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Current status of pharmacogenetic testing and their impact on atypical antipsychotic medication

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Abstract
Antipsychotic medications, introduced in the 1950s, remain the cornerstone of treatment for psychiatric disorders such as schizophrenia, bipolar disorder, and obsessive-compulsive disorder. However, high discontinuation rates (32-74%) due to adverse effects highlight the need for individualized treatment strategies. The wide interindividual variability in treatment response is influenced by both pharmacokinetic and pharmacodynamic factors. Pharmacogenetics offers a precision medicine approach by guiding drug selection and dosing based on genetic variations, particularly in cytochrome P450 (CYP) enzymes and neurotransmitter receptor genes. CYP2D6, CYP1A2, and CYP3A subfamilies are key determinants of antipsychotic metabolism, while genetic polymorphisms in dopamine and serotonin receptors (e.g., DRD2, HTR2A, HTR2C) influence therapeutic outcomes and risk of side effects such as tardive dyskinesia and akathisia. Evidence from clinical and pharmacogenetic studies demonstrates strong associations between genetic variants and altered plasma drug levels, treatment response, and extrapyramidal symptoms. Importantly, pharmacogenetic-guided therapy has shown cost-effectiveness in psychiatry, although routine clinical adoption remains limited due to turnaround time and implementation barriers. Advances in rapid genomic testing, polygenic risk scoring, and integration with clinical data hold promise for delivering near real-time recommendations, thereby improving treatment outcomes and reducing healthcare costs. This review highlights the current evidence, clinical implications, and future prospects of pharmacogenetics in optimizing antipsychotic therapy.

Keywords: Antipsychotics, pharmacogenetics, CYP2D6, CYP1A2, CYP3A4

Introduction
Antipsychotic were first introduced in 1950s to treat psychiatric disorder like obsessive compulsive disorder, bipolar disorder and other psychiatric condition but their side effect is high, due to which around 32 to 74% of people discontinue their treatment [1]. Treatment selection always a trial-and-error process requiring multiple medication changes and adjustment of dose to achieve a safe and effective balance between therapeutic response and tolerability.

The widely observed variation in response among patient with identical treatment has leads us to understand the multiple factors including clinical and demographic factor can alter drug metabolism (pharmacokinetic) and drug action (pharmacodynamic). Pharmacogenetic testing is a new modality of diagnostic procedure for advancing a precision medicine approach through optimizing antipsychotic treatment and dosing strategies, but still its not a standard of practice as it will take 2-3 weeks to provides results. Due to high accuracy of genomic testing, polygenic risk score, there is a positive response toward treatment.

Atypical antipsychotic include clozapine, olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, amisulpride, zotepine which has a various beneficial effect but come with a lots of side effect. Atypical antipsychotic acts on a mesolimbic and meso-cortical pathway blocks block dopamine D 2 receptor and serotonin 5HT2A receptor there by simultaneously decrease positive and negative schizophrenic symptom.

Genes affecting Pharmacokinetic parameter of drugs.
Antipsychotics are primarily metabolized in the liver through the cytochrome P450 enzyme system. Among the multiple CYP families-CYP1, CYP2, and CYP3-these enzymes significantly influence drug metabolism.

CYP2D6 is the only FDA-approved biomarker for *aripiprazole*, *clozapine*, and *risperidone*, aiding in dosage adjustment and improving treatment outcomes in psychiatric patients [2]. Within the CYP2 family, active alleles such as *1, *2, *2A*, and *35* of CYP2D6 are located on chromosome 22. Drugs commonly metabolized by CYP2D6 include: azepine, quetiapine, aripiprazole, olanzapine, risperidone, sertindol. CYP3A4 and CYP3A5, members of the CYP3 family located on chromosome 7, are also involved in the metabolism of antipsychotics. The *1 allele is considered functionally active. These enzymes metabolize: aripiprazole, asenapine, ziprasidone, quetiapine, lurasidone. CYP1A2, located on chromosome 15, has active enzymatic forms such as *1A*. It is responsible for the metabolism of: asenapine, olanzapine, clozapine [3]. Variations in these alleles can lead to partial activation or complete inactivity of the enzymes, affecting drug efficacy and safety [4].

Genes affecting Pharmacodynamic parameter of drugs

Genes encoding dopamine and serotonin neurotransmitters regulate psychiatric symptoms in patients. Variations in these genes can lead to changes in therapeutic dosing. The catechol-O-methyltransferase (COMT) gene, located on chromosome 22, contains the variant rs4680, which is associated with increased clinical response in patients who are homozygous for the Met/M*et al*lele. The dopaminergic receptor D2 (DRD2) and ANKK1 genes on chromosome 11 (variant rs1800497), the dopamine receptor D3 (DRD3) gene on chromosome 3 (variant rs6280**)**, and the serotonin receptor 2A (HTR2A) gene on chromosome 13 (variant rs6313) are all associated with an increased risk of tardive dyskinesia (TD)**,** with rs1800497also linked to a decreased likelihood of treatment success [5-6]. The rs1799732 variant is also associated with an increased risk of antipsychotic-induced akathisia (AIA). The serotonin receptor 1B (HTR1B) gene variant rs13212041 is associated with a higher risk of AIA. The serotonin receptor 2A (HTR2A) gene, located on chromosome 13, includes the variant rs6313, which is associated with an increased risk of TD. Finally, the serotonin receptor 2C (HTR2C) gene variant rs3813929, located on the X chromosome, is linked to weight gain [7].

Study on CYP enzymes and how its Concentration affect EPS.

A series of pharmacogenetic studies have been conducted to explore the impact of genetic polymorphisms on the pharmacokinetics, treatment response, and clinical outcomes of antipsychotic medications in individuals with schizophrenia and healthy volunteers. One such study investigated the influence of CYP2D6 genetic polymorphisms on risperidone metabolism in a pharmacogenetic trial involving 30 healthy volunteers aged 18-30 years, classified as poor (PM), extensive (EM), or ultra-rapid metabolizers (UM). Participants received a single low dose of placebo, haloperidol (5 mg), or risperidone (2.5 mg) in a randomized, crossover design. Blood samples were collected at multiple time points and analysed using HPLC-TMS to determine pharmacokinetic parameters such as Cmax, Tmax, and AUC. PMs exhibited significantly higher plasma risperidone levels, lower 9-hydroxyrisperidone concentrations, and greater motor impairment, highlighting the importance of genotype-guided dosing to minimize adverse effects [2].

In another study, the efficacy of clozapine was evaluated in a longitudinal observational cohort of approximately 100 adults with treatment-resistant schizophrenia, aged over 18 years, including both smokers and non-smokers. Genotyping for **SLC6A4, HTR2A, CYP1A2*1F/1F, ABCB1, and DRD2* revealed that S allele carriers of SLC6A4 had lower plasma concentrations of clozapine (CLZ) and norclozapine (NCLZ) compared to L allele carriers. CYP1A2 polymorphisms, especially among smokers, were also significantly associated with altered clozapine plasma levels, suggesting that serotonin transporter and metabolic gene variants may be linked to poor treatment response, particularly in patients with prominent negative symptoms[3]. Supporting this, a retrospective cohort study of 96 Korean patients aged 23-41 years investigated the pharmacogenomics of clozapine based on 127 genetic variations across 27 annotated genes, and found a positive correlation between CYP1A2 and CYP2D6 polymorphisms and serum clozapine levels [3].

Further exploring the genetic basis of antipsychotic response, a quasi-naturalistic study involving 86 schizophrenia patients aged 18-65 years examined the role of GRM7 in early response to risperidone. It found that individuals with the rs2133450 CC genotype had a poorer response, although the biological mechanism remains undefined [8].

Another study focused on the CYP3A5 A6986G polymorphism and its impact on quetiapine pharmacokinetics, enrolling 34 healthy volunteers aged 19-46 years in a randomized, single-dose, two-period crossover study. Results demonstrated a positive association between the genetic variant and quetiapine's pharmacokinetic profile [9].

Lastly, a randomized, double-blind, parallel-group, open-label study investigated the association between PLEKHA6 polymorphisms and psychopathology and treatment response in 263 schizophrenia patients aged 17-65 years. The study found a significant link between PLEKHA6 variants and clinical outcomes, suggesting its potential role as a pharmacogenetic marker in antipsychotic treatment [10].

Study of transporter gene affecting pharmacodynamic parameter of drugs

A multicentric, prospective, longitudinal naturalistic study involving 356 patients aged 13-33 years was conducted to identify key transcription factors (TFs) relevant to the pharmacogenetics of antipsychotics. This study assessed 33 TFs expressed in the striatum and 125 SNPs disrupting transcription factor binding sites (TFBS) across 50 genes. Two SNPs, rs938112 and rs2987092, were significantly associated with antipsychotic-induced extrapyramidal symptoms (EPS) [11].

In another prospective cohort study focusing on paediatric pharmacogenetics, 89 Saudi children receiving risperidone were evaluated using 720 pharmacogenetic markers. The study identified 27 genetic variants in 20 genes that had a prominent impact on risperidone pharmacokinetic parameters, underscoring the value of targeted pharmacogenetic testing in children [12].

A randomized trial involving 99 individuals with a history of alcohol self-administration examined how dopaminergic genetic variations influence the effects of aripiprazole.

Genes such as DAT1, COMT, DRD2, and DRD4 were studied. The DAT1 10R allele was associated with lower dopamine transporter (DAT) availability in both controls and individuals with ADHD, whereas among individuals with alcohol use disorder (AUD), the 9R allele correlated with lower striatal DAT availability [6].

The cardiovascular safety of antipsychotics was investigated in a randomized, double-blind, parallel-group, open-label study involving 199 schizophrenia patients aged 18-65 years, focusing on QTc interval prolongation during short-term treatment. The study evaluated the effects of various antipsychotics alongside nine genetic polymorphisms (KCNQ1, KCNH2, SCN5A, LOC10537879, LOC101927066, NOS1AP, NUBPL). Results showed that women experienced significantly greater QTc prolongation than men. Among the antipsychotics studied, quetiapine and amisulpride had the most pronounced QTc effects, followed by aripiprazole, risperidone, olanzapine, and haloperidol [13].

A prospective cohort study of 101 patients aged 18-65 years examined the impact of the ANKS1B rs7968606 polymorphism on clinical improvement in schizophrenia patients treated with amisulpride (1000 mg/day). The study found that this variant was significantly associated with improvement in the PANSS general psychopathology score, suggesting a pharmacogenetic marker for treatment responsiveness [14].

Furthermore, findings from the CATIE trial revealed that GLP1 receptor (GLP1R) haplotypes, involving 13 SNPs in promoter and transcribed regions, may be linked to altered treatment response across multiple antipsychotics, potentially influencing outcomes in neuropsychiatric disorders [15].

Lastly, a large-scale study on atypical antipsychotic-induced weight gain was conducted on 1,627 patients, focusing on genetic variation in serotonin, dopamine, histamine, adrenergic, and muscarinic receptors. The study found that patients under 45 years of age were at higher risk for significant weight gain, with increases in BMI observed as early as the first and second months of treatment [16].

Clinical implication of Pharmacogenetic in Antipsychotic therapy

Emerging evidence illustrate the cost effectiveness pharmacogenetic implementation psychiatry. Pharmacogenetic guided antidepressant therapy has leads to significant cost saving on treatment. Till now CYP2D6 genotyping is cost effective in patient treated with neuroleptic and antidepressant. The combination of clinical, pharmacogenetic and environmental information for the personalization of treatment in resistant patient achieved a cost benefit ratio of 3.31-3.59 with a reduction in direct and total cost of patient [17].

Future prospect and feasibility of pharmacogenetic testing in the treatment

Genotyping is a key polymorphisms in CYP enzymes can be easily performed in most clinical laboratories and provides valuable information at the start of the treatment, thereby improving patient response to therapy. Pharmacogenetic testing typically takes 2-3 weeks to deliver results, including a polygenic risk score, which can predict treatment response with a high degree of accuracy. Genetic prediction of antipsychotic response is approaching 100% accuracy, and early pharmacogenetic interventions for dose adjustment could be highly beneficial by enabling the selection of the appropriate dose or alternative treatment from the outset. In the coming future, rapid pharmacogenetic testing is expected to deliver clinical recommendations within 24-48 hours, offering significant utility in guiding personalized treatment strategies.

Data Availability: Literature search.

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