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Applications of Precision Medicine in the Treatment of Psychiatric Disorders: A Literature Review

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ABSTRACT

Background: *Scientific understanding of precision medicine is rapidly evolving as new associations are made between genetic variants and tolerance to pharmaceuticals [1]. Although pharmacogenetic testing and guidelines exist for many medications, there is limited clinical application of these technologies in part due to limitations of the evidence supporting its use in psychiatric treatment as well as lack of awareness by providers and patients [2]. This narrative literature review aims to assess and summarize the past decade of research in the field of psychiatric pharmacogenetics. Specifically, it will focus on the relationship between antidepressant/antipsychotic drug responses and polymorphisms in nine commonly studied genes: CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, SLC6A4, HTR2A, and DRD2.*

Methods: *Literature from PubMed and Embase that was published between the years 2010 and 2020 was found using strategic keywords and search phrases. Each study represented was a randomized controlled trial or clinical trial tested in adults over the age of eighteen.*

Results: *Of the six CYP450 enzymes that were evaluated, all displayed impacts on the metabolism of psychiatric drugs except CYP3A4, although only one polymorphism (*1B) was included in analysis of that particular gene. Inconclusive results were discovered regarding SLC6A4 5-HTTLPR polymorphisms and further review should be done to determine its relationship with SSRI response. Additionally, review of literature pertaining to DRD2 showed unsubstantial evidence, as four out of seven articles found no connection between treatment or adverse drug reactions (ADR) associated with DRD2. In contrast, influential findings were documented by literature concerning HTR2A polymorphisms and therapeutic consequences and the evidence collected on benefits of pharmacogenomic testing supports the implementation of testing to guide psychiatric treatment with confidence that use may result in fewer failed trials prior to response or remission.*

Conclusion: *Many polymorphic mutations have a significant impact on individual responses to psychiatric treatment and implementation of pharmacogenomic testing in a clinic setting may be beneficial to psychiatric patients. Further review of polymorphic relationships should be done, especially in the case of SLC6A4 and DRD2 variations.*

Keywords
Pharmacogenomics, Polymorphism, Psychotropic drugs, Cytochrome P450.

Introduction
Within the emerging field of personalized medicine, pharmacogenetics is a tool used by clinicians to guide pharmacological treatment based on DNA testing of polymorphisms present in a number of influential gene sequences [3]. It has been found that between 30-50% of patients treated for psychiatric disorders do not respond positively to the first medication prescribed [4]. Multiple factors are responsible for poor response rates beyond biologic mechanisms including compliance with timing, dosage, and length of trial [5]. Reduced response and adverse reactions can also be related to genetic modifications, which is estimated to be responsible for 42% of disparity in treatment response [6]. The need for multiple medication trials can be overwhelmingly time consuming given that a patient must remain on pharmacotherapy for a four-to-six-week observation period before concluding non-response or gene-drug interactions [7]. The prevalence of failed treatment outcomes can cause patients to discontinue treatment and psychiatric visits and may even worsen symptoms through feelings of hopelessness regarding the possibility of remission. In addition to this, psychiatric patients may take multiple medications for comorbid conditions leading to an increased risk of drug-drug interactions in addition to gene-drug interactions [8].

This literature review focuses on nine genes which have been at the forefront of pharmacogenomic research in recent years. This includes those from the cytochrome P450 family (CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5), those affiliated with serotonergic pathway (SLC6A4, HTR2A) and those affiliated with the dopaminergic pathway (DRD2).

The Cytochrome P450 (CYP-) family of enzymes is largely responsible for detoxification in the first phase of drug metabolism [3,4]. There are more than 50 enzymes in the P450 class, but just six of them are responsible for 90% of metabolic activity [9]. The resulting range of phenotypes of P450 polymorphisms are poor metabolism (PM), normal metabolism (NM), intermediate metabolism (IM), extensive metabolism (EM), and ultra-rapid metabolism (UM) [10]. Polymorphisms are the result of a wild type (functional) allele being replaced by a mutant (non-functional) allele [9]. Poor metabolizers have two non-functional alleles and ultrarapid metabolizers have multiple functional alleles resulting in overactivity [4]. All normal, intermediate, and extensive metabolic compositions have variations of functionality in genotype within this range [4]. Depending on individual phenotype, patients may be poor metabolizers of certain psychotropic drugs resulting in little to no response to treatment.

Another family of genes that impacts psychiatric treatment outcomes are the serotonin transport and receptor genes including serotonin transporter (SLC6A4) and serotonin 2A receptor (HTR2A) which commonly alter pharmacodynamic interactions [10]. Polymorphisms present in these genes are especially influential in treatment using selective serotonin reuptake inhibitors (SSRIs) [11]. SSRIs inhibit the binding of the monoamine neurotransmitter serotonin to the serotonin transporter, which is encoded by SLC6A4, in order to increase the levels of serotonin in the brain [11]. One of the most common polymorphisms associated with SLC6A4 is 5-HTTLPR. This mutation is either an insertion or a deletion of a span of 44 base pairs in the promoter region of the SLC6A4 gene [11]. The genotypes that exist for this polymorphism are the long and short alleles which are associated with treatment outcomes in mood disorders [12]. The long allele has additional variations, LA and LG, which encode for increased or decreased expression, respectively [13].

The third class of gene explored in this review is one of the dopaminergic system, namely the dopamine receptor D2 (DRD2). Dopamine receptor D2 blockage is the primary target of many antipsychotic drugs and is thus an important component in the pharmacotherapy of schizophrenia and other forms of psychosis [14,15]. Given the impact that dopamine receptors have on the treatment of psychotic phenotypes, variants in the associated genes may contribute to medication responses [15].

The primary objective of this paper is to review the past decade of research in psychiatric pharmacogenomics in order to determine the role that gene specific polymorphisms play in the pharmacokinetic and pharmacodynamic response to antidepressants and antipsychotics typically prescribed in the treatment of psychiatric disorders. The following article is presented in accordance with the narrative review reporting checklist.

Methods
Data was collected through a review of the existing literature related to polymorphisms within the nine selected genes. All studies occurred in the setting of psychiatric treatment with antidepressants or antipsychotic medications and were published between January 2010 and December 2021. The search was conducted in PubMed (National Library of Medicine) and Embase (Elsevier) databases for appropriate resources. The reference section of each identified source was also reviewed for additional material. Studies were only accepted on the basis that they were randomized controlled trials or clinical trials. Inclusion was also dependent on the study having a sample size greater than twenty participants and was limited to those involving adults aged eighteen and older. Various review articles were used as reference material and cited appropriately but were not included as study data. Included medications were those known to have properties influenced by the selected genes. Thirty-eight different commonly prescribed antidepressants and antipsychotics from various drug classes were represented in the collected literature (as shown in Table 1). Of these, eight studies examined several medications in a single trial. A total of sixty-six references were reviewed. Forty-six of these were accounts of randomized controlled trials or clinical trials and the remaining nineteen were used as reference material.

Table 1: Medications Represented in Polymorphism and Pharmacogenomic Testing.

Psychotropic Drugs Represented	
Agomelatine	Lorazepam
Alprazolam	Mirtazapine
Amitriptyline	Nortriptyline
Aripiprazole	Olanzapine
Brexpiprazole	Oxazepam
Bupropion	Paliperidone
Buspirone	Paroxetine
Chlordiazepoxide	Perazine
Citalopram	Perphenazine
Clomipramine	Pregabalin
Clonazepam	Quetiapine
Duloxetine	Risperidone
Escitalopram	Sertraline
Fluoxetine	Trazodone
Fluvoxamine	Venlafaxine
Haloperidol	Vilazodone
Hydroxyzine	Vortioxetine
Imipramine	Ziprasidone
Levomilnacipran	Zuclopenthixol

Results

CYP2C19

The gene CYP2C19 is a member of the Cytochrome P450 family and is responsible for the metabolism of several drugs. Some examples of psychiatric drugs metabolized by this enzyme include Citalopram/Escitalopram, Sertraline, Venlafaxine, Imipramine, and other medications within these drug classes [10,16,17]. CYP2C19 has numerous polymorphisms which affect metabolism and drug tolerance [18]. The most common allele resulting in loss of function (poor metabolism) is variant allele CYP2C19*2, although alleles *3-*8 are also known to cause similar outcomes [17,18]. The only known polymorphism that results in overactivity (ultra-rapid metabolism) is CYP2C19*17 [18]. CYP2C19*17 does not encode for a duplication of functional alleles, but rather a mutation in the promoter that increases the rate of transcription in patients that possess this sequence [19].

Nine studies were specifically chosen to explore CYP2C19 and its relationship with various classes of psychiatric medications (as shown in Table 2). Five studies showed a correlation between pharmacokinetic variables and CYP2C19 genotype when the study drug was administered, but only four of these were proven to be statistically significant ($p<0.05$). In addition to this, two studies were found to have results that did not support a correlation and two studies did not include prominent pharmacokinetic assessments. Connern et al. [20] found no connection between the genotypes CYP2C19*2, CYP2C19*3, and CYP2C19*17 on Bupropion metabolism. This is likely because Bupropion is mainly metabolized by CYP2B6 and only minimally by CYP2C19 and CYP2D6 enzymes [20]. Jacquenoud Sirot et al. [21] also found no association in their examination of genotypes CYP2C19*1, CYP2C19*2, and CYP2C19*3 on Mirtazapine pharmacokinetics. Similar to Bupropion, CYP2C19 enzymes do not have a prominent place in Mirtazapine metabolism [21].

Beyond metabolic measurements, pharmacodynamic relationships and distinct treatment outcomes were also observed. Mrazek et al. [22] researched polymorphisms *2, *3, *4, *5, *6, *7, *8, and *17 in 1,074 subjects previously enrolled in The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial by the National Institute of Health (NIH) which studied patients whose first trial of antidepressants did not result in recovery. Mrazek et al. [22] found that patients with the *2 allele had lower levels of tolerance and patients with the *17 allele had lower levels of remission when administered citalopram ($p=0.02$, $p=0.04$ respectively). Another study by Jukic et al. [18] reported that poor metabolizers and ultra-rapid metabolizers had a higher incidence of switching to another antidepressant from escitalopram when compared to extensive metabolizers. Conflicting information was found in the study by Tsai et al. [23] who reported no difference in the treatment response of poor metabolizers and extensive metabolizers as measured by the Hamilton Depression Rating Scale and the Hamilton Anxiety Rating Scale (HAM-D, HAM-A). Ryu et al. [24] investigated pharmacodynamics on amitriptyline response in genotypes *1, *2, and *3 with no statistically significant results on blood pressure, dry mouth, sedation, or pulse.

CYP2D6

CYP2D6 is also a member of the Cytochrome P450 and is known for being highly polymorphic and has more than 100 variants currently identified [27]. The most studied polymorphisms with two non-functional alleles are CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, and CYP2D6*7 which are phenotypically poor metabolizers [28]. The genotypes CYP2D6*9, CYP2D6*10, CYP2D6*17, and CYP2D6 *41 result in decreased metabolic function and are known phenotypically to be intermediate metabolizers with regards to CYP2D6 activity [28]. Ultra-rapid metabolism typically occurs when there is a duplication of the CYP2D6 gene and is shown as CYP2D6*1xN [29]. Polymorphic frequency depends greatly on ethnicity resulting in many studies focusing on a single population of people. For example, CYP2D6*4, a genetic variant that results from an incorrect splicing site, has been found in 21% of Caucasians but only 1% of Asians possess this particular allele [23]. In contrast, CYP2D6*10 variant can be found in 50-70% of Asian populations [23].

Twelve studies were included to review the influence of CYP2D6 polymorphisms (shown in Table 3). Six studies resulted in a statistically significant relationship between genotype and pharmacokinetic outcome and three studies did not find a correlation between these variables. The remaining three articles reviewed did not include prominent pharmacokinetic testing in their procedures. Being one of the reports that did not show significant pharmacokinetic results, Nikisch et al. [31] concluded that the antipsychotic Quetiapine is only minimally metabolized by CYP2D6 compared to CYP3A4 which takes a major role. Similarly, Olanzapine as studied by Cabaleiro et al. [30] did not display a remarkable link with CYP2D6 as it is principally metabolized by CYP1A2. Despite these findings, positive results were seen in kinetic testing with the psychiatric drugs Aripiprazole, Haloperidol, Risperidone, Zuclopenthixol, Amitriptyline, and Mirtazapine [24,27,29,31-34].

Table 2: CYP2C19 Summary of Findings.

Reference	Sample	Drug	Polymorphism	Result	P-value
Saiz-Rodríguez et al. [12]	46	Sertraline	*2, *3, *17	(+) effect on ADR and pharmacokinetics (AUC)	0.344
Connern et al. [20]	30	Bupropion	*2, *3, *17	(-) effect on pharmacokinetics	---
Jin et al. [25]	320	Escitalopram	*2, *3, *17	(+) effect on pharmacokinetics (drug clearance)	<0.005
Cabaleiro et al. [26]	79	Quetiapine	*1, *2, *4	(+) effect on pharmacokinetics (Cmax).	0.012
Mrazek et al. [22]	1,074	Citalopram	*2, *3, *4, *5, *6, *7, *8, *17	*2 allele = lower levels of tolerance *17 allele = lower levels of remission	0.02 0.04
Tsai et al. [23]	100	Escitalopram	*1, *2, *3, *17	(-) effect on treatment response (HAM-D/HAM-A) scores	---
Ryu et al. [24]	24	Amitriptyline	*1, *2, *3	(-) effect on pharmacodynamics (+) effect on pharmacokinetics (AUC) (+) effect on pharmacokinetics (MR)	>0.05 0.015 0.0003
Jukic et al. [18]	2,087	Escitalopram	*1, *2, *3, *4, *17	(+) effect on medication changes. (+) effect on pharmacokinetics (Conc.)	<0.001
Jacquenoud Sirot et al. [21]	45	Mirtazapine	*1, *2, *3	(-) effect on pharmacokinetics	>0.05

(+) refers to a reported correlation between variables; (-) refers to a no correlation between variables; ADR, Adverse drug reaction; Cmax, peak serum concentration of drug; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; AUC, Area under curve; MR, Metabolic ratio; Conc., Concentration.

Table 3: CYP2D6 Summary of Findings.

Reference	Sample	Drug	Polymorphism	Result	P-value
Saiz-Rodríguez et al. [12]	46	Sertraline	*3, *4, *5, *6, *7, *9	(-) no effect on pharmacokinetics (+) effect on ADR	--- 0.054
Cabaleiro et al. [30]	63	Olanzapine	PM/IM/EM/UM (Phenotype)	(-) effect on pharmacokinetics	---
Gassó et al. [29]	25	Risperidone	*1xN, *3, *4, *5, *6	(+) effect on pharmacokinetics (AUC/Cmax) (+) effect on negative symptoms	0.006 0.040 0.021
Nikisch et al. [31]	22	Quetiapine	*1, *3, *4, *6	(-) effect on clinical response (-) effect on pharmacokinetics	---
Yoo et al. [32]	80	Risperidone	*2, *5, *10	(+) effect on pharmacokinetics (Cl) (+) effect on pharmacokinetics (K_a)	<0.01 <0.005
Koller et al. [33]	31	Aripiprazole	*3, *4, *5, *6, *7, *9	(+) effect on pharmacokinetics (AUC) (+) effect on pharmacokinetics (Cmax)	0.025 0.010
Mrazek et al. [22]	1074	Citalopram	*2A, *4, *10, *12, *6, *17, *8/*14, *4, *3, *9, *2/*17, *7, *41	(-) effect on pharmacodynamics (-) effect on remission rates	>0.05
Tsai et al. [23]	100	Escitalopram	*1, *4, *5, *10	(+) effect on treatment response (HAM-D/HAM-A) scores	0.001
Novalbos et al. [34]	71	Risperidone	*3, *4, *5, *6, *7, *9	(+) effect on pharmacodynamics (+) effect on pharmacokinetics ($T_{1/2}$ and AUC)	>0.05
van der Schans et al. [28]	181	Nortriptyline Venlafaxine	*3, *4, *5, *6, *10,*17, *41	(+) effect on prevalence of ADR	<0.001
Ryu et al. [24]	24	Amitriptyline	*1, *5, *10	(-) effect on pharmacodynamics (+) effect on pharmacokinetics (MR)	>0.05 0.002
Lisbeth et al. [27]	82	Aripiprazole Haloperidol Risperidone Paliperidone Zuclopenthixol	*1, *2, *35 *9, *10, *17, *29, *41 *3, *4, *5, *6, *7, *8, *11, *15	(+) effect on pharmacokinetics (conc.) in all except Paliperidone	<0.05
Potkin et al. [35]	145	Iloperidone Ziprasidone Quetiapine	*4, *10	(+) effect on pharmacodynamics in *10	0.0281

(+) refers to a reported correlation between variables; (-) refers to a no correlation between variables; $T_{1/2,}$ half-life; K_a, Absorption rate constant; PM, poor metabolism; EM, extensive metabolism; IM, intermediate metabolism; UM, ultra-rapid metabolism.

Table 4: CYP1A2 Summary of Findings.

Reference	Sample	Drug	Polymorphism	Result	P-value
Song et al. [39]	72	Agomelatine	*1F, *1C, rs2472304, rs2470890	(+) effect on pharmacokinetics (MR)	0.026
Zhu et al. [40]	175	Venlafaxine	rs2470890	(+) effect on remission rates	0.0049
Jaquenoud Sirot et al. [21]	45	Mirtazapine	*1F	(+) effect on pharmacokinetics (AUC and Cmax)	<0.05
Cabaleiro et al. [26]	79	Quetiapine	*1F, *1C	(+) effect on pharmacokinetics (AUC)	0.026
Cabaleiro et al. [30]	63	Olanzapine	*1F	(-) effect on pharmacokinetics	>0.05

(+) refers to a reported correlation between variables; (-) refers to a no correlation between variables

Pharmacodynamic relationships and changes in treatment outcomes were also observed in six papers out of eight that included such assessments although one result was not statistically significant (p=0.054). According to Tsai et al. [23] patients whose genotype corresponded to intermediate metabolism had faster remission rates compared to other metabolic strengths as measured by HAM-D and HAM-A scores after 8 weeks of escitalopram treatment. Mrazek et al. [22] and Cabaleiro et al. [30] found no statistically significant changes in treatment outcomes among the studied genotypes after dosing with citalopram or mirtazapine, respectively. Effects on adverse drug reactions or negative symptomology was found in four reports. Gasso et al. [29] discovered a significant correlation between CYP2D6 poor metabolism and the presence of motor impairment in patients taking Risperidone according to actigraphy results that measured motor activity and wakefulness (0.021). Van der Schans et al. [28] reported that patients with variant phenotypes (PM, IM, UM) had a higher incidence of adverse events than patients with the normal phenotype for Nortriptyline and Venlafaxine intake (p<0.001). Analysis of QTc intervals by Potkin et al. [35] found that patients with the *10 polymorphism had increased chances of having a prolonged QTc intervals. Finally, Saiz-Rodriguez et al. [12] noted that phenotypes with reduced expression (PM, IM) had a higher rate of adverse reactions, but this result was not quite statistically significant (p=0.054).

CYP3A5 and CYP3A4

CYP3A5 and CYP3A4 both belong to the CYP3A subfamily of enzymes and therefore are structurally very similar [17]. The CYP3A family has four genes, but only CYP3A4 and CY3A5 are expressed at high concentrations in the liver with CYP3A4 being the most abundant [10,17]. One of the most studied CYP3A4 polymorphisms is *1B which is a promoter mutation that results in increased expression [36]. This variation has not been found in Asian populations whereas 45-66% of African Americans and 4.5-9.6% of Caucasians possess it [36]. Of the polymorphisms that exist for CYP3A5, the most important is the variant CYP3A5*3 which disables the enzymatic activity of the CYP3A5 gene due to mRNA splicing deficits which results in incorrect reading frame and termination codon [37,38].

A total of six studies were included for literature examination, split evenly among CYP3A4 and CYP3A5. All three studies on CYP3A4*1B showed no association between the genotype and pharmacokinetic measures. Of these same papers, one statistically significant relationship was discovered in CYP3A4*1B that indicated a higher incidence of dry mouth side effect in this genotype (p=0.0231) [30]. In the three reports on CYP3A5*3, two pharmacokinetic links were observed [30,31]. Nikisch et al. [31] highlighted an effect on the AUC for Risperidone in patients who had both CYP3A5*3 and CYP2D6*10 mutations (p<0.05). Cabaleiro et al. [30] also listed a statistically significant relationship between Olanzapine AUC and CYP3A5*3 genotypes (p = 0.013).

CYP1A2

CYP1A2 is of the same class of enzymes as all studied thus far. It has several polymorphisms associated with it, but many have not been studied extensively including the polymorphisms rs2472304 and rs2470890 [39]. The allelic variant *1F (rs762551) is known to result in higher enzyme adaptability and the allelic variant *1C (rs2069514) is known to result in decreased enzyme activity [39]. An interesting property of CYP1A2 is that is has proven to be induced by the chemical present in cigarette smoke leading to excess clearance of first-generation antipsychotics like haloperidol and chlorpromazine [8,21]. This can lead to adverse events in patients who change their smoking habits while on such a drug because the metabolism is altered.

A total of five studies were included regarding CYP1A2 polymorphisms (as shown in Table 4). Of these, three showed positive correlations and one showed no correlation between genotype and pharmacokinetic measures. Zhu et al. [40] reported significance in a linkage with polymorphism rs2470890 and greater remission in subjects with C alleles over T alleles when Venlafaxine was administered. Cabaleiro et al. [30] discovered no effect on metabolism by CYP1A2 which is the opposite of expected since the study drug, Olanzapine, is primarily metabolized by this enzyme. In this case procedural choices may have impacted results as each participant only received a single dose of Olanzapine and pharmacokinetic changes were observed in other studies with drugs of the same class [30].

CYP2B6

CYP2B6 is also a member of the CYP P450 class and is located on chromosome 19 [41]. CYP2B6 is unique because it is expressed in both the liver and the brain [17]. It assists in the metabolism of many drugs, most notably in psychiatry being bupropion and methadone [17]. CYP2B6 is excessively polymorphic and has over 100 known variants [41]. Some commonly studied allelic variants include CYP2B6*4, CYP2B6*6, and CYP2B6*9 [42]. The *4 variant has shown to increase the enzymatic activity of CYP2B6 compared to the wild type *1 allele [42]. The *9 is the

most abundant mutation observed in humans, but its function is not well defined [17]. Finally, the *6 variant is the most studied and results in reduced functionality [42].

Five studies of CYP2B6 properties were identified and reviewed. Results of three out of four articles that evaluated pharmacokinetics reported a correlation between measurements and genotype. Connern et al. [20] did not find a statistically significant relationship between Bupropion metabolism and CYP2B6 which conflicts with the results of other literature. Connern et al. [20] contributed this to a small sample size but Ma et al. [42] used similar procedures and sample size and obtained statistically significant results that matched previous findings. Interestingly, in another study by Jacquenoud Sirot et al. [21] the *6 allele variant was connected to improved treatment outcomes as measured by a greater reduction in HAM-D scores (p=0.016). Only one of the included studies, by Saiz-Rodriguez et al. [12], commented on pharmacodynamic relationships. This paper identified higher rates of ADR in reduced function phenotypes, but these results were not statistically significant (p=0.388) [12].

SLC6A4

The SLC6A4 gene encodes the SLC6A4 protein, which allows transport of serotonin from the synaptic cleft to the serotonergic neurons [11]. SSRIs operate by inhibiting the binding of serotonin to SLC6A4 to reduce the concentration of serotonin available [11]. This polymorphism 5-HTTLPR, which is the result of an insertion or a deletion of a span of 44 base pairs in the promoter region of the gene, is a widely studied variant [43]. Other genotypes that will be examined include rs140701, rs3813034, and 5-HTT I2 VNTR [13,44-46]. Rs3813034 exists in the 3' untranslated region of the SLC6A4 gene [47]. Similarly, Rs140701 is associated with the serotonin transporter SLC6A4, but exists outside the promoter region in intron 9 [45].

Seven articles were included in the analysis of the SLC6A4 gene/enzyme (as shown in Table 5). Su et al [48] discontinued study on this enzyme because only 28% of the population displayed the genotype in question. Of the three reports that included treatment response statistics, two of them showed a correlation between treatment outcomes and genotype [44,45]. Zou et al. [45] concluded that patients with the short allele variant of 5-HTTLPR had a decreased response to sertraline in the treatment of panic disorder. Interestingly, they also found a significant connection between the rs140701 mutation and an increased risk of having panic disorder [45]. In contrasting study by Serpina et al. [44] it was reported that patients with the short allele variant of 5-HTTLPR had improved response to SSRIs (sertraline, citalopram, paroxetine, or escitalopram).

Adverse drug reactions were examined by both Strohmaier et al. [11] and Garfield et al. [13] who assessed sexual dysfunction as a response to escitalopram. Garfield et al. [13] found statistically significant adverse reactions including diminished sexual desire and excess dry mouth. Oppositely, Strohmaier et al. [11] found no correlation between medication use and sexual side effects. This may be contributed to the fact that Garfield et al. [13] performed a double-blind procedure and Strohmaier et al. [11] did not. Finally, Lopez-Rodriguez et al. [49] discovered a relationship among ADR dizziness and the presence of at least one long allele compared to short alleles in 5-HTTLPR. Dizziness was also more common in patients taking Olanzapine or Risperidone versus Quetiapine [49].

HTR2A

Serotonin 2A receptor (HTR2A) is one of the primary receptors for serotonin in the human brain and commonly alters pharmacodynamic interactions [10]. The gene HTR2A is made up of three exons and two introns with the most frequently studied polymorphisms being rs6313 (exon 1) and rs6314 (exon 3) [50]. A nonfunctional serotonin receptor can result in reduced levels of serotonin in the brain and symptoms of depression, schizophrenia, and some neurological disorders [50]. Many polymorphisms are associated with this gene and may affect drug efficacy and patient tolerance levels.

Table 5: SLC6A4 Summary of Findings.

Reference	Sample	Drug	Polymorphism	Result	P-value
Seripa et al. [44]	234	Escitalopram Sertraline Paroxetine Citalopram	5-HTTLPR	(+) effect on treatment response	0.021
Su et al. [48]	166	Escitalopram	5-HTTLPR	(-) study discontinued due to inadequate sample with polymorphism	---
Strohmaier et al. [11]	473	Escitalopram Nortriptyline	5-HTTLPR	(-) no effect on ADR (sexual dysfunction)	0.939
Zou et al. [45]	233	Sertraline	5-HTTLPR rs140701 rs3813034	(+) effect on risk of panic disorder (+) effect on treatment outcomes	<0.05 <0.001
Perlis et al. [46]	250	Duloxetine	5-HTTLPR (Promoter) 5-HTT I2 VNTR (Intron 2)	(-) effect on treatment response	>0.05
López-Rodríguez et al. [49]	211	Risperidone Olanzapine Quetiapine	5-HTTLPR	(+) effect on ADR (dizziness)	<0.05
Garfield et al. [13]	177	Escitalopram	5-HTTLPR	(+) effect on ADR (dry mouth and sexual dysfunction)	<0.05

(+) refers to a reported correlation between variables; (-) refers to a no correlation between variables

A total of nine articles were included to evaluate polymorphic impacts on treatment outcomes using multiple psychiatric medications (as shown in Table 6). No pharmacokinetic measurements were included or observed in the included articles. Out of five documents that assessed treatment outcomes, four of them found that genotype had a significant impact. An interesting correlation was found between the rs12860002 mutation and worsened response to Quetiapine as measured by the Positive and Negative Syndrome Scale (PANSS) scores of participants in the study by McClay et al. [54]. As shown in Table 6, relationships between rs7997012, rs2770296, and 9526240 were observed to impact treatment outcomes.

Two studies evaluated the ADR hyperprolactinemia as reported different results. Koller et al. [33] found no association between rs6313/rs6314 and increased prolactin levels in patients administered Aripiprazole. Oppositely, Cabaleiro et al. [30] found significant association between histamine polymorphisms and increased prolactin in patient's taking Olanzapine. Given that Aripiprazole and Olanzapine are of the same drug class, hyperprolactinemia may be associated with genetic mutations rather than medication.

DRD2

DRD2 is of another class of genes which encodes for the dopamine receptor D2, a major target for regulation of the dopaminergic system and a significant player in treatment using both typical and atypical antipsychotics [15]. One commonly studied polymorphism is TaqIA restriction fragment length polymorphism (rs1800497) which is a switch in Gly and Lys at position 713 that can result in allele variants *A1 and *A2 and may affect DRD2 expression and binding specificity [56,57]. TaqIA is approximately 10,500 bp downstream from the termination of DRD2 and is actually located in the ANKK1 gene, but has proven to influence DRD2 behaviors [57]. Another frequently analyzed polymorphism is rs6277, a mutation that effects mRNA stability and has been associated with increased risk of schizophrenia [57]. These and several other polymorphisms can impact the functionality of the dopamine receptors and therefore affect treatment outcomes in many patients.

Seven studies were included in the analysis of DRD2 although Tybura et al. [55], Koller et al. [33], Zivkovic et al. [14], and Saung et al. [58] did not find statistically significant results between polymorphisms and treatment response or ADR. One finding reported by Giegling et al. [57] stated that patients with the rs1124493 (SNP intron variant) had improved clinical outcomes as measured by a reduction in the PANSS score (p=0.001). Lopez-Rodriguez et al. [49] discovered ADR headaches occurred in 75% of patients with *A1 alleles compared to 49% in *A2 alleles when treated with risperidone. Similarly, ADR gastrointestinal symptoms were present in 40% of patients with *A1 allele compared to 5-6% in *A2 allele [49].

Does Pharmacogenetic Testing Influence Clinical Responses?

Despite the highlighted advancements in the knowledge of molecular and genetic medicine, does pharmacogenetic testing actually improve clinical outcomes in practice? Seven studies were selected to evaluate the effectiveness of testing compared to treatment as usual in psychiatric patients (as shown in Table 7). These studies used genetic tests such as Neuropharmagen® or the GeneSight Psychotropic Test. Each patient was tested for genotype and reported included guidelines based on genetic information for several medications to aid the clinician in choosing the most appropriate individualized option.

Table 6: HTR2A Summary of Findings.

Reference	Sample	Drug	Polymorphism	Result	P-value
Su et al. [48]	166	Escitalopram	rs1386494 rs6313	(-) effect on treatment outcomes	>0.05
Lucae et al. [51]	637	Variety of Antidepressants	rs7997012 rs1928040	(+) effect on treatment outcome in rs7997012 only	0.004
Cabaleiro et al. [30]	63	Olanzapine	His/His, His/Tyr	(+) effect on ADR (hyperprolactinemia) (+) effect on ADR (dry mouth)	0.036 0.007
López-Rodríguez et al. [49]	211	Risperidone Olanzapine Quetiapine	rs6314 rs6313	(+) effect on ADR (hypotension)	0.004
Tiwari et al. [52]	582	Bupropion	rs2770296 rs9526240 Many more	(+) effect on treatment outcomes in rs2770296 (+) effect on treatment outcomes in rs9526240	0.027 0.041
Lohoff et al. [53]	156	Venlafaxine	rs7997012	(+) effect on treatment outcomes	0.002
McClay et al. [54]	738	Quetiapine	rs12860002 Many more	(+) effect on treatment outcomes (Positive PANSS) (+) effect on treatment outcomes (Negative PANSS)	0.00098 0.014
Tybura et al. [55]	191	Olanzapine Ziprasidone Perazine	rs6311	(-) effect on ADR (body weight)	0.31
Koller et al. [33]	31	Aripiprazole	rs6313 rs6314	(-) effect on ADR (hyperprolactinemia)	>0.05

(+) refers to a reported correlation between variables; (-) refers to a no correlation between variables; PANSS, Positive and Negative Syndrome Scale.

Table 7: Pharmacogenomic Testing Summary of Findings

Reference	Sample	Genes	Result	P-value
Pérez et al. [59]	280	30 genes represented	(+) response difference in patients with previous failed trials	0.0058
Winner et al. [60]	51	5 genes represented (CYP2D6, CYP2C19, CYP1A2, SLC6A4, HTR2A)	(+) difference between PGx guided and TAU (as measured by HAM-D)	0.03
Thase et al. [61]	1541	8 genes represented (CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP2B6, CYP2D6, SLC6A4, HTR2A)	(+) remission difference between PGx guided and TAU (+) difference in gene-drug interactions after medication change	0.008 >0.05
Bradley et al [62]	685	10 genes represented (CYP2D6, SLC6A4, CYP2C19, CYP3A4, 5HT2C, DRD2, CACNA1C, COMT, ANK3, MTHFR)	(+) remission difference between PGx guided and TAU (+) difference in HAM-D/HAM-A scores between groups (-) difference in ADR between groups	0.03 0.01/0.02 >0.05
Espadaler et al [63]	182	20 genes represented	(+) difference between PGx guided and TAU	0.011
Brennan et al [64]	685	10 genes represented (CYP2D6, CYP2C19, CYP3A4, CYP3A5, CYP2C9, CYP1A2, HTR2A, SLC6A4, MTHFR, COMT)	(+) difference between PGx guided and TAU	<0.01
Jürgens et al [65]	528	CYP2D6 CYP2C19	(-) difference between PGx guided and TAU	>0.05

(+) refers to a reported correlation between variables; (-) refers to a no correlation between variables; PGx, pharmacogenetic testing; TAU, treatment as usual.

Of the seven trials examined, six of them reported a positive correlation between the use of PGx testing and improved treatment outcomes (as shown in Table 7). The study by Jürgens et al. [65] did not find a statistically significant relationship, although only two genes were included in genotype testing. The remainder of the studies which concluded the benefit of PGx testing genotyped between 5-30 genes as part of their pre-trial procedure. One notable finding by Perez et al. [59] stated that in patients who had failed 1-3 previous medication trials, 51% of subjects had a positive response to medications selected by PGx testing compared to 31% in the control group ($p = 0.0058$). Espadaler et al. [63] concluded that patients who were treated using PGx recommendations showed 4x the rate of improvement of patients receiving treatment as usual based on their Clinical Global Impression- Severity (CGI-S) scores ($p=0.011$).

Conclusions and Future Directions

Precision Medicine, or Pharmacogenetics, has advanced substantially in recent years. In individual analysis of the influence of nine genes on pharmacokinetic and pharmacodynamic outcomes, significant conclusions were drawn for CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A5, and HTR2A indicating an influence of polymorphic genotypes on metabolism and clinical responses. The polymorphisms associated with CYP3A4, SLC6A4, and DRD2 gave inconclusive evidence to support a correlation. The lack of evidence for CYP3A4 can be contributed to the fact that *1B was the only polymorphism represented and given that allelic variation *1B is known to be primarily observed in African American populations, a mixed ethnicity sample likely led to inconclusive data. All other CYP 450 enzymes included in analysis displayed an overall impact on metabolism in studied drugs. This is expected due to the large responsibility of CYP450 enzymes in the first phase of drug metabolism [3,4]. In addition to this, six out of seven (85.7%) studies on the effectiveness of pharmacogenomic testing in clinical practice indicated a beneficial relationship when compared to treatment as usual.

Conflicting conclusions were found in four cases. Jukic et al. [18] and Tsai et al. [23] had opposite findings on the effect of CYP2C19 phenotypes in treatment responses to escitalopram. Garfield et al. [13] and Strohmaier et al. [11] listed opposite reactions on sexual dysfunction as an adverse side effect of escitalopram intake. An additional conflict was found in the papers by Connern et al. [20] and Ma et al. [42] who studied bupropion metabolism by enzyme CYP2B6. This result was surprising given that Bupropion is largely metabolized by CYP2B6 as noted in multiple other sources [41,66]. Finally, incompatible results were noted by Serpina et al. [44] and Zou et al. [45] in the connection between the short allele variant of 5-HTTLPR and SSRI treatment response. Further review of literature in these areas would be beneficial.

Limitations of this review include a relatively small sample of research included as an average of eight studies per gene were consulted and many examined distinct polymorphisms or medications. Future research could include a more systematic review style that refers to a greater number of research reports to draw conclusions. Further analysis should also be done regarding adverse events, particularly in the association with antipsychotics and increased body weight as well as prolonged QTc intervals [34,55]. In addition to this, more evidence needs to be collected regarding the benefits of pharmacogenomic treatment in terms of patient/clinician perceptions and cost effectiveness of guided treatment. In conclusion, many polymorphic mutations have a significant impact on individual responses to psychiatric treatment and implementation of pharmacogenomic testing in a clinic setting may be beneficial to psychiatric patient.

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