REVIEW ARTICLE

Precision Medicine in Psychotherapy: The Past, Present and Future

Bhavatharini Sukumaran, Sharumathi SM, Rinu M Xavier, Arun KP, Deepalakshmi M[*]

Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamil Nadu, India

ABSTRACT

Precision medicine has sparked a fierce debate about the pros and cons of a more individualized healthcare strategy. Advances in precision medicine have challenged traditional paradigms of healthcare decision-making. Pharmacogenomics is part of precision medicine. Although genetic testing in drug therapy is still a relatively recent development, it is growing rapidly. Pharmacogenetic tests reveal genetic biomarkers that indicate a person's drug susceptibility. They are increasingly being used to improve medication adherence; however, their utility in older people with polypharmacy remains to be well-studied. Mental illness is a major public health problem at both the individual and societal levels. Despite advances in psychopharmacology and better knowledge of therapeutic principles, there is still a long way to go to incorporate pharmacogenetic and pharmacogenomic research into psychiatry's clinical practice. Numerous genetic variants have been associated with anti-psychiatric responses and adverse effects of treatment. The aim of this review is to summarise responses to psychotropic drugs in the context of pharmacogenetic polymorphisms.
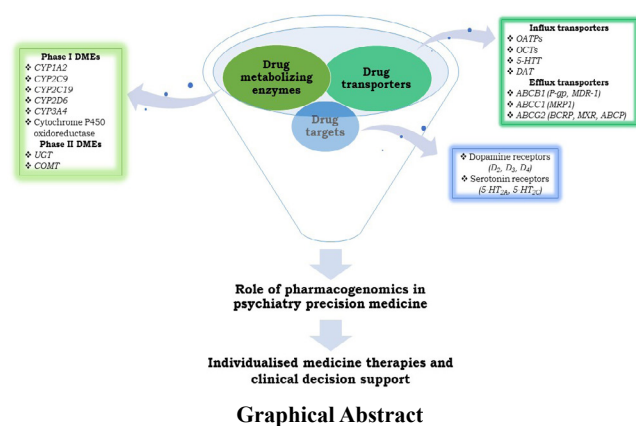
Keywords: Precision medicine, Psychotherapy, Gene predictors, Pharmacogenomics, Polymorphism, Drug metabolizing enzymes, Drug transporters, Drug targets.

Graphical Abstract

INTRODUCTION

Precision medicine (PM) is a term that refers to individualized treatment that involves the use of novel diagnostics and therapeutics tailored to a patient's specific needs based on genetic, biomarker, phenotypic, or psychosocial characteristics.[1] The core principle of PM is that healthcare treatment is personalized for each individual based on his or her genes, lifestyle, and environment. However, developments in genetics and the increasing availability of health data offer the opportunity to make accurate, personalized patient care a clinical reality.[2]

"Pharmacogenetic studies hold the promise of transforming our lives with the promise of individualized therapies; however, initial enthusiasm should be tempered in light of certain considerations."

Pharmacogenomics is studying how a person's genetic makeup affects the body's response to drugs using human genomics and bioinformatics data. It is useful not only for the rational use of drugs but also for the development of tailored drugs.[3] Individual responses to psychotropic medications, which include antidepressants, antipsychotics, and mood stabilizers, varies widely. It has been suggested that genetic polymorphisms are responsible for the considerable interindividual variability in response to psychotropic drugs. It is well known that treatment response varies within a heterogeneous population, with good and poor responders. Genetic predisposition, cohort heterogeneity, ethnicity, slow or fast metabolizers, epigenetic factors, and early or late illness influence patient and treatment response. These parameters impact whether a given individual responds well or poorly to a given treatment. The purpose of PM is to allow clinicians to predict the best course of action for a patient quickly, effectively, and accurately.[4,5] Thus, pharmacogenetics can be

*Author for Correspondence: deepapharmacy@jssuni.edu.in

used to reliably predict response to psychotropic treatment and guide the selection of appropriate psychiatric treatment in a way that maximizes drug efficacy and minimizes drug toxicity.[6,7] The interplay of various gene products that influence pharmacokinetics and pharmacodynamics, such as drug-metabolizing enzymes (DMEs), drug transporters, and drug targets, determines the majority of these drug responses.[8] This review provides an overview of the genetic predictors and drug responses to DMEs, transporter, and receptor gene polymorphisms associated with psychiatric treatments.

Role of Precision Medicine in Psychiatry

PM is a concept that has recently gained importance in all areas of medicine. In psychiatry, it is particularly important given the high societal cost of psychiatric illness and, more importantly, the long time that elapses before benefits from therapies are seen and the diversity of responses.[9] Despite psychiatry being deeply rooted in a personalized approach, the transition to precision medicine, which requires additional data sources such as neuroimaging and/or biological measurements, still lags behind other areas of medicine. However, attempts to integrate precision medicine concepts into psychiatry are recent. The dexamethasone suppression test, for example, has moderate sensitivity (50–65%) but high specificity (96%) in predicting future depressive episodes as well as response to antidepressant medication. However, because altered hypothalamic–pituitary–adrenal (HPA) axis function is present in virtually all major psychiatric disorders, these results have limited clinical utility with respect to precision medicine.[10]

The problem is that developing new treatments is incredibly expensive and takes a lot of time. Tailoring the use of existing drugs to individual patients is a parallel and perhaps more immediate way to improve therapeutic efficacy and reduce common side effects. On the other hand, the field of PM has struggled to develop reliable methods for predicting response to psychotropic medications. Pharmacogenetic analyses of potential genes thought to be important in drug pharmacokinetics and pharmacodynamics have been the first step. The fact that there is generally no comprehensive mechanistic information on drug action hampered these studies. Today, thanks to the study of genetic diversity on a genome-wide scale, developments in genomics have made it possible to obviate the need for such knowledge. This has led to a number of positive results. For example, the human leukocyte antigen locus has been linked to clozapine-induced agranulocytosis, the melanocortin-4 receptor (MC4R) gene has been linked to antipsychotic-induced weight gain, and the contactin-associated protein-like 5 (CNTNAP5) 4,5 gene has been linked to reduced symptoms associated with antipsychotic use in genome-wide association and/or whole-exome sequencing studies.[11]

Based on genetic information, dosing recommendations for psychotropic drugs such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), atomoxetine, and carbamazepine are gradually being introduced. Specifically, the genotypes of CYP2D6 (atomoxetine) and/or CYP2C19 (SSRIs and TCAs), two genes encoding enzymes that contribute to the metabolism of various antidepressants, can be used to adjust dosing or select an alternative treatment based on recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC) or the Dutch Pharmacogenetics Working Group (DPWG). These activities are an important step toward overcoming one of the major obstacles to precision psychiatry: the difficulty of converting pharmacogenetic findings into practical treatment recommendations.[12]

Genetic predictors in psychiatry

Genetic profiles in pharmacogenetic studies predict individual differences in therapeutic response or risk of side effects. Treatment selection in psychiatric practice is still primarily a trial-and-error process.[13] A major goal of personalized medicine is to develop validated predictors of efficacy or toxicity. Several genetic variations related to drug response have been uncovered in different medical areas and have proven clinically valuable. To date, however, progress in psychiatric pharmacogenetics has been slow. There are a number of genetic correlates for antidepressants, antipsychotics, and mood stabilizers, most of which focus on candidate genes, but none have been established or shown clinical benefit. There were two fairly large GWAS meta-analyses of antidepressant responsiveness (N > 2200, with substantial sample overlap), neither of which found genome-wide significant associations. In another study, using GWAS data from the first meta-analysis, it was calculated that 42% of the total variance in antidepressant response was due to common genetic variations. Thus, like psychiatric disorders themselves, antidepressant response appears to be a strongly polygenic trait. Recent research has looked at genetic predictors of response to psychotherapy, a concept known as therapy genetics. However, few studies of candidate genes have been published to date, and no predictors have been identified.[14]

Pharmacogenomics of Drug-Metabolizing Enzymes

Individual heterogeneity of enzyme activity is caused by genetic polymorphisms arising from single base pair variations in the DNA sequence, which are common in DMEs.[15] DME activity has historically been divided into phase I (oxidation, reduction, and hydrolysis) and phase II (conjugation reactions between an endogenous molecule such as glucuronic acid and a xenobiotic or its metabolite). Phase I DMEs include cytochrome P450 enzymes (CYP), flavin-containing monooxygenases, monoamine oxidase, reductases, esterases, and alcohol dehydrogenases. Glutathione S-transferases, N-acetyltransferases, UDP-glucuronosyltransferases, epoxide hydrolases, and sulfotransferases are among the phase II DMEs.[16]

Polymorphisms in Genes Encoding Phase I DMEs

The CYP enzymes that convert drugs, toxins, and certain endogenous molecules such as steroids, lipids, and vitamins are responsible for the majority of phase I reactions. They play a key role in drug metabolism and are responsible for 70 to 80% of phase I metabolism.[17] Over 2,000 mutations have been

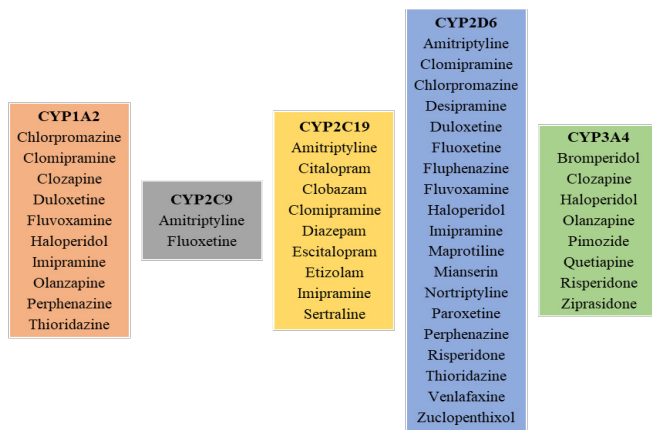| **CYP1A2**		**CYP2C19**	**CYP2D6**	**CYP3A4**
Chlorpromazine		Amitriptyline	Amitriptyline	Bromperidol
Clomipramine		Citalopram	Clomipramine	Clozapine
Clozapine	**CYP2C9**	Clobazam	Chlorpromazine	Haloperidol
Duloxetine	Amitriptyline	Clomipramine	Desipramine	Olanzapine
Fluvoxamine	Fluoxetine	Diazepam	Duloxetine	Pimozide
Haloperidol		Escitalopram	Fluoxetine	Quetiapine
Imipramine		Etizolam	Fluphenazine	Risperidone
Olanzapine		Imipramine	Fluvoxamine	Ziprasidone
Perphenazine		Sertraline	Haloperidol	
Thioridazine			Imipramine	
			Maprotiline	
			Mianserin	
			Nortriptyline	
			Paroxetine	
			Perphenazine	
			Risperidone	
			Thioridazine	
			Venlafaxine	
			Zuclopenthixol	

Figure 1: CYP enzymes and psychotropic medications[16,19,20]

identified, with specific single nucleotide polymorphisms (SNPs) significantly impacting activity CYP. CYPs, therefore, play a key role in individual drug response, and their genetic variability should be considered in personalized medicine.[18] Since the identification of all major enzymes that metabolize drugs (CYP) and their major gene variants, pharmacogenetics has had a significant impact on psychotherapeutic drug therapy. CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 are the major CYP enzymes in psychiatry, as shown in Figure 1.[16] Polymorphisms in genes encoding phase I DMEs are listed in Table 1.

CYP1A2

CYP1A2 in the human liver is a major DME, accounting for 13–15% of the total CYP enzyme.[21] Many clinically used drugs (e.g., clozapine, olanzapine, theophylline, and tacrine) and several endogenous substances (e.g., melatonin, estrone, and estradiol) are metabolized by this enzyme.[22] CYP1A2 activity is known to be induced or inhibited by a number of drugs. Fluvoxamine, a potent CYP1A2 inhibitor, increases plasma concentrations of typical antipsychotics (e.g., haloperidol).[23] Smoking, a known inducer of CYP1A2, significantly decreases plasma levels of most typical antipsychotics.[24] When clozapine doses were studied between smokers and nonsmokers, they were almost twice as high in smokers.[25] Smoking cessation, on the other hand, was associated with an increase in chlorpromazine plasma concentrations and adverse effects.[26]

CYP2C9 and CYP2C19

The CYP2C enzyme subfamily (which includes CYP2C8, CYP2C9, CYP2C18, and CYP2C19) accounts for approximately 18% of CYP protein content in the human liver and metabolizes approximately 20% of currently prescribed drugs.[27] CYP2C9 and CYP2C19 are most involved in the metabolism of xenobiotics.[28] They are polymorphically expressed, with 12 allelic variants for CYP2C9 and 16 for CYP2C19. Many of these variants, of which the most common are *2 and *3, are associated with decreased substrate metabolism[29,30] CYP2C9 plays a role in the metabolism of a number of psychotropic drugs (tetrahydrocannabinol, fluoxetine, amitriptyline, phenytoin, etc.). Endogenous substrates such as epinephrine and serotonin have been shown to affect CYP2C9 activity.[31]

Plasma concentrations of fluoxetine and norfluoxetine after administering the same dose of the drug show wide interindividual variability, which may be partly due to differences in CYP2D6 and CYP2C9 activity.

CYP2C19 plays a role in the oxidative metabolism of a number of antidepressants, including TCAs, SSRIs, and benzodiazepines.[32] CYP2C19 extensively metabolizes the tertiary TCAs amitriptyline, imipramine, and clomipramine to secondary amines, with CYP2C9, CYP3A4, and CYP1A2 contributing.[33] In-vivo CYP2C19 polymorphisms appear to affect N-demethylation of amitriptyline. Subjects with two mutant CYP2C19 alleles (*2, *3) had higher amitriptyline serum concentrations and a greater amitriptyline/nortriptyline ratio at steady state than those with wild-type genotype.[34] Citalopram and escitalopram are metabolized primarily by CYP2C19 and CYP3A4 and to a lesser extent by CYP2D6. Compared with homozygous and heterozygous EMs, PMs have lower oral clearance of citalopram.[35] Several isoforms of CYP are involved in the demethylation of sertraline to a nearly inactive metabolite, of which CYP2C19 is the most important.[36]

CYP2D6

CYP2D6 accounts for only 5% of the total content of CYP in the liver. CYP2D6 is involved in the metabolism of several antidepressants, including TCAs, SSRIs, and other newer drugs. Some cases of adverse effects associated with increased serum TCA concentrations in CYP2D6 PMs or treatment failure due to decreased concentrations in CYP2D6 UMs have been reported.[33] Polymorphic CYP2D6[37] metabolizes SSRIs such as fluoxetine, paroxetine, fluvoxamine and citalopram/escitalopram. Within the SNRI class, CYP2D6 polymorphisms appear to have a significant impact on venlafaxine metabolism; in particular, CYP2D6 appears to play a key role in the synthesis of the active metabolite O-desmethylvenlafaxine.[38] For some TCAs in PMs, the average dose reduction was 50 to 80%, and for some SSRIs, 30%. For UMs, dose increases of 260% were reported for desipramine and 230% for nortriptyline.[39]

CYP2D6 is involved in the metabolism of a number of antipsychotics. CYP2D6 PMs had higher haloperidol serum concentrations, lower clearance, and longer half-life than Ems.[40] Several studies showed that CYP2D6 PM patients on risperidone had a higher rate of adverse effects such as QTc interval prolongation, parkinsonism, and treatment discontinuation.[41,42] In patients with the CYP2D6-PM phenotype, aripiprazole exposure is increased by 80% and dehydroaripiprazole exposure is decreased by 30%, resulting in a 60% increase in total exposure to the drug. Elimination half-lives of aripiprazole and dehydroaripiprazole also increases dramatically with PMs.[43] In summary, there is strong evidence that CYP2D6 genetic polymorphisms are associated with the pharmacokinetic parameters of numerous psychotropic drugs.

CYP3A4

CYP3A4 is the most abundant CYP isoform, accounting for 30% of the total CYP in the human liver and 70% in the small intestine.[44] It is involved in the biotransformation of several antidepressants (TCAs, sertraline, citalopram, escitalopram,

venlafaxine, mirtazapine, reboxetine), antipsychotics (haloperidol, pimozide, clozapine, quetiapine, risperidone, aripiprazole, ziprasidone, lurasidone), mood stabilizers (carbamazepine), and benzodiazepines (eg, alprazolam,

Table 1: Polymorphisms in genes encoding Phase I DMEs

S. No.	Name of the drug	Gene	Variant	Effects observed	Year of research
1.	Haloperidol[50]	CYP2D6	CYP2D6*1 CYP2D6*5 CYP2D6*10	CYP2D6 *5 and *10 are associated with decreased metabolism of haloperidol in people with schizophrenia compared with CYP2D6 *1	2001
2.	Clomipramine[51]	CYP2C19	CYP2C19*1 CYP2C19*2	CYP2C19 *2 is associated with increased dose- and weight-corrected mean clomipramine concentrations and a higher clomipramine/desmethyl clomipramine metabolic ratio during clomipramine treatment in people with mental disorders compared with CYP2C19 *1/*1	2001
3.	Zuclopenthixol[52]	CYP2D6	CYP2D6*1 CYP2D6*3 CYP2D6*4	CYP2D6 *3 and CYP2D6 *4 are associated with decreased metabolism of zuclopenthixol in people with schizophrenia compared with CYP2D6 *1	2002
4.	Amitriptyline[53]	CYP2C19	CYP2C19*1 CYP2C19*2 CYP2C19*3	CYP2C19 *1/*3 + *2/*3 are associated with increased dose- and weight-corrected amitriptyline/nortriptyline ratios when treated with amitriptyline in people with mental disorders compared with CYP2C19 *1/*1	2002
5.	Haloperidol[40]	CYP2D6	CYP2D6*1 CYP2D6*5	CYP2D6 *5 is associated with decreased metabolism of haloperidol in people with schizophrenia, compared with CYP2D6 *1	2003
6.	Haloperidol[54]	CYP2D6	CYP2D6*1 CYP2D6*4	CYP2D6 *4/*4 is associated with decreased metabolism of haloperidol in healthy individuals compared to CYP2D6 *1/*1 + *1/*4	2003
7.	Haloperidol[55]	CYP2D6	CYP2D6*1 CYP2D6*2	CYP2D6 *2/*2 is associated with increased concentrations of haloperidol in people with schizophrenia compared to CYP2D6 *1/*1 + *1/*2	2003
8.	Paroxetine[56]	CYP2D6	CYP2D6*1 CYP2D6*3 CYP2D6*4 CYP2D6*5	CYP2D6 *3/*4 + *4/*4 + *4/*5 is associated with increased plasma concentrations of paroxetine during treatment with paroxetine in patients with major depressive disorder compared with CYP2D6 normal metabolizers	2003
9.	Venlafaxine[57]	CYP2D6	CYP2D6*1 CYP2D6*4 CYP2D6*5 CYP2D6*6	CYP2D6 *5/*4 + *6/*6 + *6/*4 are associated with an increased risk of adverse events during treatment with venlafaxine in patients with major depressive disorder compared with CYP2D6 *1/*1	2006
10.	Risperidone[58]	CYP2D6	CYP2D6*1 CYP2D6*3 CYP2D6*4 CYP2D6*5	CYP2D6 ultrarapid metabolizer phenotype is associated with increased risperidone clearance in patients with psychotic disorders compared with CYP2D6 *1/*3 + *1/*4 + *1/*5 (assigned as intermediate metabolizer phenotype)	2013
11.	Clozapine[59]	CYP1A2	CYP1A2*1A CYP1A2*1F	CYP1A2 *1F/*1F is associated with increased risk of seizures when people with schizophrenia are treated with clozapine compared with CYP1A2 *1A/*1A + *1A/*1F	2013
12.	Quetiapine[60]	CYP2D6	CYP3A4*1 CYP3A4*22	CYP3A4 *1/*22 + *22/*22 is associated with increased quetiapine concentrations in people with psychotic disorders, compared with CYP3A4 *1/*1	2014
13.	Citalopram[61]	CYP2C19	CYP2C19 poor metabolizers	CYP2C19 poor metabolizers are associated with an increased risk of prolonged electrocardiogram rate when treated with citalopram compared with CYP2C19 normal metabolizers	2014
14.	Aripiprazole[62]	CYP2D6	CYP2D6 poor metabolizer genotype	CYP2D6 Poor metabolizer genotype is associated with increased dose-adjusted trough concentrations of aripiprazole in people with psychotic disorders compared with normal CYP2D6 metabolizer genotype	2015
15.	Risperidone[63]	CYP3A4	rs35599367	Genotype AG is associated with decreased risperidone clearance in people with psychosis compared to genotype GG	2015
16.	Escitalopram[64]	CYP2C19	CYP2C19*1 CYP2C19*2 CYP2C19*3 CYP2C19*4	CYP2C19 *2 + *3 + *4 are associated with increased exposure to escitalopram compared to CYP2C19 *1/*1	2018
17.	Sertraline[65]	CYP2C19	CYP2C19*1 CYP2C19*2 CYP2C19*3	CYP2C19 *2/*2 + *2/*3 (assigned as poor metabolizer phenotype) are associated with decreased metabolism of sertraline compared to CYP2C19 *1/*1 (assigned as normal metabolizer phenotype)	2020

midazolam, and triazolam), and it is also responsible for the metabolism of the newer antipsychotics quetiapine and lurasidone. Functional variability is associated with decreased activity of CYP3A4*6, CYP3A4*17, CYP3A4*20, and CYP3A4*22 variants, whereas CYP3A4*18A is associated with increased activity.[45]

Cytochrome P450 oxidoreductase

POR is an electron donor for several oxygenates, including heme oxygenase, cytochrome b5, 7-dehydrocholesterol reductase, squalene monooxygenase, and CYP enzymes, and plays an important role in steroid and drug metabolism.[46] According to research, the gene POR is highly polymorphic, and it may play a role in the interindividual variability of drug metabolism and drug responses by influencing the activity of the enzymes CYP.[47] CYP3A4 and CYP3A5 are the enzymes that metabolise midazolam, a benzodiazepine. Elens *et al.* found that POR *28 mutations decreased midazolam metabolism in CYP3A5*1 carriers with solid tumors and that the decrease in CYP3A5 activity was related to POR *28, demonstrating that POR genetic variants can alter the therapeutic efficacy of midazolam.[48] For clobazam, a longer-acting benzodiazepine metabolized by CYP3A4 and CYP2C19 in the liver, there are POR polymorphisms associated with clobazam efficacy, according to the research.[49]

Polymorphisms in Genes Encoding Phase II DMEs

The most important group of phase II enzymes are the glucuronidation enzymes. UDP-glucuronosyltransferases (UGTs) are a family of liver enzymes that metabolize certain psychotropic drugs.[66] One of the enzymes that degrade catecholamines such as dopamine, epinephrine, and norepinephrine is catechol-O-methyltransferase (COMT).[67] Since all antipsychotics have an effect on the dopamine system, this may help to moderate their effects.[68]

UGT

The isozyme UGT1A4 was discovered to be the most important isozyme for glucuronidation of some TCAs and antipsychotics, both typical and atypical.[69,70] According to the results of Erickson-Ridout *et al.* the UGT1A1A(TA)7TAA and UGT1A4 Leu48Val polymorphisms significantly affect clozapine and/or N-desmethyl clozapine (dmCLZ) glucuronidation *in-vitro*, whereas the UGT1A448Val and UGT2B1067Tyr variants significantly alter olanzapine glucuronidation *in-vitro*, which may be useful in determining interindividual differences in clozapine, dmCLZ, and olanzapine metabolism *in-vivo*. UGT1A4 is a substrate for imipramine, amitriptyline, chlorimipramine, and doxepin.[71]

COMT

The COMT gene has several allelic variants, the best studied of which is rs4680, which causes a change in enzyme structure [Val (108/158) Met] that affects activity (high activity in the Val/Val genotype, moderate activity in the Val/Met genotype, and low activity in the Met/Met genotype).[72] This polymorphism has been associated with antidepressant

treatment, with rs4680 particularly affecting responsiveness to fluoxetine and paroxetine.[73]

Pharmacogenomics of Drug Transporters

Because of their importance in the mechanisms controlling the pharmacokinetic properties of drugs and in the development of cellular drug resistance through decreased uptake or increased efflux, drug transporter proteins are gaining importance in a variety of therapeutic areas. Membrane transporters, which belong to the ATP-binding cassette transporter family, and solute carriers are the two most commonly studied membrane transporters.[74] The genes encoding these transporters are polymorphic, resulting in transporters with varying levels of expression and potency. As a result, mutations in transporters are often associated with variations in drug pharmacokinetics and treatment response.[75] Some transporters, called influx transporters, accelerate and assist drug entry into target cells, while others, called efflux transporters, slow and prevent it. Both the influx and efflux transporters play a role in determining a drug's effect by regulating the drug's availability in the blood.[76] Polymorphisms in genes encoding drug transporters are listed in Table 2.

Polymorphism in genes encoding influx transporters

Several types of influx or uptake transporters transport substrates against a concentration gradient to mediate drug uptake and reabsorption in cells. The OATPs, OCTs, concentrative nucleoside transporters (CNTs), PEPTs, and mono-carboxylate transporters (MCTs) are the major influx transporters in the solute carrier family (SLC).[77]

A large number of pharmacogenetic studies have focused on genes that control or affect serotonin neurotransmission. The pharmacogenetics of the HTTLPR (l/s) polymorphism has been investigated as a possible marker of SSRI symptom response. In a study by Smeraldi *et al.*, carriers of the l allele showed a stronger response to fluvoxamine than homozygotes of the short variant (s/s)[78] in patients with major depression, and Pollock *et al.* found a similar effect on response to paroxetine treatment in major depression.[79] Many studies have examined the effects of the neuronal dopamine transporter (DAT) 9/10 repeat on treatment response in schizophrenia and depression and found an association with clozapine responsiveness.[80]

Polymorphism in genes encoding efflux transporters

The ATP-binding cassette transporter family (ABC) is involved in the transmission of several drugs. ABCB1 (P-glycoprotein, MDR-1), ABCC1 (MRP1), and ABCG2 (BCRP, MXR, ABCP) are among the 49 known ABC genes that use ATP to transport substrates across membranes.[81] These transporters are responsible for preventing the absorption of drugs through the intestinal wall, transporting substrates from tissues into the bloodstream, and ultimately mediating drug clearance.[82]

P-glycoprotein (P-gp) is a membrane transport protein (ABCB1). It is also known as multidrug resistance protein 1 (MDR1) and is responsible for the efflux of a variety of drugs. Due to its position at the blood-brain barrier, P-gp can modulate the concentration of antidepressants and atypical antipsychotics

Table 2: Polymorphisms in genes encoding drug transporters

S. No	Name of the drug	Gene	Variant	Effects observed	Year of research
1.	Nortriptyline[76]	ABCB1	rs1045642	The genotype AA is associated with an increased likelihood of orthostatic hypotension with nortriptyline treatment in patients with major depressive disorder compared with the genotypes AG + GG	2002
2.	Amitriptyline Citalopram Paroxetine Venlafaxine[86]	ABCB1	rs7787082	Allele A is associated with an increased likelihood of remission when people with depression are treated with amitriptyline, citalopram, paroxetine, or venlafaxine compared with allele G	2008
3.	Risperidone[87]	ABCB1	rs1128503	Genotypes AA + AG are associated with better response to risperidone than genotype GG in children with autistic disorder	2010
4.	Clozapine[88]	ABCB1	rs7787082	Allele G is associated with a lower response to clozapine in people with schizophrenia compared to allele A	2012
5.	Olanzapine[89]	BDNF	rs6265	Genotype CC is associated with an increased response to olanzapine in people with schizophrenia compared to genotypes CT + TT	2014
6.	Fluoxetine[90]	ABCB1	rs2032582	Allele A is associated with an enhanced response to fluoxetine in children with depressive disorder compared to allele C	2014
7.	Haloperidol[91]	ABCB5	rs17143212	The genotype CT is associated with increased drug toxicity when treated with haloperidol in people with psychotic disorders compared to genotype CC	2015
8.	Clozapine[92]	ABCB1	rs1045642	Genotype AA is associated with an increased risk of agranulocytosis and neutropenia with clozapine treatment compared with genotypes AG + GG	2017
9.	Lithium[93]	ADCY1	rs1521470	Allele A is associated with decreased response to lithium in people with bipolar disorder compared with allele G	2018
10.	Olanzapine[94]	ABCB1	rs4728709	Genotype GG is associated with an increased likelihood of asthenia on olanzapine in healthy individuals compared to genotypes AA + AG	2021

in the brain.[67] As shown by a correlation between the 3435T allele, olanzapine plasma levels, and a reduction in positive symptoms of schizophrenia, P-gp polymorphisms may influence olanzapine penetration into the central nervous system.[83] One study found that patients with SNP C3435T had a significantly higher incidence of postural hypotension after nortriptyline therapy. This was hypothesized to be due to a relative increase in the accumulation of nortriptyline or its metabolites in the brain as a result of impaired P-gp function.[84] The ABCB1 genotype has been shown to be significantly related to response to paroxetine treatment.[85]

Pharmacogenomics of Drug Targets

Polymorphisms in several genes that are direct targets of psychotropic drugs, particularly polymorphisms in the dopamine and serotonin receptor genes (5- HT), have been the subject of numerous studies. As shown in Figure 2, studies have found associations between these polymorphisms and response to antipsychotics or antidepressants, as well as extrapyramidal symptoms triggered by antipsychotics (e.g., tardive dyskinesia, acute akathisia).[95] Polymorphisms in genes encoding drug targets are listed in Table 3.

Dopamine receptors

Dopamine receptors are divided into a D1-like family (D1 and D5, which are coupled to a Gs protein and activate adenylate cyclase) and a D2-like family (D2, D3, and D4, which are coupled to a Gi protein and inhibit adenylate cyclase). Only the D2-like family has been associated with response to

psychotherapy.[67] The D2 receptor has a substantial number of polymorphisms, including a mutation that alters structure (Ser311Cys) and a polymorphism that alters function (–141 Ins/Del).[96] Studies have shown that schizophrenic patients with the 141C Ins/Del polymorphism respond poorly to clozapine in the first episode, take longer to respond to olanzapine and risperidone, and respond less often to chlorpromazine.[68] Antipsychotic-induced tardive dyskinesias, for which homozygosity for the glycine variant of the D3-Ser9Gly polymorphism has been associated with a higher risk of developing tardive dyskinesias.[97]

Serotonin receptors

The mode of action of atypical antipsychotics is significantly related to the 5-HT2A receptor. According to Olajossy-Hilkesberger *et al.*, the polymorphisms in the 5-HT2A receptor gene (His452Tyr and T102C) can alter the individual response to olanzapine, especially to positive symptoms.[98] According
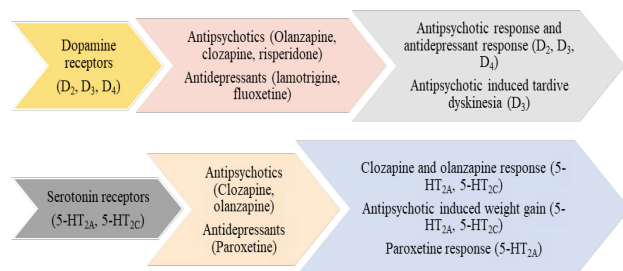

Figure 2: Drug target polymorphisms and psychotropic medications

Table 3: Polymorphisms in genes encoding drug targets

S. No	Name of the drug	Gene	Variant	Effects observed	Year of research
1.	Risperidone[102]	DRD2	rs1800497	Allele A is associated with increased prolactin levels when treated with antipsychotics in people with schizophrenia, compared to allele G	2004
2.	Fluoxetine[103]	HTR1A	rs6295	Genotype CC is associated with increased response to fluoxetine in people with major depressive disorder compared to allele G	2006
3.	Citalopram[104]	CRHR2	rs2270007	The genotypes CC + CG are associated with a decreased response to citalopram in people with major depressive disorder compared to genotype GG	2007
4.	Fluoxetine[105]	CRHR1	rs242941	Genotype CC is associated with increased response to treatment with fluoxetine in people with major depressive disorder and severe anxiety compared to allele A	2007
5.	Olanzapine[106]	ADRB3	rs4994	Genotype GG is associated with an increased risk of weight gain with olanzapine treatment in people with schizophrenia, compared with genotypes AA + AG	2008
6.	Olanzapine[107]	DRD2	rs2734842	Allele G is associated with increased prolactin levels during treatment with olanzapine in women, compared with allele C	2011
7.	Olanzapine[108]	HTR2C	rs1414334	Allele G is associated with increased weight gain during treatment with olanzapine in women with mental disorders, compared with allele C	2012
8.	Bupropion[109]	DRD1	rs11746641	Allele G is associated with increased likelihood of smoking abstinence in slow nicotine metabolizers when exposed to bupropion or nicotine in individuals with tobacco use disorder, compared with allele T	2012
9.	Risperidone[110]	ADRB2	rs1042713	Allele G is associated with an increased likelihood of sexual adverse events when treated with risperidone in people with schizophrenia compared with allele A	2013
10.	Duloxetine[111]	DRD3	rs167770	Genotype AG is associated with a lower response to duloxetine in people with anxiety disorders compared to genotypes AA + GG	2013
11.	Aripiprazole[112]	DRD2	rs2514218	The CC genotype is associated with increased severity of psychomotor agitation on aripiprazole in people with psychotic disorders, schizoaffective disorder, or schizophrenia compared with the CT + TT genotypes	2015
12.	Citalopram & Sertraline[113]	HTR2A	rs6311	Allele T is associated with increased likelihood of sexual dysfunction, psychologically, by citalopram or sertraline in people with major depressive disorder, compared to allele C	2020

to Gunes *et al.*, the 5-HT2C and 5-HT2A receptor-encoding genes and HTR2C and HTR2A polymorphisms are associated with metabolic abnormalities in patients receiving olanzapine or clozapine.[99] Another meta-analysis found that HTR2C polymorphisms, particularly Cys23Ser, are associated with response to antipsychotics in male schizophrenia patients, especially clozapine with HTR2C antagonism or partial agonism.[100] The 5-HT2A receptor, which is overexpressed in depressed patients, has been shown to be downregulated by paroxetine in several studies.[101]

Precision Medicine: Future Perspective

PM is a rapidly expanding approach to health care that focuses on discovering treatments and interventions that work for people based on their genetic makeup rather than their symptoms. An emerging trend in PM is the use of artificial intelligence and machine learning to improve traditional symptom-based medicine and enable early intervention with advanced diagnostics and better, more cost-effective therapies. However, we need to improve healthcare genetic testing procedures and integrate genetic composition and metabolic function

research into traditional healthcare. We also need to establish prophylactic and therapeutic interventions and a library of information on the application of genetics in health care.[114]

CONCLUSION

In summary, pharmacogenetic studies have identified a number of genetic variables that influence response to psychotropic drug treatment, including antipsychotic efficacy, antidepressant response, and the occurrence of drug-induced adverse events. In particular, variants in CYP enzymes, dopamine, and serotonin genes have been associated with various improvements in response and treatment-related adverse events in numerous events. These results are still preliminary and need to be replicated and validated. It is expected that the field of pharmacogenomics will be able to provide individualized medical therapies based on genetic profiling, which could be important for future therapeutic methods.

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