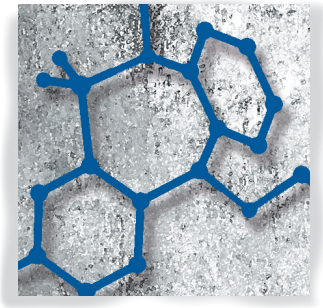
# *Pharmacogenetics and outcome with antipsychotic drugs*

*Jennie G. Pouget, BSc; Tahireh A. Shams; Arun K. Tiwari, PhD; Daniel J. Müller, MD, PhD*



*Antipsychotic medications are the gold-standard treatment for schizophrenia, and are often prescribed for other mental conditions. However, the efficacy and side-effect profiles of these drugs are heterogeneous, with large interindividual variability. As a result, treatment selection remains a largely trial-and-error process, with many failed treatment regimens endured before finding a tolerable balance between symptom management and side effects. Much of the interindividual variability in response and side effects is due to genetic factors (heritability, $h^2$ ~ 0.60 – 0.80). Pharmacogenetics is an emerging field that holds the potential to facilitate the selection of the best medication for a particular patient, based on his or her genetic information. In this review we discuss the most promising genetic markers of antipsychotic treatment outcomes, and present current translational research efforts that aim to bring these pharmacogenetic findings to the clinic in the near future.*

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## Introduction

Pharmacotherapy is a pillar of the modern medical approach to treating disease. Although all drugs must have demonstrated overall efficacy and safety to receive regulatory approval, there are often large interindividual differences in their efficacy and side-effect profiles among individual patients. More specifically, most drugs are effective for only 30% to 60% of patients,[1] and an estimated 7% of patients receiving drug therapy experience a serious adverse reaction.[2] These interindividual differences in drug response present a challenge for the clinician, who must select the best drug to prescribe for a particular patient. For many drugs, treatment selection remains a "trial-and-error" process, with multiple failed trials required before achieving an acceptable balance between response to therapy and side effects.

Differences in the way patients respond to the same drug are the result of a combination of factors that affect drug metabolism (*pharmacokinetics*) and drug ac-

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## Selected abbreviations and acronyms

| | |
|---|---|
| ***CYP*** | *cytochrome P450* |
| ***DRD*** | *dopamine receptor* |
| ***GWAS*** | *genome-wide association study* |
| ***HLA*** | *human leukocyte antigen* |
| ***HTR*** | *serotonin receptor* |
| ***SNP*** | *single nucleotide polymorphism* |
| ***ZNF*** | *zinc-finger domain-containing protein* |

tion (*pharmacodynamics*). In order to improve clinical outcomes, research efforts have focused on identifying the pharmacokinetic and pharmacodynamics factors underlying interindividual differences in drug efficacy and side effects. The ultimate goal of this research is to provide clinicians with a tool that enables them to prescribe the right dose of the right drug to a patient when they first present with an illness, a concept referred to as *personalized medicine*.[3] While clinical factors such as disease severity, diet, and concurrent medications clearly contribute to the variability in response to drug therapy, inherited differences in the metabolism and action of drugs at their target sites also have a large effect.[1]

The term *pharmacogenetics* was first coined in 1959[4] to describe the use of genetic factors to predict an individual's response to a drug both in terms of efficacy and side effects. The complexity of drug response, which is multifactorial, variable over time, and often assessed using subjective clinical scales, makes it challenging to identify genetic variants that robustly predict drug response. Additionally, drug response is a polygenic trait, influenced by numerous genetic variants in multiple pathways of drug metabolism and drug activity. As such, it is rare that an individual genetic variant will predict drug response effectively on its own. Despite these challenges, pharmacogenetics has an established track record of improving treatment outcomes, with genotype-directed therapy now a reality for a number of cancers.[5]

A similar pharmacogenetic landscape is emerging in the field of psychiatry. There is a clear genetic contribution to the variability in response to psychotropic medications.[6-10] Furthermore, side effects of psychotropic medications may have an even stronger genetic component.[11-13] For example, Asians who are carriers of the class I human leukocyte antigen B (HLA-B)*15:02 allele have a significantly elevated risk of developing a potentially lethal cutaneous side effect such as Stevens-Johnson syndrome.[14]

The identification of the specific genetic variants underlying the heritability of response to psychotropic drugs has been an active area of research over the past 20 years. Initial efforts are under way to implement pharmacogenetics in the treatment of psychiatric diseases. Here we review the most promising pharmacogenetic findings with respect to antipsychotic drugs, the mainstay of treatment for schizophrenia. We then provide an overview of currently available pharmacogenetic tests, and discuss the next steps required to move towards clinical translation of pharmacogenetic findings into antipsychotic treatment.

## Identifying genetic predictors of antipsychotic treatment outcomes

The most common methodological approaches to identifying genetic predictors of antipsychotic treatment outcomes have been candidate gene studies and genome-wide association studies (GWAS). Both approaches test for differences in the frequency of genetic variants, most commonly single-nucleotide polymorphisms (SNPs), between individuals who respond differently to a psychotropic drug. Candidate gene studies test for association of selected SNPs in genes of interest based on biological evidence, while GWAS take a hypothesis-free approach and test for association of millions of SNPs across the entire genome. While the two approaches can be seen as complimentary, if a variant is truly associated with the trait, replication should be seen in either type of study. Given the large number of pharmacogenetic investigations that have been conducted to date and the small sample sizes typically under investigation (n<1000), we limit this review to the most promising findings (ie, those that have been replicated in independent samples and those that have remained significant in meta-analysis). In the future, the field would benefit greatly from collaborative efforts to accumulate large, deeply phenotyped samples from research centers across the world, in order to increase the robustness of pharmacogenetic findings.

### Antipsychotic metabolism

As most antipsychotic medications undergo extensive first-pass metabolism, drug-metabolizing enzymes may play an important role in patient response to antipsychotic treatment by determining the proportion of the

drug that reaches the systemic circulation and is available to act on its targets in the brain. The cytochrome P450 (CYP) enzymes are the major family of drug-metabolizing enzymes that influence antipsychotic metabolism.[15] Antipsychotic drugs are metabolized primarily by CYP1A2, CYP2D6, and CYP3A4, with CYP2C19 playing an important role in clozapine metabolism, as well as the metabolism of many antidepressants[16] (see *Table I* for further details).

The genes encoding these CYP enzymes are polymorphic, and their variation leads to differences in catalytic activity and/or the amount of the enzyme that ultimately influence the metabolism of antipsychotic medications. Combinations of CYP genotypes that affect catalytic activity are classified as "star (*) alleles." An individual's phenotype for a particular CYP enzyme is commonly referred to as "poor metabolizer" (PM, two inactive star alleles), "intermediate metabolizer" (IM, one inactive star allele + one active or decreased activity star allele, or two decreased activity star alleles), "extensive/normal metabolizer" (EM, two active star alleles), or "ultra-rapid metabolizer" (UM, gene duplication of active star alleles). Alternative classification of the CYP2D6 star alleles has been recommended, especially for tricyclic antidepressants,[17] with individuals classified as PM carrying two nonfunctional alleles, IM carrying one reduced function and one nonfunctional allele, EM carrying either two functional alleles or two reduced function alleles or one functional and nonfunctional allele or one functional and reduced-function allele, and UM carrying duplications of functional alleles.[17] Considering the lack of a standardized classification system, an activity-based score has also recently been proposed.[17]

| | First-generation | Second-generation |
|---|---|---|
| **Metabolism** | **CYP2D6**<br>● Chlorpromazine<br>● Fluphenazine<br>● Haloperidol<br>● Perphenazine<br>● Thioridazine<br><br>**CYP3A4**<br>● Haloperidol<br>● Loxapine<br>● Pimozide<br><br>**CYP1A2**<br>● Chlorpromazine<br>● Loxapine<br>● Perphenazine<br>● Thioridazine<br>● Thiothixene<br>● Trifluoperazine | **CYP2D6**<br>● Aripiprazole<br>○ Clozapine<br>● Iloperidone<br>○ Olanzapine<br>● Risperidone<br><br>**CYP3A4**<br>● Aripiprazole<br>● Clozapine<br>● Iloperidone<br>○ Lurasidone<br>○ Quetiapine<br>● Risperidone<br>● Ziprasidone<br><br>**CYP1A2**<br>● Clozapine<br>● Olanzapine |
| ● Primary metabolism<br>○ Secondary metabolism | | |

**Table I.** Cytochrome P450 (CYP) enzymes involved in metabolism of antipsychotics.

The *CYP2D6* genotype has been most extensively investigated in association with antipsychotic metabolism, as approximately 40% of antipsychotics are major substrates for CYP2D6.[18] CYP2D6 poor metabolizers have higher plasma levels of (dose-corrected) haloperidol, perphenazine, thioridazine, aripiprazole, iloperidone, and risperidone following antipsychotic treatment (reviewed by Ravyn et al in ref 12). The FDA has approved the use of CYP2D6 enzyme activity in antipsychotic prescribing decisions, providing recommendations to reduce the dose or avoid prescribing perphenazine, pimozide, thioridazine, aripiprazole, clozapine, iloperidone, and risperidone in individuals known to be nonextensive metabolizers.[19] The *CYP2D6* genotype is robustly associated with clearance of several antipsychotics (including haloperidol, thioridazine, aripiprazole, iloperidone, and perphenazine),[12] and has also shown some association with antipsychotic-induced side effects.[12] Despite the clear role of *CYP2D6* genotype in influencing antipsychotic metabolism, most pharmacogenetic studies have not found a significant association between CYP2D6 and antipsychotic efficacy.[12] This may be due to the lack of correlation between antipsychotic plasma levels and clinical response (ie, a great variability in each patient's dose-response curve), or challenges in the methodological design of clinical studies evaluating psychosis improvement. Despite these challenges, CYP2D6 is considered a predictor of antipsychotic treatment outcomes, and is included in all currently available commercial pharmacogenetic tests.

CYP1A2 is another important enzyme with respect to antipsychotic pharmacokinetics, as approximately 20% of antipsychotics are major substrates for this enzyme.[18] Although CYP1A2 activity is inducible by environmental factors such as caffeine and smoking, genetic factors are thought to account for a large portion

of variability in CYP1A2 activity in the healthy population.[20] CYP1A2 activity was highly correlated with olanzapine clearance in a recent study by Perera et al,[21] but multiple negative findings have been reported for clozapine[22,23] and olanzapine.[24,25] Overall, the results of these initial studies suggest that the *CYP1A2* genotype may not have a major effect on antipsychotic metabolism, but further research is required.

CYP3A4 is considered the most important CYP in drug metabolism,[26] and is considered an important contributor to drug-drug interactions. Similar to CYP1A2, CYP3A4 is inducible and its activity can be altered by medications, including induction by carbamazepine, with genetic factors also contributing to variation in enzyme activity.[27] Approximately 20% of antipsychotics are major substrates for this enzyme.[18] Only two studies of *CYP3A4* genotype in association with antipsychotic metabolism have been conducted, reporting no association with clozapine[23] or risperidone[28] plasma levels, although the decreased activity of the CYP3A4*1G allele was associated with greater improvement in psychotic symptoms.[28] Further research on the role of the *CYP3A4* genotype in antipsychotic metabolism is required. Another member of the CYP3A family of enzymes, CYP3A43, shows some overlap in substrate specificity with CYP3A4 due to amino-acid sequence similarity between the two enzymes.[29] CYP3A43 polymorphism rs472660, an intronic SNP that has not yet been investigated for functional relevance, accounted for 10% of variability in olanzapine clearance among 235 subjects from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study.[30] Missense variant rs68055 in CYP3A43 was recently found to be associated with antipsychotic treatment response in an independent sample,[31] further supporting the potential importance of CYP3A43 in antipsychotic clearance and efficacy.

CYP2C19 is included in various commercially available genetic test kits, due to its partial involvement in the metabolism of clozapine and its importance in the metabolism of antidepressants.[16] Although there has been relatively little investigation of CYP2C19 genotype in association with antipsychotic metabolism, 2.3-fold higher clozapine plasma levels have been observed among CYP2C19 poor metabolizers (*2/*2 genotype) compared with extensive metabolizers.[23]

Although not directly involved in antipsychotic metabolism, P-glycoprotein is also worthy of mention. Acting as an efflux pump, P-glycoprotein removes many antipsychotics from the brain by transporting them across the blood-brain-barrier, thereby contributing to antipsychotic clearance.[32] Interestingly, many substrates and inhibitors of P-glycoprotein are shared with CYP3A4, suggesting that these proteins may work together to influence antipsychotic levels in the brain. Three polymorphisms (rs1045642, rs2032582, and rs1128503) in the gene encoding P-glycoprotein, *ABCB1*, have been investigated in association with antipsychotic efficacy in more than 10 studies, with positive findings reported in the majority of studies.[32] Notably, these polymorphisms are in significant linkage disequilibrium, and the haplotype they form has been associated with *ABCB1* expression as well as P-glycoprotein activity and substrate specificity.[33,34]

**Antipsychotic response**

Genetic variation in known antipsychotic drug targets may contribute to variability in response among patients by influencing antipsychotic binding to cell membrane receptors and downstream signaling. Identifying replicable genetic variants associated with antipsychotic response has been challenging due to a number of factors including the complexity of antipsychotic response, the lack of standardized outcome measures and thresholds for significant improvement, confounding by nongenetic factors (such as previous antipsychotic treatment, patient compliance, smoking, and concurrent medications), and low statistical power due to small sample sizes. Additionally, although many studies have included patients treated with different antipsychotics, it remains unclear whether pharmacogenetic associations are general or drug-specific. Despite these challenges, a number of interesting pharmacogenetic findings have emerged in antipsychotic response.

Given the central role of the dopaminergic[35] and serotonergic[36] neurotransmitter systems in antipsychotic efficacy, genes of these systems have received the greatest attention. Strongest support has accumulated for variation in genes encoding the dopamine D2 receptor (*DRD2*),[37] dopamine D3 receptor (*DRD3*),[38] serotonin 1A receptor (*HTR1A*),[39-41] and serotonin 2A receptor (*HTR2A*)[42] *(Table II)*. While a number of antipsychotics also show some affinity for receptors of the adrenergic, muscarinic, and histaminic systems, results from pharmacogenetic studies of these systems lack independent

replication or are inconsistent. Outside of the classic neurotransmitter systems, zinc-finger domain-containing protein (ZNF)804A gained attention as a potential pharmacogenetic candidate following its identification as a risk locus in schizophrenia GWAS.[43,44] The disease-associated A allele of the *ZNF804A* rs1344706 polymorphisms was associated with abnormalities in brain connectivity among patients with schizophrenia.[45] The precise biological functions of ZNF804A underlying its association with brain connectivity remain an active area of research. With respect to pharmacogenetics, an initial study reported no association between rs1344706 and overall antipsychotic response.[46] However, two more recent studies have reported a significant association between the A allele and less improvement in positive symptoms.[47,48] The association between rs1344706 and antipsychotic efficacy in the latter studies may be the direct result of an effect of *ZNF804A* on antipsychotic response, or an indirect result of this variant acting as a biomarker for more severe forms of schizophrenia presenting with greater treatment resistance.

The effect sizes of genetic variants associated with antipsychotic response, considered as a binary outcome, have generally been modest (OR=0.18–0.82), such that none will predict antipsychotic response in a clinically meaningful way on their own.[13] Such modest effect sizes are not surprising, given the complexity and polygenicity of drug response. The success of future efforts to improve prediction of antipsychotic efficacy using genetic information will require the development of algorithms that incorporate multiple genetic factors, and their application in deeply phenotyped samples that can tease apart the heterogeneity in drug response as an outcome measure.

## Antipsychotic-induced side effects

With an estimated noncompliance rate of 42%,[49] encouraging patients to remain on their antipsychotic medication is a major challenge in the treatment of schizophrenia. One of the strongest predictors of noncompliance among first episode schizophrenia patients is whether they experience harmful side effects.[50] The identification of genetic predictors of antipsychotic-induced side effects holds the potential to provide a rational basis for treatment selection in a way that minimizes their occurrence, thereby improving patient compliance and long-term clinical outcomes.[51] With this goal of predicting antipsychotic-induced side effects in mind, a number of studies have explored the association between genetic variants and serious side effects of antipsychotics, with greatest focus on weight gain, tardive dyskinesia, and agranulocytosis. Findings in this area have been generally more robust than for antipsychotic response, in terms of effect sizes and reported replication in independent samples.[11-13] This may be a result of the more objective nature of adverse drug reactions, in contrast to the previously discussed complexities of defining antipsychotic response.

Weight gain is a common and serious side effect of antipsychotic treatment, with up to 30% of patients gaining ≥7% of their baseline weight.[52] There is robust

| Gene | SNP | Risk allele | Outcome measure | OR (95% CI; *P*) | Functional effect |
|---|---|---|---|---|---|
| *DRD2* | -141C Ins/Del (rs1799732) | Del | Clinically significant response | 0.65[a] (0.43-0.97; *0.03*)[37] | Decreased *DRD2* expression, decreased DRD2 density in striatum[80] |
| *DRD3* | Ser9Gly (rs6280) | Ser | Clinically significant response | 0.82[b] (0.65-1.04; *0.10*)[38] | Decreased DRD3 binding affinity, decreased DRD3 signaling efficacy[81] |
| *HTR1A* | C-1019G (rs6295) | G | Negative symptom improvement[39-41] | | Increased *HTR1A* expression[82] |
| *HTR2A* | T102C (rs6313) | C | Clinically significant response | 0.61[c] (0.43-85; *0.01*)[42] | Decreased *HTR2A* expression[83] |
| | His452Tyr (rs6314) | Tyr | Clinically significant response | 0.18[c] (0.03 - 0.93; *0.02*)[42] | Decreased binding affinity of HTR2A, decreased signaling efficacy[84] |
| *ZNF804A* | rs1344706 | A | Positive symptom improvement[47,48] | | Increased *ZNF804A* expression[43] |

**Table II.** Pharmacogenetic variants associated with antipsychotic response. SNP, single-nucleotide polymorphism; DRD, dopamine receptor; HTR, serotonin receptor; ZNF, zinc finger. [a]Results are based on dominant genotypic model; [b]Results are based on allelic model; [c]Results are based on additive genotypic model

evidence that variation in genes coding for the serotonin 2C (*HTR2C*)[53] and melanocortin 4 (*MC4R*)[11,54-56] receptors are associated with antipsychotic-induced weight gain, with moderate-to-large effect sizes *(Table III)*. The protein products of these genes play important roles in appetite regulation, and may present an opportunity for therapeutic development to prevent antipsychotic-induced weight gain in the future.

Agranulocytosis is a rare (cumulative incidence 0.8% to 1.5% within the first year of treatment[57]) but potentially fatal adverse effect of clozapine treatment. Despite its demonstrated efficacy in treatment-refractory schizophrenia,[58] clozapine is currently underutilized due to the potential side effect of agranulocytosis.[59] A number of classical human leukocyte antigen (HLA) alleles have shown association with clozapine-induced agranulocytosis in small samples, but these results have not yet been replicated.[53] Importantly, the *HLA-DQB1* variant G6672C (rs113332494) showed strong association with clozapine-induced agranulocytosis across two independent samples (OR=16.9,95% CI:3.57-109).[60] *HLA-DQB1* G6672C was included in the PGxPredict:CLOZAPINE® pharmacogenetic test (PGx Health, Division of Clinical Data, Inc.), which was made commercially available in 2007 for prediction of clozapine-induced agranulocytosis. The test reportedly had 21% sensitivity and 98% specificity for predicting clozapine-induced agranulocytosis,[60] but was taken off the market due to lack of clinical up-

| Gene | SNP | Risk allele | Outcome measure | OR (95% CI; *P*) | Functional effect |
|---|---|---|---|---|---|
| **Weight gain** | | | | | |
| *HTR2C* | C-759T (rs3813929) | C | Gaining ≥7% baseline weight | *Chronic samples* 1.64[a] (0.73-3.69; *0.23*)[53], *First episode samples* 5.40[a] (2.08-14.01; *0.001*)[53] | Affects transcription factor binding to *HTR2C* promoter,[85] unclear if C allele increases[86] or decreases[87,88] *HTR2C* expression |
| *MC4R* | rs489693 | A | Weight gain (kg) from baseline | AA homozygotes gained ~3 kg more weight than other genotypes[11,56] | Unknown |
| **Agranulocytosis** | | | | | |
| *HLA-DQB1* | G6672C (rs113332494) | G | Absolute neutrophil count <500 cells/mm$^3$ and discontinuation of clozapine therapy | 16.9 (3.57-109; *<0.001*)[60] | Unknown |
| **Tardive dyskinesia** | | | | | |
| *CYP2D6* | Poor and intermediate metabolizers | At least one *3, *4, *5, *6, or *10 allele | Presence of tardive dyskinesia | *Prospective studies* 1.83 (1.09-3.08; *0.02*)[63] | Decreased CYP2D6 enzyme activity[89] |
| *DRD2* | Taq 1A (rs1800497) | C, A2 | Presence of tardive dyskinesia | 1.30[b] (1.09-1.55; *0.003*)[64] | Increased DRD2 receptor availability[90,91] |
| *HTR2A* | T102C (rs6313) | C | Presence of tardive dyskinesia | 1.64[b] (1.17-2.32; *0.004*)[65] | Decreased *HTR2A* expression,[92] decreased HTR2A receptor binding[93] |
| *HSPG2* | rs2445142 | G | Presence of tardive dyskinesia | 2.09[a] (1.07-4.06; *0.03*)[67] | Increased *HSPG2* expression[66] |

**Table III.** Pharmacogenetic variants associated with antipsychotic-induced side effects. SNP, single-nucleotide polymorphism; DRD, dopamine receptor; HTR, serotonin receptor; MCR, melanocortin receptor; HLA, human leukocyte antigen; HSPG, heparan sulfate proteoglycan. [a]Results are based on allelic model; [b]Results are based on recessive genotypic model.

take. Recently, the first whole-exome sequencing study undertaken in clozapine-induced agranulocytosis identified several non-HLA candidate genes,[61] which now require replication in independent samples.

Tardive dyskinesia, a motor system disorder characterized by repetitive and involuntary movements, is a potentially irreversible side effect experienced by an estimated 25% of patients treated long-term with first-generation antipsychotics.[62] There is evidence for a modest effect of *CYP2D6*,[63] *DRD2*,[64] and *HTR2A*[65] on susceptibility to tardive dyskinesia *(Table III)*. First identified in a GWAS by Syu et al,[66] the association between variants in *heparan sulfate proteoglycan 2, perlecan (HSPG2)* and tardive dyskinesia was replicated in two independent samples.[67] These initial results for *HSPG2* highlight the potential utility of applying GWAS in well-phenotyped samples to identify novel candidate genes, which can then be followed up in subsequent replication studies.

## Clinical application of pharmacogenetic testing in schizophrenia

Our understanding of the genetic factors accounting for individual variability in antipsychotic response is still evolving. The attitude of the general public toward using pharmacogenetic testing to select an appropriate antipsychotic medication appears to be overwhelmingly positive, provided that a diagnosis of schizophrenia has already been made, drug efficacy can be predicted, and side effects can be reduced.[68] Therefore, improving prediction of antipsychotic treatment outcomes using genetic information is a critical area of future research. Identification of pharmacogenetic variants outside of traditional systems targeted by candidate gene studies using GWAS and next-generation sequencing methods, along with the development of algorithms required for meaningful prediction of treatment outcomes, are active areas of research. As such, the successful application of pharmacogenetics in psychiatry will require immense collaboration between clinicians, bioinformaticians, and geneticists.

At the same time, evidence has accumulated in support of a number of variants with modest to moderate effect on antipsychotic metabolism, efficacy, and side effects *(Tables II and III)*. Some of these genetic variants have already been incorporated into commercially available pharmacogenetic tests. In light of the growing number of robust genetic predictors of antipsychotic treatment outcomes, deferring clinical implementation of pharmacogenetics until further refinements in prediction are achieved may unnecessarily delay patient access to safer prescribing practices. Early efforts to evaluate the benefit of applying current pharmacogenetic findings to guide antipsychotic treatment selection are already under way. These studies are a critical next step in the field, and will be instrumental in garnering the support of patients, health care providers, and insurance providers for pharmacogenetic testing in psychiatry. A growing number of tools are available to help health care providers evaluate the strength of evidence for pharmacogenetics-based treatment decisions and dosing guidelines (for an overview of these resources, see *Table IV*).

| Resource | Description |
|---|---|
| US Food and Drug Administration[19] http://www.fda.gov | Provides an up-to-date list of drugs with pharmacogenomic information in their labeling, along with any specific actions or dosing guidelines related to the genetic information. |
| The Pharmacogenomic Knowledgebase (PharmGKB)[94] http://www.pharmgkb.org | A comprehensive resource that provides up-to-date, manually curated pharmacogenetic information including variant annotation, FDA drug labeling information, dosing guidelines, and pathway summaries. |
| The Clinical Pharmacogenetics Implementation Consortium (CPIC)[76,95] http://www.pharmgkb.org/page/cpic | Established in 2009 as a shared project between PharmGKB and the Pharmacogenomics Research Network, CPIC provides freely available peer-reviewed pharmacogenetic guidelines. |
| The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) http://www.egappreviews.org/about.htm | Established in 2004 by the Centers for Disease Control and Prevention (CDC) to develop evidence-based processes for assessing genetic tests, EGAPP has developed a number of pharmacogenetics guidelines. |

**Table IV.** Pharmacogenetics resources.

In addition to pharmacogenetic testing, plasma level assessments as practiced for therapeutic drug monitoring (TDM) may be useful to assess metabolizer status and recommended guidelines are available.[16]

While the advantages of TDM include low costs, assessment for compliance and potentially undetected drug-drug interactions, the advantage of pharmacogenetic testing is that knowledge can be used to select type and dose of medication a priori. Moreover, pharmacogenetic testing is only required once and costs are becoming increasingly affordable.[69]

**Commercially available pharmacogenetic tests**

*AmpliChip™ CYP450 Test*

The AmpliChip™ CYP450 Test (Roche Molecular Systems, Inc.) genotypes pharmacokinetic variants in *CYP2D6* (33 alleles) and *CYP2C19* (3 alleles) that are associated with different metabolizing phenotypes. As CYP2D6 is a major enzyme involved in antipsychotic metabolism, the AmpliChip™ CYP450 Test may be useful in the clinical management of schizophrenia. Psychiatrists appear to have positive attitudes toward incorporating the test into their clinical decision-making.[70] Furthermore, an initial study conducted by de Leon et al in 2005 suggested the CYP2D6 phenotype provided by the test was a useful predictor of adverse reactions to risperidone treatment (OR=3.1, 95% CI: 1.4-7.0 for poor metabolizers).[71] This finding was not replicated in a smaller study with patients treated with risperidone or haloperidol.[72] In 2005, the AmpliChip™ CYP450 Test became the first-ever FDA approved pharmacogenetic test. However, further investigation of its clinical utility in guiding antipsychotic treatment selection is required to validate the utility of this test.

*DMET™ Plus Solution*

The DMET (Drug-Metabolizing Enzymes and Transporters)™ Plus Solution (Affymetrix, Inc) is one of the largest commercially available pharmacogenetic genotyping platforms, assaying a total of 1936 pharmacokinetic variants across 231 genes. It includes 95% of the "Core ADME (**A**bsorption, **D**istribution, **M**etabolism, and **E**xcretion) Markers," which were selected to represent the most robustly implicated variants in drug metabolism by an expert panel (http://www.pharmaadme.org). The DMET™ Plus Solution was developed as a pharmacogenetic variant identification platform rather than a clinical test, and has not been evaluated for efficacy in improving clinical outcomes with psychotropic drugs.

*GeneSight®*

The GeneSight® (Assurex Health®) psychotropic test provides coverage of 50 alleles in pharmacokinetic (*CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP1A2*) and pharmacodynamic genes (*5HTT*, *HTR2A)*. On the basis of this genetic information, individuals are categorized as high, intermediate, or low risk for poor response and adverse side effects to 26 psychotropic medications. Although these test categorizations have not been evaluated in relation to antipsychotic treatment outcomes, they have demonstrated some accuracy in predicting antidepressant efficacy.[73,74]

*Genecept™ Assay*

The Genecept™ Assay (Genomind, LLC) provides coverage of both pharmacokinetic (*CYP2D6*, *CYP2C19*, *CYP3A4*) and pharmacodynamic variants (*5HTT*, *HTR2C*, *DRD2*, *COMT*, *CACNA1C*, *ANK3*, *MTHFR)*. The patient's test results are provided to the ordering clinician, along with suggested therapeutic options. At the time of writing, the clinical benefit of using the Genecept™ Assay to guide treatment decisions has not been evaluated.

## Future outlook

Already, a number of commercial tests have been developed to allow the incorporation of pharmacogenetic information into clinical practice. However, currently available tests capture only a portion of the variants known to be involved in antipsychotic treatment outcomes. While the precise number of variants contributing to antipsychotic efficacy and side effects is not yet known, based on findings from other complex traits it is possible that this number ranges somewhere in the order of $10^3$- $10^4$ SNPs.[75] In the future, the development of more comprehensive tests and algorithms that are easily interpreted by clinicians will be crucial. Nevertheless, current tests cover some of the best understood pharmacokinetic variants involved in antipsychotic me-

tabolism. Preliminary studies suggest some clinical benefit in reducing side effects of antipsychotic treatment,[71] and a positive attitude towards using the test by health care providers[70] and the public.[68] Despite this, there is a lack of clinical uptake of pharmacogenetic testing, due at least in part to the lack of clinical expert consensus guidelines on the appropriate use of pharmacogenetic information in antipsychotic prescribing. Additionally, the lack of clear clinical guidelines has contributed to the hesitancy of insurance providers to include coverage for pharmacogenetic testing in the context of schizophrenia management. Thus, pharmacogenetic tests to guide antipsychotic treatment selection are not covered by most insurance providers at the present time, which presents a significant financial barrier for patients who wish to access this testing.

In other complex diseases, most notably cancer,[5] pharmacogenetic testing has already become a routine part of clinical management. Prior to clinical uptake of any pharmacogenetic test, there must be strong biological evidence for gene-drug interactions and replicated evidence that the genetic variant is linked to treatment outcomes. At this point, this level of evidence has been well-established for a number of genetic variants with respect to antipsychotic treatment outcomes. Additionally, the use of pharmacogenetic testing to guide therapy must be proven no worse than usual prescribing practice in terms of clinical outcomes.[76-78] This noninferiority requirement has not yet been met for antipsychotic therapy, and is the final push required to further the development of clinical guidelines, and engage government and insurance stakeholders to support these tests in order to remove financial barriers to access. Large-scale prospective studies evaluating the costs and benefits of genotype-directed antipsychotic prescribing, in comparison with standard prescribing practice, are therefore a critical direction for future research.

It is clear that much work remains to be done to improve the sensitivity and specificity of pharmacogenetic tests in predicting antipsychotic treatment outcomes. As such, the identification of additional genetic predictors of treatment outcomes and improved algorithms for prediction of response remain important areas of future research. Nevertheless, a number of genetic variants robustly associated with antipsychotic treatment outcomes have already been identified. It is therefore equally important to begin to apply pharmacogenetic findings available at the present time, in order to establish the necessary infrastructure to support pharmacogenetic testing for antipsychotic treatment selection. With collaboration across disciplines and study centers to support these ongoing research directions, we are confident that pharmacogenetics will improve treatment outcomes in psychiatry in the near future. ❑

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### *Los resultados de la farmacogenética con los antipsicóticos*

*Los antipsicóticos son los medicamentos utilizados como gold standard para el tratamiento de la esquizofrenia y además se emplean con frecuencia para otros trastornos mentales. Sin embargo, los perfiles de eficacia y efectos secundarios de estos fármacos son heterogéneos y con gran variabilidad interindividual. A raíz de esto, la selección del tratamiento sigue siendo un largo proceso de ensayo-error, con muchas fallas terapéuticas que se deben soportar antes de encontrar un balance aceptable entre el manejo sintomático y los efectos secundarios. Mucha de la variabilidad interindividual en la respuesta y los efectos secundarios se debe a factores genéticos (heredabilidad, $h^2$~ 0.60 – 0.80). La farmacogenética es un área emergente que posee el potencial de facilitar la selección de la mejor medicación para un paciente en particular, en base a su información genética. En esta revisión se discuten los marcadores genéticos más promisorios en los resultados del tratamiento antipsicótico, y se presentan los esfuerzos actuales de la investigación translacional que tienen como objetivo llevar estos hallazgos farmacogenéticos a la clínica en un futuro cercano.*

### *Pharmacogénétique et efficacité des antipsychotiques*

*Les médicaments antipsychotiques, traitement de référence pour la schizophrénie, sont souvent prescrits pour d'autres maladies mentales. Néanmoins, leur efficacité et leurs effets indésirables sont hétérogènes, avec une grande variabilité selon les individus. En conséquence, le choix du traitement procède en grande partie par tâtonnements, beaucoup de schémas thérapeutiques échouant avant que soit trouvé un rapport correct entre les effets sur les symptômes et les effets indésirables. Des facteurs génétiques sont responsables de la majeure partie de la variabilité interindividuelle dans les réponses au traitement et les effets indésirables (héritabilité, $h^2$ ~ 0,60-0,80). La pharmacogénétique est un domaine en plein essor qui permet d'aider au choix du meilleur traitement pour un patient donné, d'après ses informations génétiques. Nous analysons dans cet article les marqueurs génétiques les plus prometteurs dans le traitement antipsychotique et nous présentons les travaux actuels de recherche translationnelle dont le but est d'appliquer ces résultats de pharmacogénétique à la clinique dans un futur proche.*



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