemptive pharmacogenetic information (applicable to medications that patients potentially receive during their lifetime).¹¹ Furthermore, technologies for genetic detection and discovery continue to rapidly advance and decrease in cost, leading to the availability of whole exome and genome sequencing methodology in clinical genetics laboratories. These technological advancements have allowed for a more comprehensive genomic coverage, but create challenges for the integration of this information into electronic medical records and in how to translate large amounts of genomic data into clinically relevant and actionable information required for drug and dosing selection in antipsychotic treatment.

Conclusions

There is a great need to improve treatment and dosing selection for patients with psychotic disorders, and improving the precision of our treatments, in part through pharmacogenetic testing, has great potential to offer a more personalized approach to treatment decisions in

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clinical psychiatry. Genetic variations in specific drug metabolism markers may be helpful for dosing and titration approaches because of their impact on pharmacokinetics; however, product-labeling language relating to specific gene variants varies across different antipsychotic medications. Genetic variants related to antipsychotic pharmacodynamics are now included in CAPTPs, although they remain absent from drug labels or guidelines. The clinical application of antipsychotic pharmacogenetics is in its early stages but seems to be one promising approach to help us improve antipsychotic pharmacotherapy. More research is needed on using test information prospectively, although some in-

formation obtained retrospectively may help in characterizing patterns of tolerability or response for a given patient. We can begin to provide valuable information that is needed for the development and implementation of pharmacogenetic guidelines necessary for common clinical utility in antipsychotic use through: (i) increased genomics education relevant for clinicians; (ii) development of efficient infrastructure between research and clinical practice; and (iii) advancing current prediction algorithms to include both comprehensive genomic information and pertinent clinical variables. □

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Pruebas farmacogenéticas para medicamentos antipsicóticos: repercusiones clínicas y consideraciones

Con frecuencia constituye un desafío optimizar la farmacoterapia antipsicótica debido a la significativa variabilidad en la eficacia y tolerabilidad. Los factores genéticos que influyen en la farmacocinética y farmacodinámica pueden contribuir en parte a esta variabilidad. Los estudios de investigación han caracterizado estas relaciones farmacogenéticas y actualmente existen algunos marcadores genéticos como pruebas clínicas. Estos avances en la investigación farmacogenética y la disponibilidad de pruebas tienen un gran potencial para mejorar los resultados clínicos y la calidad de vida en los pacientes psiquiátricos. Para los clínicos que consideren el empleo de la farmacogenética es importante que tengan en cuenta las consecuencias clínicas y también las limitaciones de los marcadores con las pruebas disponibles en la actualidad. Esta revisión se focaliza en la farmacocinética y la farmacodinámica de las variantes génicas que están actualmente disponibles en paneles comerciales de pruebas genéticas. Se discuten las asociaciones de estas variantes con la eficacia clínica y los efectos adversos, como también otras repercusiones clínicas en la farmacoterapia antipsicótica.

Tests pharmacogénétiques pour traitements antipsychotiques : considérations et implications cliniques

La variabilité significative de l'efficacité et de la tolérance des traitements antipsychotiques rend leur optimisation souvent difficile. Cette variabilité peut être due en partie à des facteurs génétiques influant sur la pharmacocinétique et la pharmacodynamique. Des études scientifiques ont caractérisé ces relations pharmacogénétiques, et certains marqueurs génétiques sont maintenant disponibles sous forme de tests cliniques. Ces avancées (recherche pharmacogénétique et disponibilité des tests) peuvent améliorer considérablement les résultats cliniques et la qualité de vie des patients psychiatriques. Les médecins s'intéressant à la pharmacogénétique doivent comprendre les implications cliniques et les limites des marqueurs des tests actuellement disponibles. Cet article s'intéresse principalement à la pharmacocinétique et à la pharmacodynamique des variants géniques proposés aujourd'hui dans les différents tests génétiques commercialisés. Nous analysons dans la pharmacothérapie antipsychotique la relation de ces variants avec l'efficacité clinique et les effets indésirables, ainsi que d'autres implications cliniques.

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