Pharmacogenetics-Guided Advances in Antipsychotic Treatment

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Pharmacogenetics (PGx) research over the past 2 decades has produced extensive evidence for the influence of genetic factors on the efficacy and tolerability of antipsychotic treatment. However, the application of these findings to optimize treatment outcomes for patients in clinical practice has been limited. This paper presents a meta-review of key PGx findings related to antipsychotic response and common adverse effects, including antipsychotic-induced weight gain, tardive dyskinesia (TD), and clozapine-induced agranulocytosis (CIAG), and highlights advances and challenges in clinical implementation. Most robust findings from candidate gene and genomewide association studies were reported for associations between polymorphisms in *CYP2D6* and exposure and response to specific antipsychotics. As a result, product labels and guidelines from various PGx expert groups have provided selection and dosing recommendations based on *CYP2D6* metabolizer phenotypes for commonly prescribed antipsychotics. Other interesting genetic targets include DRD2 for antipsychotic response, *SLC18A2* for TD, and the human leukocyte antigen (HLA) genes, *HLA-DQB1* and *HLA-B*, for CIAG. Well-designed studies using large, well-characterized samples that leverages international collaborations are needed to validate previous findings, as well as discover new genetic variants involved in antipsychotic response and adverse effects.

Antipsychotic medications are routinely used for the treatment of not only schizophrenia and various psychotic spectrum disorders, but also for the treatment of mood disorders, obsessive-compulsive disorder, and behavioral disturbances associated with some conditions, including autism and dementia. Antipsychotics are generally efficacious in alleviating psychotic symptoms with response rates ranging from 66% for first-episode patients with schizophrenia to 47% for chronic patients.[1] However, patients on these medications often experience a lengthy "trial and error" process until the optimal medication for the treatment of their symptoms is found. As a result, 1-year discontinuation rates may be as high as 74% due to lack of efficacy and tolerability.[2]

Growing evidence suggests that genetic variability contributes to interindividual differences in response and adverse effects of antipsychotic treatment.[3] Pharmacogenetic/pharmacogenomic (PGx) research investigates genomic variations that influence an individual's response to treatment to ultimately guide medication and dosage selection, reduce nonadherence, and repeated medication switching, as well as maximize medication efficacy and tolerability. Here, we highlight recent progress in the PGx of antipsychotic treatment by presenting a meta-review of key PGx findings related to antipsychotic response and common adverse effects, and summarizing advances and challenges in clinical implementation.

METHODS

We followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[4] adapted for a meta-review. We performed an electronic search on Medline, EMBASE, and PsycInfo via OVID using the following keywords and phrases: (pharmacogenetic*) and (antipsychotic*) and (response or tardive dyskinesia or weight gain or "clozapine-induced agranulocytosis"). Two reviewers (authors F.I. and X.M.) independently screened all identified search results based on titles, keywords, and abstracts. Articles were included if they were (i) peer-reviewed systematic/narrative reviews or meta-analyses (ii) focusing on PGx findings for antipsychotic response, antipsychotic-induced weight gain, tardive dyskinesia, and/or clozapine-induced agranulocytosis, and (iii) published between January 2016 and May 1, 2021. Publications were excluded if not written in English and where full text was unavailable. The reference lists of identified reviews were examined to find additional relevant articles. Further, primary papers published after the most recent PGx review on the phenotype were retrieved and synthesized for completeness to date.

Following screening, critical appraisal of publications meeting the inclusion criteria was carried out independently by authors F.I. and X.M. using the A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2) systematic review critical appraisal tool.[5] Narrative reviews were not critically appraised because their aim and methods differ from systematic reviews. From pertinent publications, we collected relevant information from the full text for synthesis in this meta-review using the narrative synthesis approach.

META-REVIEW OF PHARMACOGENETIC FINDINGS

The PRISMA flow diagram for the selection of articles is presented in **Figure S1**. The reviews and meta-analyses identified and synthesized in this paper are listed in **Table S1**. Eighteen publications were identified as meeting the inclusion criteria, of which 7 were systematic reviews and/or meta-analyses and 11 were narrative reviews. Overall, the systematic reviews and/or meta-analyses achieved 49% item completion on the AMSTAR 2 (range: 38%–56%; **Table S1**).

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Treatment response

Pharmacokinetic-related genes. Antipsychotic medications are primarily metabolized by one or more cytochrome P450 (CYP450) hepatic enzymes, particularly the CYP1A2, CYP2C19, CYP2D6, and CYP3A4 isoforms. Genes encoding CYP450 enzymes can be highly polymorphic rendering these enzymes functionally slow (intermediate metabolizers (IMs)) or inactive (poor metabolizers (PMs)) or have rapid enzymatic activity (ultrarapid metabolizers (UMs)) compared to the wild-type form (normal metabolizers (NMs)). Among studies investigating the association between polymorphisms in CYP450 genes and antipsychotic response, there are only a few reporting positive findings. The evidence is most consistent for an association between *CYP2D6* and risperidone response in various ethnic groups. The frequency of the nonfunctional *CYP2D6*4* allele has been reported to be higher in nonresponders and partial responders compared to responders of risperidone treatment at 12 weeks in a sample of patients with schizophrenia of Indian ancestry (n = 443).[6] Likewise, the incidence of switching from risperidone to an alternative antipsychotic within 1 year was higher in UMs and PMs compared to NMs in a Scandinavian sample (n = 1,288).[7]

Furthermore, there is substantial evidence that indicates *CYP2D6* gene polymorphisms have a significant influence on antipsychotic exposure with CYP2D6 IMs and PMs showing increased serum levels of aripiprazole, risperidone, and haloperidol compared to NMs.[8] It is hypothesized that genetic differences in CYP2D6 enzymatic activity affect the metabolism of many of its antipsychotic substrates resulting in higher sum of parent drug and active metabolite serum concentrations for patients that are in the IM and PM category; therefore, this significant increase in active moiety exposure may make IMs and PMs more prone to poorer treatment response, adverse drug reactions (ADRs), or switching to another medication.[7]

Despite there being strong associations between gene variants of *CYP2D6* and plasma/serum concentrations of its antipsychotic substrates, very few PGx studies on treatment efficacy include drug exposure in their analyses, potentially leading to spurious associations or inconsistent findings. The *CYP2D6* gene alone may account for a part of the variability in treatment response, whereas including plasma/serum concentration data would also allow for the appropriate degree of correction for drug exposure. Therefore, many studies include dosage in their analyses as a proxy for actual plasma/serum drug levels. However, plasma/serum drug levels at the same dosage often vary 5–20-fold. Instead, accounting for patient plasma/serum concentrations may capture more of the pharmacokinetic variability and help uncover true associations between *CYP2D6* and antipsychotic efficacy.

As a result of these findings reporting strong associations between *CYP2D6* and antipsychotic response and exposure across different ethnic groups, dosing and prescribing guidelines based on *CYP2D6* metabolizer phenotype have been recommended for 12 common antipsychotics by expert PGx groups, including the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Royal Dutch Association for the Advancement of Pharmacy–Dutch Pharmacogenetics Working Group (DPWG). These recommendations can be found on the Pharmacogenomics Knowledgebase (PharmGKB) website, which is summarized in **Table 1**.

Another pharmacokinetic-related gene that has been extensively studied for its contributions to antipsychotic response is the *ABCB1* gene, which encodes the transmembrane efflux transporter P-glycoprotein (P-gp) involved in pumping different substrates, including antipsychotics, across the blood-brain-barrier back into the plasma, thereby modulating intracerebral drug concentrations. A number of antipsychotics are substrates of P-gp, including aripiprazole, amisulpride, paliperidone, and risperidone.[9] Findings from existing studies investigating the influence of *ABCB1* gene variants on antipsychotic outcome have been inconclusive, which may in part be due to some of these studies having low statistical power. Therefore, a meta-analysis of these studies may be warranted to address inter-study heterogeneity and to increase statistical power in order to generate new insights into any associations between *ABCB1* polymorphisms and antipsychotic treatment outcome.

Pharmacodynamic-related genes. Much of the research investigating the association of pharmacodynamic-related genes with antipsychotic response have focused on the dopaminergic system, particularly the dopamine receptor D2 (*DRD2*) gene, given that antipsychotics exert their effects via DRD2 antagonism. The most frequently studied polymorphisms of *DRD2* in relation to antipsychotic response are rs17294542 (*TaqIB*), rs1799732 (141C Ins/Del), rs1800497 (*TaqIA*), rs1800498 (*TaqID*), and rs2514218.[10,11] Among these, the rs2514218 polymorphism, located 47-kb upstream of *DRD2*, has been the most promising and well replicated. Findings from the largest genome-wide association study (GWAS) on schizophrenia risk conducted by the Psychiatric Genomics Consortium (PGC) reported rs2514218 as the top single-nucleotide polymorphism (SNP) for *DRD2* with the T allele conferring reduced schizophrenia risk.[11] In terms of antipsychotic response, homozygotes of the risk allele C showed the most reduction in positive symptoms compared to T allele carriers following 12 weeks of treatment with either aripiprazole or risperidone.[12] Similarly, the risk allele was shown to be associated with greater symptom improvement in patients on clozapine.[13]

Several other pharmacodynamic-related candidate genes have been studied in relation to antipsychotic treatment response, including *COMT*, *NFKB1*, *GRM7*, and several serotonin-pathway associated genes, such as *HTR1A*, *HTR2A*, and *HTR2C*. However, much of the evidence linking pharmacodynamic-related genes with antipsychotic treatment response have been inconclusive; therefore, there has been no clinical recommendations made by expert PGx groups based on these genes.

Adverse effects

Antipsychotic-induced weight gain. Antipsychotic-induced weight gain (AIWG) is a very common side effect in patients treated with antipsychotics, frequently leading to metabolic disturbances, such as type 2 diabetes (T2D) and cardiovascular diseases. Specifically, significant AIWG (i.e., > 7% from baseline, a measure commonly used as demarcation for severe AIWG) is observed in more than

Table 1 Summary *CYP2D6* genotype-based actionable guidelines provided by various PGx expert groups and FDA product labels by antipsychotics

Antipsychotic	CPIC[a]	FDA[b]	DPWG
Antipsychotics with actionable guidelines			
Amoxapine	Provisional	*Actionable PGx*: PMs may have higher plasma concentrations. Plasma levels should be monitored if co-administered with a CYP2D6 inhibitor.	No dosing recommendations.
Aripiprazole	Provisional	*Actionable PGx*: PMs should receive half the usual dose.	Reduce maximum dose for PMs.
Brexpiprazole	Provisional	*Actionable PGx*: PMs should have their usual dosage reduced by half. PMs on concomitant strong/moderate CYP3A4 inhibitors should be administered a quarter of the usual dose.	Use half of the standard dose for PMs.
Carpipramine	Final: consider a 50% dose reduction in PMs. For IMs, a 25% dose reduction should be considered.	*Actionable PGx*: Monitor plasma levels when co-administered with inhibitor of CYP2D6.	Dose change and monitor the effect and side effects and the plasma concentrations to set the maintenance dose for PMs and IMs. Alternatively, avoid in PMs and UMs.
Clozapine	Provisional	*Actionable PGx*: Reduce the dose for PMs.	No dosing recommendations.
Haloperidol	Provisional	—	Reduce dose by 50% or select an alternative drug for PMs.
Iloperidone	Provisional	*Actionable PGx*: PMs should have their dose reduced by one half.	No dosing recommendations.
Perphenazine	Provisional	*Actionable PGx*: PMs will metabolize the drug more slowly and experience higher concentrations as compared with NMs. This may lead to greater side effects.	No dosing recommendations.
Pimozide	Provisional	*Testing required*: CYP2D6 genotyping should be performed in children at doses above 0.05 mg/kg/day and in adults at doses above 4 mg/day. In PMs, doses should not exceed 0.05 mg/kg/day in children or 4 mg/day in adults, and doses should not be increased earlier than 14 days.	Reduce dose for IMs and PMs.
Risperidone	Provisional	*Informative PGx*: No need for dose adjustment based on *CYP2D6* genotype	Reduce dose for PMs. Use an alternative drug or titrate dose according to the maximum dose for the active metabolite for CYP2D6 UMs.
Thioridazine	Provisional	*Actionable PGx*: This drug is contraindicated in patients with reduced level of CYP2D6 activity.	No dosing recommendations.
Zuclopenthixol	Provisional	—	Reduce dose or use an alternative drug that is not metabolized by CYP2D6 for IMs and PMs. Increase dose or use an alternative drug that is not metabolized by CYP2D6 for UMs who have low plasma concentrations.
Antipsychotics without current actionable guidelines			
Acepromazine, Acetophenazine, Amisulpride, Asenapine, Benperidol, Blonanserin, Bromperidol, Butaperazine, Carfenazine, Cariprazine, Chlorproethazine, Chlorpromazine, Chlorprothixene, Clocapramine, Clopenthixol, Clorotepine, Clotiapine, Cyamemazine, Dixyrazine, Droperidol, Fluanisone, Flupentixol, Fluphenazine, Fluspirilene, Lenperone, Levomepromazine, Levosulpiride, Loxapine, Lurasidone, Melperone, Mosapramine, Mesoridazine, Metitepine, Molindone, Moperone, Nemonapride, Olanzapine, Oxypertine, Penfluridol, Perazine, Periciazine, Pipamperone, Piperacetazine, Pipotiazine, Paliperidone, Perospirone, Prochlorperazine, Promazine, Prothipendyl, Quetiapine, Remoxipride, Reserpine, Sertindole, Spiperone, Sulforidazine, Sultopride, Tiapride, Thiopropazate, Thioproperazine, Thiothixene, Timiperone, Trifluoperazine, Trifluperidol, Triflupromazine, Veralipride, Ziprasidone, Zotepine, Zuclopenthixol			

Data was extracted from the PharmGKB website.
CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Royal Dutch Association for the Advancement of Pharmacy – Pharmacogenetics Working Group; FDA, US Food and Drug Administration; IMs, intermediate metabolizers; NMs, normal metabolizers; PGx, pharmacogenetics/pharmacogenomics; PharmGKB, Pharmacogenomics Knowledgebase; PMs, poor metabolizers; UMs, ultrarapid metabolizers.
[a]CPIC level status assignments, "provisional" or "final", indicate that gene/drug pair remains to be reviewed or has been reviewed as part of CPIC guidelines, respectively. [b]PharmGKB extracted FDA-approved product labels and interpreted the level of action implied by the label into four categories: "testing required," "testing recommended," "actionable PGx," and "informative PGx", see https://www.pharmgkb.org/page/drugLabelLegend.

Table 2 Overview of associations between gene variants and antipsychotic response or adverse effects

Gene[a]	Variant(s)[b]
Antipsychotic response	
ABCB1	rs1045642 (C3435T), rs1128503 (C1236T), and rs2032582 (G2677T)
COMT	rs4680 (Val158Met)
CYP2D6	*Normal*: rs16947 (*2); *Null*: rs35742686 (*3), rs3892097 (*4), rs5030655 (*6); *Reduced function*: rs5030656 (*9), rs1065852 (*10) and rs28371725 (*41); *Whole gene deletion*: *5
DRD2	rs1079597, rs1799732, rs1800497, and rs2514218
HTR1A	rs1364043, rs6295, and rs878567
HTR2A	rs6313, rs6314
HTR2C	rs3813929
GRM7	rs2069062, rs2133450
NFKB1	rs230493, rs3774959, rs230504
Antipsychotic-induced weight gain	
ADRA2A	rs1800544
ADRB3	rs4994
BDNF	rs6265
CIDEA	rs62097526
DGKB	rs1525085
RD2	rs1799732
GNB3	rs5443
HTR2C	rs3813929, rs6318, and rs518147
INSIG2	rs17047764
MC4R	rs489693
MEIS2	rs1568679
OGFRL1	rs9346455
PRKAR2B	rs13224682
PTPRD	rs10977144 and rs10977154
SNAP25	rs1051312
Tardive dyskinesia	
CYP2D6	rs3892097 (*4)
CYP1A2	rs762551 (*1F)
DRD2	rs1076560, rs1124491, and rs1800497
DRD3	rs6280
ERBB4	rs839523
GRIN2A	rs1345423
HSPG2	rs2445142
HTR2A	rs1928040, rs9567733
HTR2C	rs1801412 (in female), rs2015586, rs363390, rs353224
SLC18A2	rs2015586, rs363390, rs363224, and rs14240
SLC6A11	rs4684742
SLC6A11	rs4684742
Clozapine-induced agranulocytosis	
HLA	HLA-DQB1(126Q), HLA-B (158T), HLA-B*59:01, HLA-DQB1 (6672G>C)
ABCB1	rs1045642 (C3435T), rs1128503 (*C1236T*), rs2032582 (G2677T)
NQO2	1541AA
SLCO1B3/7	rs1546308/rs149104283

[a]Complete gene names can be found in **Table S2** of the **Supplementary Materials**. [b]Association between gene variant and the phenotype reported by at least one study.

30% of patients.[14] Family and twin studies strongly support the involvement of genetic factors in susceptibility to AIWG, suggesting that it is in part heritable. Genetic susceptibility to AIWG is highly polygenic, which has been reported in several comprehensive PGx reviews (e.g., genes related to antipsychotic metabolism, neurotransmitter systems, and neuroendocrine systems).[14–16]

To date, the targeted gene approach has identified several susceptibility genes of AIWG including *ADRA2A*, *ADRB3*, *BDNF*, *CNR1*, *DRD3*, *GNB3*, *HTR2C*, *INSIG2*, *LEP*, *MC4R*, *NDUFS1*, *NPY*, *SNAP25*, *TNF*, and *TSPO*.[3,17] A meta-analysis in 6,770 patients from 46 nonoverlapping samples that included PGx studies on AIWG until 2014 found 13 SNPs from 9 genes (*ADRA2A*, *ADRB3*, *BDNF*, *DRD2*, *GNB3*, *HTR2C*, *INSIG2*, *MC4R*, and *SNAP25*) showing significant associations with AIWG.[15] Among them, SNPs in *ADRA2A* (rs1800544), *DRD2* (rs1799732), *HTR2C* (rs3813929, rs6318, and rs518147), and *MC4R* (rs489693) had the largest effect sizes (Hedges' g's = 0.30–0.80, odds ratios (ORs) = 1.47–1.96).[15] In addition to these findings from the candidate gene approach, it is worth noting that GWAS have also been conducted to identify gene variants associated with AIWG despite the limited number of GWAS and relatively small sample sizes (n = 139–738).[18–20] These studies implicated *CIDEA* (rs62097526), *DGKB* (rs1525085), *PTPRD* (rs10977144 and rs10977154), *OGFRL1* (rs9346455), *MC4R* (rs489693), *PRKAR2B* (rs13224682), and *MEIS2* (rs1568679) genes in AIWG.

However, current genetic findings on AIWG are still being investigated for their use in clinical practice. Given that AIWG has polygenic architecture, analyzing combined effects of candidate variants in AIWG and comprehensive combined effects of a number of polymorphisms using polygenic risk score analysis could provide additional insight into the development of an algorithm for predicting AIWG in clinical practice.

Tardive dyskinesia. Approximately one-third of individuals receiving treatment with first-generation antipsychotics have been reported to experience tardive dyskinesia (TD), which is characterized by involuntary and repetitive movements of the face, trunk, and extremities. During the past two decades, evidence from PGx studies suggest associations between certain gene polymorphisms with TD. A large number of studies have investigated the association of CYP450 genes, particularly *CYP2D6*, with TD susceptibility, and have reported mixed findings. Extreme CYP2D6 metabolizer phenotypes have been associated with the occurrence of TD with CYP2D6 PMs and UMs being at a higher risk.[3,17] This increased risk may be due to PMs having a higher plasma level of the parent drug, and UMs experiencing increased oxidative stress and neurotoxic metabolites.

A notable development in the PGx of TD is the *SLC18A2* gene, encoding the vascular monoamine transporter 2 (VMAT2), which functions in the storage and release of monoamines implicated in TD, such as dopamine, norepinephrine, and serotonin. Particularly, the C allele of *SLC18A2* SNP, rs363224, related to high VMAT2 expression, was associated with increased risk and severity of TD.[17] These findings are consistent with the clinical evidence showing that the selective inhibition of VMAT2 using valbenazine or deutetrabenazine to be efficacious in reducing TD severity in patients with schizophrenia.[17] Therefore, *SLC18A2* appears to be a promising marker for TD susceptibility, but nevertheless, requires further validation.

Other possibly promising genes associated with susceptibility to TD include *DRD2*, *DRD3*, *ERBB4*, *GRIN2A*, *HSPG2*, *HTR2A*, *HTR2C*, and *SLC6A11*. Many of these associations, however, require replication in large, independent samples. Consequently, reliable genetic biomarkers for the prediction of antipsychotic-induced TD remains to be discovered.

Clozapine-induced agranulocytosis. Clozapine-induced agranulocytosis (CIAG) is a rare but potentially lethal adverse drug reaction occurring in ~ 0.8% of individuals on clozapine characterized by a low white blood cell count (absolute neutrophil count < 500).[17] Although its etiology remains unclear, it is hypothesized that immune-mediated mechanisms may be involved in CIAG pathophysiology. On the basis of this hypothesis, variations in genes within the human leukocyte antigen (HLA) system, which encodes proteins involved in immune processes, have been investigated for their involvement in the development of CIAG. Several HLA polymorphisms have shown an association with CIAG occurrence, including *HLA-DQB1* 126Q, *HLA-B* 158T, *HLA-B**59:01, and *HLA-DQB1* 6672G>C.[16] The association of the latter polymorphism, HLA-DQB1 6672G>C (rs113332494), with CIAG was replicated in independent samples and led to the development of a PGx test.[21] However, the test was not clinically useful due to its low sensitivity (21.5%), and, as a result, failed commercially. Other genes reported to be associated with CIAG include *CYP2D6, Fcγ*R, *MPO*, *NQO2*, and *SLCO1B3/SLCO1B7*. Further research is required to validate these existing associations and discover reliable genetic variants with large effects related to CIAG, which can be incorporated in a PGx test.

ADVANCES TOWARD CLINICAL IMPLEMENTATION

Despite growing interest in incorporating personalized medicine to daily clinical practice, with consistent recommendations from expert reviews, widespread implementation of PGx testing in psychiatry has been limited. This is because there are a number of barriers to the translation of PGx to clinical practice. First, there is considerable heterogeneity in genetic studies of antipsychotic treatment efficacy and tolerability as described in this review. There are several possible explanations that may account for some of this low replicability. Because genotype frequencies and disease risk differ by geographic region and ethnicity, differences in study population may be a source of conflicting findings between studies and limit generalizability of findings from one geographic or ethnic group to another. For instance, two variants (rs10977144 and rs10977154) of the *PTPRD* gene were discovered to be associated with AIWG in Han Chinese patients.[22] However, this association could not be validated in European and African American patients; instead associations were found between other *PTPRD* gene variants with AIWG in these samples.[22] Additionally, there

is great heterogeneity in the definition and measurements of study outcome parameters. For instance, studies differ in terms of the rating scale used to measure response (e.g., Positive and Negative Syndrome Scale (PANSS); Brief Psychiatric Rating Scale (BPRS); and Clinical Global Impressions (CGI)), and in the cutoff used to determine response, because there currently is no consensus on an appropriate clinically meaningful response cutoff. Further, a number of studies conduct their analysis on samples treated with different antipsychotics, which have varying pharmacokinetic properties and mechanisms of actions. Such an approach can lead to spurious associations that often cannot be replicated due to heterogeneity between samples. Finally, there may be additional mechanisms contributing to treatment outcome, besides the gene variants of interest, that may not be accounted for, including gene–gene and gene–environment interactions. New approaches that incorporate epigenetic and transcriptomic data capturing both genetic and environmental factors may help to explain more of the variance in antipsychotic response and adverse effects.

A second barrier to the implementation of PGx in psychiatric clinical practice is the clinical efficacy and generalizability of PGx testing. Some of the gene variants reported in this review are currently available on commercial PGx testing panels, including *CYP2D6*, *ABCB1*, *DRD2*, *COMT*, *HTR2A*, and *HTR2C*. The commercial pharmacogenetic testing company selects genetic variants to be included on a panel based on the evaluation of existing scientific literature, as there presently are no standardized guidelines for this process. Studies on the clinical efficacy of commercial PGx testing in psychiatry have been mixed with some studies showing that testing improves the likelihood of achieving remission compared to treatment as usual, whereas others have reported inconclusive or negative findings.[23] Furthermore, evidence of clinical efficacy of PGx testing has primarily been conducted in European populations. PGx algorithms that is based on European data have shown to fail in predicting outcomes in different ethnic and geographic groups due to differences in allele frequencies.[24] Therefore, further research is warranted to replicate the findings of each genetic variant on a PGx testing panel in different populations before it can be considered universally applicable.[24]

Currently, *CYP2D6* is the only gene for which there is validated evidence of its association with antipsychotic response and exposure across different ethnic groups, thus many PGx expert groups have prioritized making selection and dosing recommendations based on predicted *CYP2D6* metabolizer phenotypes. However, the translation of *CYP2D6* genotype to phenotype, which involves assigning a function to each allele and then deriving a phenotype from the combination of these alleles an individual possesses, has been inconsistent between test providers. This is in part because the complexity of the *CYP2D6* locus contribute to making prediction of phenotype from genotype data challenging. *CYP2D6* sequence variations include SNPs, insertions or deletions of one or more nucleotides, gene copy number variations, and rearrangements with non-functional pseudogene, *CYP2D7*.[25] SNPs that can occur in complex haplotype combinations also alter enzymatic function and vary by ancestry (e.g., polymorphisms -1584C>G and -2988G>A are linked in White people allowing for accurate discrimination between *CYP2D6*2* and **41* alleles, but not in individuals of African or Japanese ancestry).[25] For a number of these rare sequence variations and haplotype combinations in the *CYP2D6* gene, the functional consequences remain elusive. Furthermore, for allelic variants for which activity is relatively well understood, there is a lack of standardization of genotype to phenotype translation resulting in individuals of the same *CYP2D6* genotype receiving differing pharmacotherapy recommendations. These overarching issues have served as a barrier to implementing *CYP2D6* testing in clinical practice. Recently, *CYP2D6* PGx experts of CPIC and DPWG have proposed a standardized method for the translation of *CYP2D6* genotype to metabolizer phenotype to reduce interlaboratory discrepancies and differences in recommendations. The revised method is described in detail on the CPIC webpage: https://cpicpgx.org/resources/cyp2d6-genotype-to-phenotype-standardization-project/.

CONCLUSIONS

PGx findings for antipsychotic response and adverse effects are summarized in **Table 2**. Based on currently available evidence from PGx studies, CYP2D6 metabolizer phenotype demonstrates the strongest association with antipsychotic response. As a result, the Food and Drug Administration (FDA) product labels and guidelines from various expert groups, such as the CPIC and DPWG, provide dosing recommendations based on CYP2D6 metabolizer phenotype for commonly prescribed antipsychotics. The other genes reported in this review require further research and validation for their association with antipsychotic response and/or occurrence of adverse effects.

Although there are major barriers to the clinical implementation of PGx that need to be addressed, PGx research over the past two decades has made major strides in identifying promising genetic markers that have contributed to elucidating the mechanisms underlying antipsychotic drug action. Further well-designed studies using large, well-characterized samples that leverages international collaborations are essential to develop PGx-based algorithms that reliably predict antipsychotic treatment outcome for widespread clinical use.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

D.J.M. and C.C.Z. are co-inventors on two patent assessing risk for antipsychotic-induced weight gain (pending). D.J.M. reports to be a co-investigator on two pharmacogenetic studies where genetic test kits were provided as in-kind contribution by Myriad Neuroscience. He did not receive any payments or any equity, stocks, or options from any pharmacogenetic companies. K.Y. has received manuscript fees from Sumitomo Dainippon Pharma, fellowship grants from the Japan Research Foundation for Clinical Pharmacology, and Azrieli Adult Neurodevelopmental Centre Postdoctoral Fellowship at CAMH, and consultant fees from Signant Health and VeraSci within the past three years. All other authors declared no competing interests for this work.

1. Haddad, P.M. & Correll, C.U. The acute efficacy of antipsychotics in schizophrenia: a review of recent meta-analyses. *Ther. Adv. Psychopharmacol.* **8**, 303–318 (2018).
2. Lieberman, J.A. *et al*. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N. Engl. J. Med.* **353**, 1209–1223 (2005).
3. Yoshida, K. & Müller, D.J. Pharmacogenetics of antipsychotic drug treatment: update and clinical implications. *Mol. Neuropsychiat.* **5**, 1–26 (2020).
4. M.J. *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* **372**, n71 (2021).. . .
5. Shea, B.J. *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* **358**, j4008 (2017)..
6. Kaur, G. *et al*. Identification of genetic correlates of response to Risperidone: Findings of a multicentric schizophrenia study from India. *Asian J. Psychiatr.* **29**, 174–182 (2017).
7. Jukic, M.M., Smith, R.L., Haslemo, T., Molden, E. & Ingelman-Sundberg, M. Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. *Lancet Psychiatr.* **6**, 418–426 (2019).
8. Milosavljević, F. *et al*. Association of CYP2C19 and CYP2D6 poor and intermediate metabolizer status with antidepressant and antipsychotic exposure: a systematic review and meta-analysis. *JAMA Psychiatr.* **78**, 270–280 (2021).
9. Wang, R., Sun, X., Deng, Y. & Qiu, X. ABCB1 1199G > A polymorphism impacts transport ability of P-gp-mediated antipsychotics. *DNA Cell Biol.* **37**, 325–329 (2018).
10. Ma, L. *et al*. Association between dopamine receptor gene polymorphisms and effects of risperidone treatment: a systematic review and meta-analysis. *Basic Clin. Pharmacol. Toxicol.* **124**, 94–104 (2019).
11. Ripke, S. *et al*. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421–427 (2014).
12. Zhang, J.-P. *et al*. Association of a schizophrenia risk variant at the DRD2 locus with antipsychotic treatment response in first-episode psychosis. *Schizophr. Bull.* **41**, 1248–1255 (2015).
13. Huang, E. *et al*. Preliminary evidence for association of genome-wide significant DRD2 schizophrenia risk variant with clozapine response. *Pharmacogenomics* **17**, 103–109 (2015).
14. Barton, B.B., Segger, F., Fischer, K., Obermeier, M. & Musil, R. Update on weight-gain caused by antipsychotics: a systematic review and meta-analysis. *Expert Opin. Drug Saf.* **19**, 295–314 (2020).
15. Zhang, J.-P. *et al*. Pharmacogenetic Associations of antipsychotic drug-related weight gain: a systematic review and meta-analysis. *Schizophr. Bull.* **42**, 1418–1437 (2016).
16. Zhang, J.-P. & Malhotra, A.K. Recent progress in pharmacogenomics of antipsychotic drug response. *Curr. Psychiatr. Rep.* **20**, 24 (2018).
17. Zai, C.C., Tiwari, A.K., Zai, G.C., Maes, M.S. & Kennedy, J.L. New findings in pharmacogenetics of schizophrenia. *Curr. Opin. Psychiatr.* **31**, 200–212 (2018).
18. Maciukiewicz, M. *et al*. Genome-wide association study on antipsychotic-induced weight gain in Europeans and African-Americans. *Schizophr. Res.* **212**, 204–212 (2019).
19. Yu, H. *et al*. Genome-wide association study suggested the PTPRD polymorphisms were associated with weight gain effects of atypical antipsychotic medications. *Schizophr. Bull.* **42**, 814–823 (2016).
20. Brandl, E.J. *et al*. Genome-wide association study on antipsychotic-induced weight gain in the CATIE sample. *Pharmacogenomics J.* **16**, 352–356 (2016).
21. Legge, S.E. *et al*. Genome-wide common and rare variant analysis provides novel insights into clozapine-associated neutropenia. *Mol. Psychiatr.* **22**, 1502–1508 (2017).
22. Maciukiewicz, M. *et al*. Genetic validation study of protein tyrosine phosphatase receptor type D (PTPRD) gene variants and risk for antipsychotic-induced weight gain. *J. Neural. Transm.* **126**, 27–33 (2019).
23. Bousman, C.A. *et al*. Review and consensus on pharmacogenomic testing in psychiatry. *Pharmacopsychiatry* **54**, 5–17 (2021).
24. El Shamieh, S. & Zgheib, N.K. Pharmacogenetics in developing countries and low resource environments. *Hum. Genet* https://doi.org/10.1007/s00439-021-02260-9.
25. Gaedigk, A. Complexities of CYP2D6 gene analysis and interpretation. *Int. Rev. Psychiatr.* **25**, 534–553 (2013).