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Review Article

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Pharmacogenomics and Precision Medicine in Psychiatry: A Comprehensive Review

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ABSTRACT

Three primary phenotypes in psychiatry have been the focus of pharmacogenetic studies: the development of side effects related to psychotropic drug treatment, the clinical effectiveness of antipsychotic drugs, and the efficacy of antidepressant medications. The present study aimed to provide a comprehensive review of pharmacogenomics and precision medicine in psychiatry. Pharmacokinetic or pharmacodynamic effects are the two categories into which pharmacogenetic studies of antidepressants can be divided. Genetic variations that impact antidepressant metabolism can alter pharmacokinetic parameters like plasma drug concentration and half-life. Pharmacodynamics may be changed by polymorphisms that impact the expression or operation of receptors and signal transduction molecules in the brain. Changes in pharmacokinetics and pharmacodynamics can impact antidepressant effectiveness and adverse effects. Using molecular genetic techniques offers a new way to analyze the variability in the response to psychotropic drugs. Traditionally known as "pharmacogenetics," this area of study offers several unique benefits for identifying informative correlates of psychotropic drug response. This shift from a one-size-fits-all approach to a targeted, patient-specific strategy holds the potential to revolutionize psychiatric care, providing more effective and efficient treatments. Additionally, precision medicine in psychiatry contributes to reducing trial-and-error prescribing, ultimately improving patient outcomes and the overall quality of mental health care.

Keywords: *Pharmacogenetics, Pharmacokinetics, Pharmacodynamics, Antidepressants, Antipsychotics*

INTRODUCTION

The paradigm for disease prevention and treatment is changing, moving away from a one-size-fits-all approach and toward more individualized, patient-specific modalities [1]. One of the newer methods in precision medicine is pharmacogenomics, which fine-tunes dosage and medication choices based on a patient's genetic characteristics. The ultimate aim of precision medicine is to precisely match each treatment plan to the biological profile of the patient. Precision medicine has made extensive use of genetics, and one new area of application is pharmacogenomics-informed pharmacotherapy, which modifies drug selection and dosage based on a patient's genetic characteristics. When used professionally, the combined application of various pharmacological layers of information—such as variations in drug targets' gene expression and function and pharmacokinetic profiles—acquired through creative statistical and bioinformatic skills may be able to explain the predictable causes of interpatient variability in drug effects. This will advance precision medicine [2].

A therapeutic strategy known as "personalized medicine" makes use of a person's genetic and epigenetic data. By using genomics techniques, which allow us to identify inter-individual variability at the genomic, transcriptomic, proteomic, and metabolomic levels, we can achieve this level of personalization. This also foresees the risk associated with the disease and patients' response to the pharmacotherapy. In terms of response, therapeutic choices that are based on a person's genetic profile and medical testing may be more precise and effective [3].

In this article, we address the potential of personalized medicine to provide more tailored and effective pharmacotherapies that address genetic diversity and target patient groups with similar biology rather than merely symptoms. For the past thirty years, the development of medications to treat mental illnesses has stagnated. In the developed world, mental illness is currently the main cause of lost healthy life, and its prevalence is rising quickly in developing nations [4].

Although they are generally characterized by a more comprehensive range of reported symptoms, diagnostic categories like schizophrenia, depression, or autism may each consist of discrete biological entities with unique pathophysiologies that call for different therapies. The core of precision medicine, or as it has recently been termed, personalized medicine. Which emphasizes notable or distinctive features of each patient while using data from their genome for diagnosis, prognosis, and treatment planning. The main focus is on genetic markers that are associated with positive or negative treatment outcomes. Optimizing efficacy while reducing unfavorable events is the aim. Genetic variation can have a range of effects on an individual's medication-handling abilities, from toxicity to absorption. Personalized medicine will advance the goal of treating every patient as an individual that psychiatrists have always held dear by providing greater insights, treatment options, and improved outcomes. While it is not the complete solution, genetics is an ideal way to start. For the majority of patients with neuropsychiatric disorders, optimal, curative treatments will require further understanding of the fundamental disease processes at the cellular and molecular levels [5]. To provide truly personalized psychiatry, the fields of pharmacogenetics and pharmacogenomics aim to provide predictive tools for the response to psychopharmacologic agents in the therapy of psychiatric disorders [6]. Gene information is employed in pharmacogenomics to examine how different people react to medications. Clinical decisions based on genetics may be made in cases where a patient's gene variant is linked to a specific drug response, potentially involving dosage adjustments or drug substitution [7]. A disease can have several genetic variations linked to it. Different patients may have different levels of gene expression. Patients exhibiting elevated protein expression levels will exhibit distinct responses in comparison to those exhibiting lower or no expression levels of the same protein [3]. Research on psychiatric pharmacogenomics got less emphasis, even though it has the potential to improve patient outcomes and clinical practice. Both pharmacokinetic (or "what the body does to a drug") and pharmacodynamic (or "what the drug does to the body") effects are included in the pharmacogenomics of treatment response [8].

Although the causes of the lack of advancement in prevention and treatment are multifaceted, they include a lack of knowledge about pathogenesis, pathophysiology, the mechanism of action of current therapies, and the reasons why many people do not respond well to them. Only a small percentage of patients continue on prescribed treatments for the entire therapeutic course of mental medication, often due to adverse drug reactions or lack of effectiveness. Individual differences in treatment response in psychiatric disorders have been linked to several factors, including symptom profiles (frequency, severity, and stage of illness, age at onset, comorbidities), treatment provision (primary or secondary care, treatment adherence monitoring, concurrent prescription of other drugs or psychotherapy), and demographics and lifestyle traits (sex, age, ancestry, body mass index, smoking habits, socioeconomic status). More precisely, genetic variation plays a significant role in both the occurrence of medication side effects and the variability in treatment response. The goal of pharmacogenomics is to understand and predict individual variability in drug response, and this opens the possibility of applying the numerous advancements in human genomics to this end. Presently, each year more than 1,000 fundamental pharmacogenomics research studies are published [9] and as of May 2021, the PharmGKB repository contained 165 guidelines on the use of pharmacogenomic information for particular drug-gene pairs, 33 of which were pertinent to psychiatry [10]. These guidelines' recommendations come from a rigorous process of standardized variant annotation and literature curation [11]. In part consistent with the guidelines of the US National Academy of Medicine [12], the PharmGKB guidelines also assess the strength of the supporting data and provide genotype-based prescribing recommendations where appropriate.

ADRs represent a significant cause of morbidity and mortality, and the risk of developing them is significantly influenced by genetic variation. ADRs can be categorized as "Type A" (pharmacological) or "Type B" (idiosyncratic) in their most basic form. Pharmacological reactions result from an unfavorable reaction to a medication's established mode of action. Idiosyncratic adverse drug reactions, on the other hand, account for 20% of all adverse drug reactions and are less common, but they can be fatal and seriously harm organs. Numerous psychiatric drugs are referred to as "dirty drugs" because they act on several receptor targets and have wide-ranging side effects [13, 14]. This is contrary to the common belief of "magic bullet" drug development, which held that single-target medications would enhance therapy by reducing side effects [15]. Although a genetic basis for individual differences. In response to drugs is well established, but it has not yet resulted in practical

therapeutic advancements in psychiatry [10]. The nested relationship between personalized medicine, genomic medicine, and pharmacogenetics & genomics is shown in **Figure 1**.

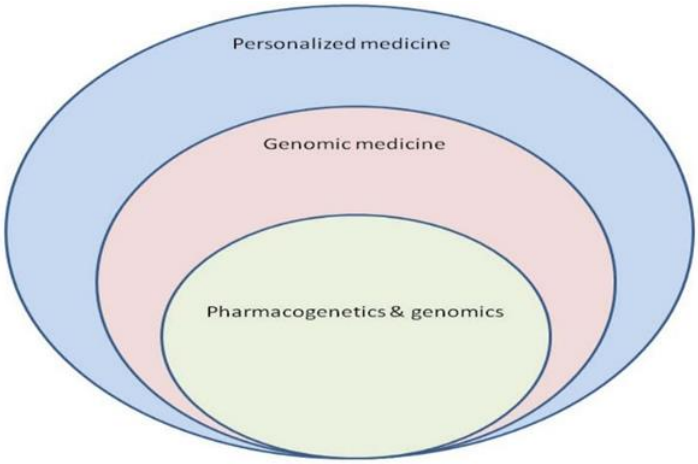

Figure 1. The nested relationship between personalized medicine, genomic medicine, and pharmacogenetics and genomics.

The present study aimed to provide a comprehensive review of pharmacogenomics and precision medicine in psychiatry.

RESULTS AND DISCUSSION

Pharmacogenomic testing in psychiatry

Based on the available PGx evidence, it is recommended that genetic variation in CYP2D6, CYP2C19, CYP2C9, HLA-A, and HLA-B be taken into account when prescribing various medications used in psychiatry. However, the processes for testing, reporting, and interpreting the genomic variations linked to the tested genes—as well as comprehending the difficulties and limitations of testing—are necessary to make the integration of PGx into clinical practice easier. PGx testing should not be seen as a replacement for standard treatment protocols, but rather as a tool to help with thoughtfully implementing good clinical care [16]. Medications represented in polymorphism and pharmacogenomic testing are given in **Table 1**.

Table 1. Medications represented in polymorphism and pharmacogenomic testing

Aripiprazole	**Haloperidol**
Alprazolam	Amitriptyline
Risperidone	Oxazepam
Fluoxetine	Venlafaxine
Pregabalin	Ziprasidone

Factors affecting response to drug

Genetic polymorphism

Drug response variation arises from both alterations in the function of related genes and mutations in a single gene. Gene variations related to the pharmacokinetics and pharmacodynamics of drugs can lead to adverse effects, changes in response, or no response at all. Genome-wide association studies (GWAS) and next-generation sequencing (NGS) have enabled the individualization of therapy based on a patient's genetic composition and have also made it feasible to comprehend the genetic mechanisms underlying disease. The entire human genome has been sequenced by the Human Genome Project, including 99.9% of the genome that is shared by all people in terms of genetic composition.

Epigenetic and other factors

The therapeutic response of a drug is also determined by epigenetic factors, which include age, sex, liver and kidney function, lifestyle, past medical history, and adverse reactions. It has been noted that there is a substantial hormonal difference between males and females, which could explain why males and females react

differently to drugs. It is imperative to consider the pharmacokinetics and pharmacodynamics of drug-drug and herb-drug interactions when prescribing medication for therapeutic purposes.

Pharmacogenomics biomarker

Depending on the level of the biomarker and whether its variants are present or not, pharmacogenomics biomarkers are used to prescribe drugs or their dosages. It stands for the medications that are only recommended to patients who have a specific biomarker variant. When prescribing safe and efficient therapy based on the biomarker, this can be very helpful [9]. It has been observed that the first prescribed medication does not have a positive effect on 30–50% of patients with psychiatric disorders. Nine genes that have recently been the focus of intense pharmacogenomic research. These include connected to the serotonergic pathway (SLC6A4, HTR2A), the dopaminergic pathway (DRD2), and the cytochrome P450 family (CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5).

One of the main roles of the Cytochrome P450 (CYP-) family of enzymes in the initial stage of drug metabolism is detoxification. Patients may be poor metabolizers of specific psychotropic drugs, leading to little to no response to treatment, depending on their unique phenotype. To raise serotonin levels in the brain, selective serotonin inhibitors (SSRIs) block the monoamine neurotransmitter serotonin's binding to the serotonin transporter, which is encoded by SLC6A4. 5-HTTLPR is one of the most prevalent polymorphisms linked to SLC6A4. In the SLC6A4 gene's promoter region, this mutation is either an insertion or a deletion spanning 44 base pairs. The dopaminergic system's dopamine receptor D2 (DRD2) is the third class of genes examined in this review. Since many antipsychotic medications primarily target dopamine receptor D2 blockage, this is a key feature of pharmacotherapy used to treat schizophrenia and other forms of psychosis.

CYP2C19- A member of the Cytochrome P450 family, the gene CYP2C19 is in charge of several drugs' metabolism. This enzyme metabolizes several psychiatric medications, such as sertraline, imipramine, venlafaxine, and citalopram/escitalopram. Variant allele CYP2C19*2 is the most frequently found allele to cause loss of function (poor metabolism), though alleles *3–*8 have also been linked to comparable effects. CYP2C19*17 is the only polymorphism known to cause hyperactivity or ultra-rapid metabolism. Nine studies were specifically picked to investigate the relationship between CYP2C19 and different classes of psychiatric medications. Mrazek *et al*. Conducted research on polymorphisms of *2,*3,*4,*5, 6,*7,*8, and *17 and concluded that patients with the *2 alleles had decreased levels of tolerance and the patients having *17 alleles had lower levels of remission when given citalopram.

CYP2D6- The most researched polymorphisms that have two non-functional alleles are phenotypically poor metabolizers CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, and CYP2D6*7. Reduced metabolic function is the outcome of the CYP2D6*9, CYP2D6*10, CYP2D6*17, and CYP2D6 *41 genotypes, which are also known to be intermediate metabolizers in terms of CYP2D6 activity. Twelve studies were conducted to understand the impact of CYP2D6 polymorphism and concluded that CYP2D6 plays a minor role in the metabolism of quetiapine, whereas CYP3A4 plays a major one. Correspondingly, olanzepine did not signify a link with CYP2D6 since it is majorly metabolized by CYP1A2.

However, optimistic results were identified in kinetic testing with antipsychotics like Aripiprazole, Haloperidol, Risperidone, Zuclopenthixol, Amitriptyline, and Mirtazapine. Compared to patients with other metabolic strengths, those with a genotype associated with intermediate metabolism experienced faster rates of remission after 8 weeks of treatment with escitalopram. Actigraphy results measuring motor activity and wakefulness revealed a significant correlation between CYP2D6 poor metabolism and the presence of motor impairment in patients taking Risperidone.

CYP2B6- Since it is expressed in both the liver and the brain, CYP2B6 is particular. It aids in the metabolism of several medicines, methadone, and bupropion being the most known in psychiatry. Allelic variants like CYP2B6*4, CYP2B6*6, and CYP2B6*9 are some that are frequently researched. Five studies have been conducted to report the properties of CYP2B6 and stated that greater reductions in HAM-D scores were indicative of better treatment outcomes associated with the *6 allele variant.

SLC6A4- The protein SLC6A4 is encoded by the gene SLC6A4, which is responsible for the conduct of serotonin from the synaptic cleft to the serotonergic neurons. To lower the amount of serotonin that is available, SSRIs work by preventing serotonin from binding to SLC6A4. This variant, known as 5-HTTLPR, has been extensively researched. It arises from an insertion or deletion of a span of 44 base pairs in the gene's promoter region. The genotypes that are studied include rs140701, rs3813034, and 5HT12VNTR. Based on several articles on SLC6A4 it is concluded that the patients with short allele

variant of 5-HTTLPR had decreased and increased response to sertraline and SSRIs in the treatment of panic disorder respectively [17, 18].

Genes that code for different receptors, drug-metabolizing enzymes, and/or transport proteins may have polymorphisms, which can affect treatment response and adverse effect profile [18].

Commonly prescribed drugs in psychiatry.

Aripiprazole

Aripiprazole was recently approved for the treatment of major depressive disorder and as an adjuvant therapy to antidepressants for the treatment of manic and mixed episodes of bipolar I disorder. Aripiprazole exhibits antagonistic activity at 5HTR2A receptors and partial agonist activity at DRD2 and 5HTR1A receptors. It has been demonstrated that aripiprazole is metabolized in the liver, mostly by the cytochrome P450 enzymes CYP2D6 and CYP3A4. Patients with CYP2D6 poor metabolizer status should start with half the recommended dose and work their way up to a more favorable clinical response.

Clozapine

It is a tricyclic dibenzodiazepine used for the treatment of resistant schizophrenia and lowers suicidal behavior in same. Since it eliminates delusions, hallucinations, and other psychotic symptoms by acting as a variable antagonist on D2, 5HT2, M1-5 muscarinic, alpha-adrenergic 1 & 2, and H1 histaminic receptors, it is regarded as "atypical." There is a greater likelihood of developing clozapine-induced agranulocytosis in patients with the C genotype. Additionally, the FDA mandates that clozapine have black box warnings for myocarditis, agranulocytosis, seizures, and other adverse cardiovascular and respiratory effects in older patients with psychosis related to dementia.

Olanzapine

An atypical antipsychotic medication that is prescribed to treat schizophrenia, acute manic or mixed episodes linked to bipolar I disorder treatment, and maintenance bipolar I disorder treatment. Due to the antagonistic relationship between dopamine and serotonin type 2 (5HT2), olanzapine is effective in treating schizophrenia. Olanzapine's principal metabolic pathways include glucuronidation and oxidation mediated by cytochrome P450 (CYP) via CYPs 1A2 and 2D6. Strong CYP1A2 inducers, like carbamazepine, have been demonstrated to raise olanzapine clearance by about 50%.

Role of pharmacogenetics in precision medicine

Due to the possibility of differential gene expression or function resulting from DNA variations, the genetic contributions to treatment response are crucial.

Genetic variations can develop somatically, be inherited, or arise de novo in a germ cell or during embryogenesis. Getting pharmacogenetics data from the bench to the bedside is still a challenge to the long-term, successful application of precision medicine. Well-established gene-drug combinations, in which a known genetic variant can result in different drug reactions, are the most promising choices for integration into the clinical laboratory setting. The application of evidence-based guidelines on how pharmacogenomics can be used in the optimization of patient care and the success of treatment is important [1]. Pharmacogenomics research has been carried out on medications used to treat depression, diabetes, cancer, immunotherapy, anticonvulsants, anti-infectives, cardiovascular disease, and psychotropic medications, among other therapeutic interventions. Numerous fatalities are brought on by the medication's side effects. Adverse drug reactions have decreased as a result of pharmacogenomics testing. The clinical Pharmacogenomics test is offered by PGxOneTM, which also produces a pertinent clinical and medical report that can direct patients' treatment. For certain medications, PGxOneTM offers dose-related guidelines [3].

Current and future developments

Its basis lies in descriptive psychopathology and phenomenology, which stem from a precise examination and comprehension of the internal aberrant processes that are manifested in every individual. However, attempts to apply precision medicine techniques to psychiatry were made not too long ago. A test that demonstrated a moderate sensitivity (50–65%) and a high specificity (96%) for predicting future episodes of depression as well as the response to antidepressant treatment was the dexamethasone suppression test [19].

The main objectives of pharmacogenomics include enhancing patient safety and care for those who require extra close observation, which may help with medication substitution when necessary.

Increasing the effectiveness and cost of healthcare the right medication can be prescribed for the right patient at the right time to maximize the resources—drugs and human resources—that go into the patient's care [20]. Challenges of pharmacogenomics studies in mood disorders are given in **Table 2**.

Table 2. Challenges of pharmacogenomics studies in mood disorders

Potential challenges	Description
Establishing a hard-end definition of treatment outcome (response and remission)	Due to the extreme heterogeneity of mood disorders, it is impossible to define objective standards for both diagnosis and treatment outcomes. The sensitivity and specificity of the assessment instruments used in mood disorder diagnosis and treatment follow-up are low.
Optimizing sample size	One of the main obstacles to the success of pharmacogenomic studies on mood disorders is underpowered, and to improve the current efforts, a global collaboration is needed.
Bioinformatics tools for integrative analysis	A thorough assessment of the information gathered from the various omics investigation pillars, such as genomics, epigenomes, proteomics, metabolomics, and microbiomes, is necessary to make an evidence-based decision regarding a patient. Such integrative analysis requires sophisticated bioinformatics tools.
Replication of findings and moving to clinical application	Results from GWASs and candidate gene studies are not well translated, and they are rarely replicated [20].

Barriers to precision medicine in psychiatry [19]

The successful application of precision psychiatry is highly anticipated. Several obstacles, though, could prevent or at least postpone this paradigm change. Confidentiality and privacy issues are becoming more important since precision psychiatry is closely linked to the analysis of large datasets (phenotypic, neuroimaging, or biological). Creating a suitable ethical-legal framework is essential in this situation as it would enable safe data sharing. Self-determination suggests that a patient has the freedom to select (or reject) new diagnostic and prognostic methods after being fully informed about them. Being able to use precision psychiatry tools (electronic monitoring tools, neuroimaging, genotyping, and general laboratory tests) requires the patient to play an active role, which is closely tied to the idea of self-determination. Patients with severe depression, social disengagement, and/or disorganized behavior, as in schizophrenia, may be excluded from precision psychiatry, even though this is easily achievable in less severe mental disorders (permanent depressive disorder, anxiety disorders, etc.). Stigma is another factor that profoundly affects precision psychiatry. Precision psychiatry implementation can be impacted by both the public (the prejudice that the general public harbors toward patients who suffer from mental illness) and self-stigma (which arises when the patient internalizes this prejudice). One last point to consider is the potentiality that, at least initially, precision psychiatry tools may not be financially advantageous. Agranulocytosis/neutropenia in patients treated with clozapine [HLA-B (158T) and HLA-DQB1 (126Q)], or pharmacogenetic testing of polymorphisms within the HLA region for the onset of Stevens-Johnson syndrome/toxic epidermal necrolysis in Asian patients treated with carbamazepine (HLAA*31:01) are examples of cost-effectiveness [21].

CONCLUSION

In conclusion, pharmacogenomics holds significant promise in revolutionizing psychiatric treatment by tailoring medications to individual genetic profiles. The integration of genetic information into psychiatric care can enhance medication efficacy, minimize adverse effects, and ultimately improve patient outcomes. As research in this field progresses, a personalized approach to prescribing psychotropic medications based on genetic variations may become a standard practice, ushering in a new era of precision psychiatry. However, ongoing research, ethical considerations, and widespread adoption are essential factors to address before fully realizing the potential benefits of pharmacogenomics in psychiatric practice.

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