

The use of pharmacogenetic testing in patients with schizophrenia or bipolar disorder: A systematic review

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Abstract

Introduction: Pharmacogenetic testing may assist in identifying an individual's risk of developing a mental illness as well as predict an individual's response to treatment. The objective of this study is to report published outcomes of pharmacogenetic testing in patients with schizophrenia or bipolar disorder.

Methods: A systematic review using PubMed and EBSCOhost through April 2017 was performed to identify articles that reported pharmacogenetic testing in adult patients with either bipolar disorder or schizophrenia using the keywords *pharmacy, pharmacogenomics, pharmacogenetics, psychiatry, bipolar disorder, schizophrenia, mood stabilizer, and antipsychotic*.

Results: A total of 18 articles were included in the final literature review. A wide variety of genes amongst adult patients with varying ethnicities were found to be correlated with the development of schizophrenia or bipolar disorder as well as response to antipsychotics and mood stabilizers.

Discussion: While current studies show a correlation between genetic variations and medication response or disease predisposition for patients with schizophrenia and bipolar disorder, research is unclear on the type of therapeutic recommendations that should occur based on the results of the pharmacogenetic testing. Hopefully interpreting pharmacogenetic results will one day assist with optimizing medication recommendations for individuals with schizophrenia and bipolar disorder.

Keywords: pharmacy, pharmacogenomics, pharmacogenetics, psychiatry, bipolar disorder, schizophrenia, mood stabilizer, antipsychotic

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Introduction

Genetics

Pharmacogenetics is the study of variability in drug response based on heredity and is influenced by ethnicity, age, and sex.¹ Pharmacogenetic testing may establish differences in the effects of drugs due to inter-individual variations.¹ For this reason, studies have been created to evaluate genetic variations in specific populations around the world. Through testing, genetic variations have been identified and linked to the risk of developing medical conditions as well as responses to medication treatment.² Applying pharmacogenetic results clinically may improve

the selection of medications, optimize dosage regimens, and reduce the number of adverse effects.²

Mental Health

According to the National Alliance on Mental Illness, serious mental illnesses, such as schizophrenia and bipolar disorder, cost Americans over \$193 billion in lost earnings per year.³ Worldwide, 81 million people live with schizophrenia or bipolar disorder, and many more are affected in some way by these psychiatric illnesses.³ Individuals with schizophrenia or bipolar disorder are at an increased risk of developing chronic medical conditions, such as hypertension, diabetes, and liver disease. These individuals die on average 25 years earlier than those without mental health disorders.³ They also face many social issues, including discrimination and prejudice, and inadequate treatments may lead to homelessness and incarceration.^{3,4}

The decision to use a particular medication regimen in schizophrenia or bipolar disorder can be difficult because of the complexity of genetics and variations in drug metabolism with cytochrome P450 enzymes. Medication therapies for schizophrenia and bipolar disorder are patient-specific. Interindividual differences in antipsychotic and mood stabilizer responses and the number of refractory disease processes are considered the most challenging problems in clinical psychiatry according to National Alliance on Mental Illness.³

Genetics in Mental Health

Evidence of genetic components influencing the development of psychiatric disease states and treatment decisions has been published.⁵ For example, the risk of developing schizophrenia increases in close relatives, such as twins. Additionally, family members often respond similarly to the same treatments.⁵ Polymorphisms in the 5-HT serotonin transporter gene have helped identify the increased risk of developing depression. This specific transporter facilitates reuptake of serotonin from the synaptic cleft into the presynaptic neuron, and studies have shown that an insertion (the addition of a piece of DNA) or deletion (the removal of a piece of DNA) in the promoter region (defined as the 5-HT transporter-linked polymorphic region or 5-HTTLPR) of the short allele has been associated with a decrease in serotonin transporter expression and reuptake.⁶ Polymorphisms in the length of alleles may determine response to selective serotonin reuptake inhibitors (SSRIs; ie, long alleles may correspond to favorable SSRI response rates while short alleles may correspond to decreased SSRI response rates and result in an increased risk of patient suicide).⁷ Through genetic testing numerous variants of the gene that codes for the CYP2D6 allele, the enzyme responsible for metabolizing

many antipsychotics and mood stabilizers, have been discovered along with metabolic variations (ie, poor and ultra-rapid metabolizers).⁸ Metabolic variations may result in more or less exposure to drug concentrations. Genetic testing may also determine whether or not patients are predisposed to side effects, such as agranulocytosis with clozapine therapy.⁹ Another example of genetic findings in schizophrenia is the HTR2C allele that codes for the serotonin 2C receptor. Allelic variations in HTR2C, along with CYP1A2 and CYP2C19, may promote weight gain, dyslipidemia, and diabetes in patients who take antipsychotics.¹⁰ The Clinical Pharmacogenetics Implementation Consortium, available at <https://cpicpgx.org/>, is a valuable resource that provides standardized terms of pharmacogenetics nomenclature and may aid in interpreting clinical pharmacogenetic test results.

Genes Discussed in Review

While most pharmacogenetic studies look at genotypes, or an individual's inherited genetic identity, some may also look at phenotypes, or physical characteristics, which can be influenced by a specific genotype.¹¹ For this systematic review, studies primarily analyzed the genotypes presented in the Table.¹²

The only comprehensive reviews to date include a systematic review of pharmacogenetics and antidepressants that highlight an association between antidepressant-induced mania and a serotonin transporter-linked promoter region polymorphism and allele length,¹³ and a systematic review in attention-deficit/hyperactivity disorder (ADHD) that analyzed genes involved in the development of ADHD as well as response to ADHD medication treatments.¹⁴ Comprehensive reviews of pharmacogenetic studies in patients with schizophrenia or bipolar disorder are lacking. The objective of this study is to evaluate the relationship between pharmacogenetic testing in patients with schizophrenia or bipolar disorder and report published outcomes. This study aims to describe the clinical value of pharmacogenetic testing in psychiatric pharmacy practice as it pertains to adult patients with schizophrenia or bipolar disorder.

Methods

A systematic review was performed to identify articles that used pharmacogenetic testing in adults (ages 18 to 64 years) with either bipolar disorder or schizophrenia. English-language articles published through April 30, 2017 were identified through the search engines PubMed and EBSCOhost. Search terms used to narrow down results to the most relevant articles were *pharmacogenomic testing OR pharmacogenetic testing AND psychiatry antipsychotics mood stabilizers pharmacokinetics pharma-*

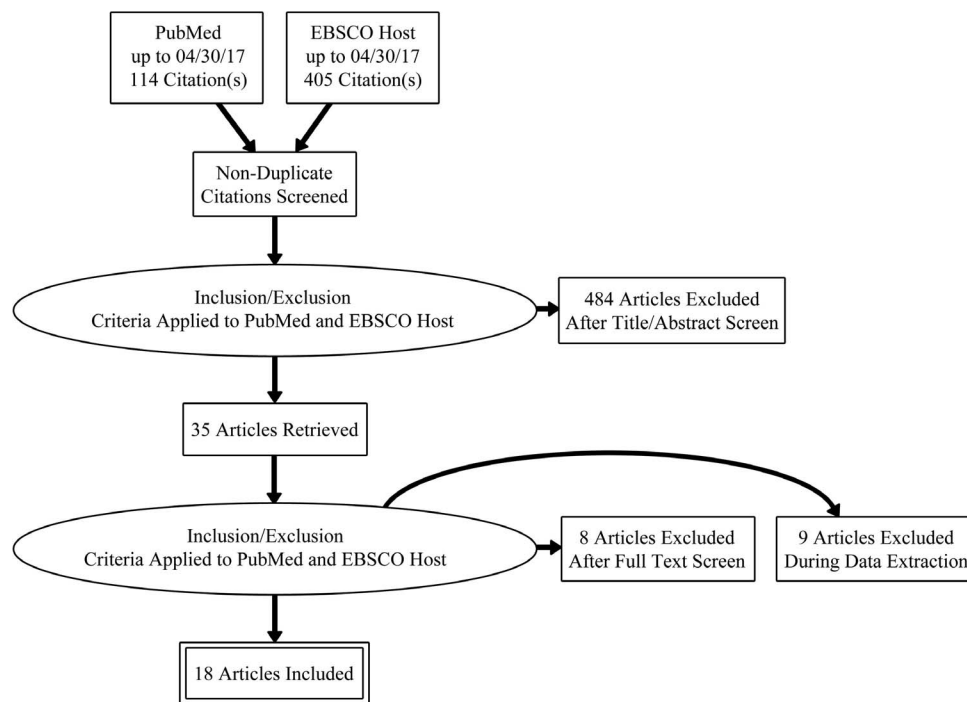


FIGURE: Data retrieval process

codynamics. The literature search identified 114 articles in PubMed and 405 articles in EBSCOhost. The reviewers independently searched the databases and found articles that fit the inclusion criteria based on abstract review. Duplicate citations were removed, and articles pertaining to psychiatric disease states other than bipolar disorder or schizophrenia and medication classes other than mood stabilizers or antipsychotics were excluded, but some articles were used for background information. Additional exclusion criteria included ages less than 18 or older than 64 years, non-English citations, available as abstracts only, or animal studies. The Figure from PRISMA Flow Diagram Generator shows the data retrieval process used for excluding articles, which narrowed down the results to 18 articles. The Table illustrates the final 18 articles and key outcomes.

Results

Patient Characteristics

In studies where ethnicity was a main focus, 6 out of 18 looked specifically at white populations.¹⁵⁻²⁰ The populations in the remaining studies include Chinese, Indian, Japanese, Australian, and African.²¹⁻²⁷ Of the 18 studies compiled for this analysis, 12 looked at participants between the ages of 18 and 55 years.^{17-23,25,28,29,31} The studies that explicitly stated the amount of males versus females included in their patient population tended to have no significant difference between the 2 sexes. Only 4

studies included predominantly male patients,^{18-21,25,29} while only 2 included predominantly female patients.^{17,22}

Additionally, the majority of the studies included in this review identified patients receiving antipsychotic monotherapy or mood stabilizer monotherapy for schizophrenia or bipolar disorder. Of the studies that characterized participants with their diagnosis, 11 focused on schizophrenia,^{15-21,24,27,29-30} while only 4 focused on bipolar 1 disorder.^{19,22,28,32} Likewise, the effect of genetic changes on mood stabilizers and/or antipsychotic response was the focus of 12 out of 18 studies. Medications included sodium valproate, carbamazepine, lithium, and atypical antipsychotics such as clozapine, olanzapine, quetiapine, and risperidone.^{15,16,18,20-22,24,27-29,31,32}

Genes Studied

The dopamine receptor DRD2 was the most widely studied gene among the articles because dopamine dysregulation is one of the major causes of both schizophrenia and bipolar disorder.^{18,24,29,31} Other genes studied include SCN1A IVS5N+5, PDLIM5, HLA-A, HLA-B, HLA-DRB1, SVC2, 5-HT2A, COMT, BDNF, TFGB1, GRM3, Synapsin II, and RGS4.^{15,19,21,24,28,30} Two studies looked at a multitude of genes and their response to antipsychotic treatments: ADRB2, DRD3, and SLC6A4, as well as EHF, SLC26A9, DRD2, GPR137B, CHST8, and IL1A^{20,31} One study looked specifically at phenotypes of induced pluripotent stem cells (iPSCs).³² Finally, 2 articles studied

TABLE: Effects of genetic variations on various psychiatric medications/disease states¹⁵⁻³²

Study (Year)	Gene Studied	Role of the Gene	Medication/Disease State Studied	Study Outcomes
Kapelski et al ¹⁷ (2016)	TFGB1	TFGB1 is a signaling protein that is essential for proliferation, development, differentiation, and regeneration of neurons	Schizophrenia	No direct correlation was found in this study between TFGB1 and schizophrenia.
He et al ²³ (2016)	HLA-A, HLA-B, and HLA-DRB1	HLA-A, HLA-B, and HLA-DRB1 cause hypersensitivity reactions to certain medications within various subsets of patient populations	Adverse reaction to carbamazepine	HLA-B was the most polymorphic gene among the 3 studied. When comparing the alleles to Han Chinese in other regions of China, the data supported that the HLA allele and haplotype distribution was different among a variety of ethnic populations.
Teh et al ²⁸ (2016)	HLA-B*15:02	HLA-B causes hypersensitivity reactions to certain medications	Carbamazepine	HLA-B*15:02 is a predictor of SJS/TEN (17.5% positive in prospective group, 32.6% positive in retrospective group) and researchers recommend prescreening patients of Chinese descent.
Mertens et al ³² (2016)	Cellular phenotypes of iPSCs	Gene expression was affected by lithium	Lithium/BPD	BPD iPSC model was found to be directly associated with clinical symptoms of mania in patients with BPD. Lithium can affect gene expression of the lithium responsive neurons and rescue genes in the lithium responsive patients that are key for the pathology of BPD and lithium response.
Zhang et al ²⁹ (2015)	DRD2	DRD2 is involved in the modulation of locomotion, reward, reinforcement, and memory/learning	AP/schizophrenia	Found that rs2514218 (the most common DRD2 SNP) is associated with AP response in patients with schizophrenia.
Blasi et al ¹⁸ (2015)	DRD2 and HTR2A	DRD2 is involved in the modulation of locomotion, reward, reinforcement, and memory/learning; HTR2A codes for the serotonin 2A receptor	AP	Combined DRD2 and HTR2A genetic variations affect physiological prefrontal efficacy during working memory as well as response to APs.
Bishop et al ³⁰ (2015)	GRM3	GRM3 is associated with cognitive processes; polymorphisms may influence symptoms and cognitive dysfunction in schizophrenia	AP/schizophrenia	Suggests that there are pharmacogenetic relationships between GRM3 variants and changes in cognition and symptom response with exposure to APs.
Zhang et al ¹⁶ (2013)	BDNF	BDNF aids in the growth of axons and is the major regulator of synaptic transmission in adult synapses	Clozapine	BDNF gene was found to be associated with AP treatment resistance with clozapine as a proxy.
Tan et al ¹⁹ (2014)	Synapsin II	Synapsin II is involved in the modulation of neurotransmitter release	AP/schizophrenia and BPD	This study suggests that impairment of synaptic transmission by a decrease in synapsin II may contribute to dysregulated mechanisms that result in neuronal characteristics of schizophrenia.

TABLE: Effects of genetic variations on various psychiatric medications/disease states¹⁵⁻³² (continued)

Study (Year)	Gene Studied	Role of the Gene	Medication/Disease State Studied	Study Outcomes
Ramsey et al ¹⁵ (2013)	SVC2	SVC2 is associated with functions related to synapses and catecholamine-mediated activities	Atypical AP	16 out of 106 SNPs were found to be significant. rs11960832, rs31244, and rs2270927 showed a poorer response to olanzapine and quetiapine; rs10214163 showed a poorer response with olanzapine, and better response to quetiapine.
Almoguera et al ²⁰ (2013)	ADRB2, DRD3, and SLC6A4	ADRB2 mediates smooth muscle relaxation and bronchodilation; DRD3 is involved in the modulation of locomotion, reward, reinforcement, and memory/learning; SLC6A4 stops the action of serotonin when it is no longer needed	Risperidone/schizophrenia	Allele 16Gly of ARDB2 was significantly associated with a higher risk of sexual adverse events. There were non-significant trends with DRD3 and SLC6A4.
Haerian et al ²¹ (2012)	SCN1A IVS5N+5	SCN1A IVS5N+5 aids in sending action potentials in the neurons	Valproic acid	Malaysian patients were seen to have a positive association (both allelic and genotypic) in response to valproic acid when compared to Chinese and Indian patients.
Zain et al ²² (2012)	PDLIM5	PDLIM5 polymorphisms are associated with BPD	BPD	No significant difference was seen in PDLIM5 mRNA expression between patients before and after olanzapine treatment in terms of side effects. There was, however, a major difference in the expression of PDLIM5 mRNA in BPD patients compared to controls, which may show that it is a good marker for BPD in general.
Azuma et al ²⁵ (2012)	CYP2D6	Phase I drug metabolism	Aripiprazole	Aripiprazole was found to be safe to use in combination with paroxetine and fluvoxamine in both extensive metabolizers and intermediate metabolizers.
McClay et al ³¹ (2011)	EHF, SLC26A9, DRD2, GPR137B, CHST8, and IL1A	EHF is a transcription factor involved in gene regulation; SLC26A9 stops the action of serotonin when it is no longer needed; DRD2 is involved in the modulation of locomotion, reward, reinforcement, and memory/learning; GPR137B mediated the effects of olanzapine on working memory; CHST8 produces sex hormones; IL1A is a cytokine involved in immune and inflammatory responses	AP/schizophrenia	Several candidate genes for AP response have been generated, but further research is required.

TABLE: Effects of genetic variations on various psychiatric medications/disease states¹⁵⁻³² (continued)

Study (Year)	Gene Studied	Role of the Gene	Medication/Disease State Studied	Study Outcomes
Zhang et al ²⁶ (2008)	CYP1A2 and CYP3A4	Phase I drug metabolism	Clozapine	Suggests that both CYP1A2 and 3A4 may determine the clearance pathways of clozapine and that phenotyping approaches could assist the optimization of clozapine dosage and minimize pharmacokinetic interactions with other medications.
Campbell et al ²⁷ (2008)	RGS4	Decreased amount of RGS4 correlated to schizophrenia	AP/schizophrenia	RGS4 genotypes predicted both the severity of baseline symptoms and relative responsiveness to AP treatment.
Yamanouchi et al ²⁴ (2003)	DRD2, 5-HT2A, and COMT	DRD2 is involved in the modulation of locomotion, reward, reinforcement, and memory/learning; 5HT2A associated with response to AP; deletion of COMT in the 22 chromosome region results in too little COMT and has also been found to be associated with panic disorder and schizophrenia	Risperidone	DRD2 haplotype correlated with better clinical performance.

AP = antipsychotics; BPD = bipolar disorder; iPSC = induced pluripotent stem cells; SJS/TEN = Stevens Johnson syndrome/toxic epidermal necrolysis; SNP = single nucleotide polymorphism.

cytochrome P450 enzyme variations specifically and how they influence medication response.^{25,26}

Outcomes

Variations in Treatment Response

Many of the studies identified a correlation between the genetic variation studied and its predisposition to a disease state or response to a medication (Table). Synaptic Vesicle Protein 2C (SVC2) is thought to be associated with many functions related to the synapses and catecholamine-mediated activities of the brain.¹² Subjects that were homozygous for the T allele of rs11960832 (a single nucleotide polymorphism [SNP] found on the SVC2 gene) displayed a poorer response to olanzapine and quetiapine. The rs10214163 SNP on the same gene showed a poorer response with olanzapine and a better response to quetiapine. Coding SNPs rs31244 and rs2270927 were also seen to have poorer responses to both olanzapine and quetiapine.¹⁵

The BDNF (brain derived neurotrophic factor) gene aids in the growth of axons and is the major regulator of synaptic transmission in adult synapses.¹² The BDNF was shown to be associated with antipsychotic treatment resistance with clozapine in 89 white patients with a schizophrenia diagnosis receiving clozapine treatment when compared to 190 white patients not receiving clozapine.¹⁶ DRD2 and DRD3 are dopamine receptors that

are involved in the modulation of locomotion, reward, reinforcement, and memory/learning.¹² The most common DRD2 SNP, rs2514218, was found to be associated with better antipsychotic response in patients with schizophrenia, and it has been specifically correlated with better clinical performance with risperidone.^{24,29} Similarly, a combination of variations in DRD2 and HTR2A affect both working memory and response to antipsychotics. 5HT2A is a serotonin transporter that has been found in recent studies to be associated with schizophrenia, as well as a change in response to antipsychotics, including clozapine and risperidone.¹² Subjects with SNPs in either the DRD2 or HTR2A allele had greater MRI prefrontal activity during working memory as well as better responses to antipsychotics in patients with schizophrenia.¹⁸ Additionally, studies have been done on COMT (catechol-O-methyltransferase) in relation to psychiatric disorders. COMT is an enzyme involved in the metabolism of certain medications used for the treatment of hypertension, asthma, and Parkinson's disease. Deletion of COMT in the 22 chromosome region, resulting in too little COMT, has also been found to be associated with panic disorder and schizophrenia.²⁴ ADRB2 is a beta-adrenergic receptor that binds to epinephrine, mediates smooth muscle relaxation, and bronchodilation.¹² The 16Gly allele of ARDB2 was significantly associated with a

higher risk of sexual adverse events in patients taking risperidone.²⁰

The results of 1 particular study concluded that Malaysian patients experience a positive treatment response to valproic acid therapy in comparison to Chinese and Indian patients when they express the functional SCN1A IVS5N+5 polymorphism.²¹ This gene is involved in voltage-gated sodium channels and aids in sending action potentials in the neurons.¹² Aripiprazole was found to be safe to use in combination with SSRIs that are CYP450 enzyme inhibitors based on coadministration of both aripiprazole and either paroxetine (a potent CYP2D6 inhibitor) or fluvoxamine (a moderate CYP3A4 inhibitor) to CYP2D6 extensive metabolizers (also known as normal metabolizers) and intermediate metabolizers. Although there was a difference seen in the pharmacokinetics between extensive metabolizers and intermediate metabolizers, the difference was not substantial enough to conclude that these 2 medications could not be coadministered.²⁵ The RGS4 (Regulator of G Protein Signaling) gene is a target of antipsychotic medications, and a decreased amount of these proteins have been seen in patients with schizophrenia.¹² RGS4 genotypes help to predict severity of baseline schizophrenia symptoms as well as relative response to antipsychotic treatment. RGS4 markers rs2661319 and rs2842030 were associated with more severe symptoms at baseline and a better response to perphenazine over quetiapine or ziprasidone.²⁷

The HLA-A, HLA-B, and HLA-DRB1 (major histocompatibility complex) genes all present foreign antigens to the immune system and therefore will cause hypersensitivity reactions to certain medications within various subsets of patient populations.¹² Patients with the HLA-B*15:02 allele have a much higher chance of developing Stevens-Johnson syndrome/toxic epidermal necrolysis.²⁸ The Food and Drug Administration recommends prescreening patients of Asian origin for HLA-B*15:02 prior to starting carbamazepine therapy.³³

Type-3 metabotropic glutamate receptor gene (GRM3) is associated with cognitive processes, and disruption of glutamate transmission due to polymorphisms to this gene could influence symptoms and cognitive dysfunction related to schizophrenia.¹² One study³⁰ found a relationship between GRM3 variants and changes in cognition and symptom response with exposure to antipsychotics. Spatial working memory worsened in patients with GRM3 rs1468412 following antipsychotic treatment. Patients with GRM3 rs6465084 showed improvement in negative symptoms following antipsychotic treatment.

Variations in Schizophrenia/Bipolar Disorder Development

There were also some correlations found between genetic variations and the risk of developing bipolar disorder and schizophrenia. Synapsin II is a gene involved in the modulation of neurotransmitter release and is believed to play a role in several neuropsychiatric diseases.¹² A

decrease in synapsin II may contribute to an impairment of synaptic transmission, dysregulated neuronal mechanisms, and resultant neuronal characteristics of schizophrenia.¹⁹ The PDLIM5 gene is expressed in the brain in a similar manner to synapsin, and polymorphisms within this gene have been associated with bipolar disorder.¹² Patients with bipolar disorder had a much larger expression of PDLIM5 mRNA compared to controls in 1 study, suggesting that this may be a good marker for bipolar disorder.²² Induced pluripotent stem cells in bipolar disorder was found to be directly associated with mania symptoms.³²

Several studies listed in the Table did not show a correlation between the genetic variation studied and a change in response to medication or the development of schizophrenia or bipolar disorder. Transforming growth factor beta 1 (TFGB1) is a signaling protein that is essential for proliferation, development, differentiation, and regeneration of neurons. However, no correlation was found between TFGB1 expression and schizophrenia.¹⁷ A second study³¹ looked at the correlation in several candidate genes and response to antipsychotics along with the development of schizophrenia. SLC6A4 and SLC26A9 are serotonin transporters that stop the action of serotonin when it is no longer needed and allow for its reuptake into the synaptic cleft.¹² The ETS homologous factor (EHF) is located on chromosome 11.¹² EHF is expressed at high levels in epithelial tissues, mostly in the prostate, pancreas, salivary gland, and trachea. CHST8 is a protein that produces sex hormones, such as luteinizing hormone (LH). IL1A is a cytokine that is used in various immune and inflammatory responses in the body and would likely have a similar effect as the HLA genes. GPR137B is a G protein-coupled receptor that achieved genome-wide significance for mediating the effects of olanzapine on working memory. More research is needed to determine if there is a true correlation with any of these candidate genes and medication response or development of schizophrenia.^{12,31}

Discussion

Pharmacogenetics and pharmacogenomics are emerging topics in the field of pharmacy. Health care professionals such as physicians, nurses, and pharmacists have begun working together to gather information about the genetic profiles of patients in order to encourage and eventually guide treatment plans for certain disease states. This type of individualized treatment may one day lead to lower medication costs by preventing the *trial and error* approach that commonly occurs and may mitigate unwanted adverse effects. Review of pharmacogenetic profiles may potentially allow providers to prescribe a specific medication regimen unique to each patient that will provide the best outcome early on in the treatment process.

There are several important considerations before implementing pharmacogenetic testing for patients with schizophrenia or bipolar disorder. The majority of the studies used blood samples analyzed via polymerase chain reaction to determine genetic variations in each patient population. Blood samples and saliva samples are equally as effective in collecting genetic information from patients, however, blood samples are more commonly used in research settings because of the equipment available in the laboratories to analyze the samples.³⁴ In clinical practice, pharmacogenetic samples are most often obtained by saliva samples or buccal swabs. Insurance companies may not cover the cost of the genetic tests, and mental health facilities often function on restricted budgets and do not necessarily have the funds to implement genetic testing in their patients. Patients with paranoid schizophrenia may also not be receptive to the idea of having their cheek swabbed or their blood drawn to find out the results of a genetic test, especially individuals who lack insight into their illness.

The anticipation is that pharmacogenetic testing can be performed in patients with schizophrenia or bipolar disorder in the near future, prior to treatment initiation, in order to guide medication selection and prevent potential adverse effects. Some genetic testing companies provide specific *psychiatry panels* and may screen for many of the genetic variants discussed in this review while other companies conduct comprehensive genetic panels – the end result is generally the same with targeted variants including those that affect drug absorption, metabolism, and activity. For example, if a pharmacogenetic test shows someone with first-episode psychosis treated with antipsychotics is homozygous for the C allele at rs2514218 at the DRD2 locus, then that individual may experience a greater reduction in positive symptoms when compared to T allele carriers.²⁹ In reference to side effects, if a C/C homozygote at rs2514218 on the DRD2 locus is prescribed aripiprazole then the individual may experience more akathisia when compared to T allele carriers. Currently, research is not clear on what therapeutic recommendations should be made based on results from pharmacogenetic testing. In the future, the hope is that these test results will provide specific medication recommendations for individuals based on one's unique genetic profile.

Although studies have been conducted on the use of pharmacogenetic testing in schizophrenia and bipolar disorder, no clear decision can be made on its use in pharmacy practice at this time because of the limitations of the current studies. One limitation seen in these studies is limited sample size. This can be seen in nearly all of the studies compiled for this review. Although study sizes ranged from 10 to 8 333 participants,^{23,32} the majority of studies only looked at sample sizes between 50-300 participants, which cannot necessarily be extrapolated to

larger diverse populations. Additionally, the biggest limitation is that the studies compiled for this review did not seek to show the clinical use of pharmacogenetic testing. Therefore, forthcoming studies for this specific purpose are needed to strengthen the recommendation of using pharmacogenetic testing in clinical practice.

In order to assess the clinical use of pharmacogenetic testing in patients with schizophrenia and bipolar disorder and make specific recommendations, more studies are needed. Future studies should include larger sample sizes to determine which variations correlate to entire ethnicities and population subsets and include patients taking multiple medications to improve generalizability. The more specific genetic variations that are found, the more individualized the treatment can be for patients. Additional studies should also be performed with the specific purpose of determining the clinical use of pharmacogenetic testing. It is also important for health care professionals to advance their knowledge about the use of genetic testing and the importance of pharmacogenetics in psychiatry.

References

1. Ozaki N. Pharmacogenetics of antipsychotics. *Nagoya J Med Sci.* 2004;67(1-2):1-7. PubMed PMID: [15279062](#).
2. Bolhuis PA. [Importance of pharmacogenetics]. *Ned Tijdschr Geneeskd.* 2001;145(1):15-8. PubMed PMID: [1198959](#). Dutch.
3. Mental health by the numbers [Internet]. Arlington (VA): National Association on Mental Illness; c2018 [cited 2017 Jul 1]. Available from: <https://www.nami.org/Learn-More/Mental-Health-By-the-Numbers>
4. Mental Disorders [Internet]. Geneva: World Health Organization; c2018 [updated 2018 Apr 9; cited 2017 Jul 1]. Available from: <http://www.who.int/mediacentre/factsheets/fs396/en/>.
5. Tsuang MT, Stone WS, Faraone SV. Genes, environment and schizophrenia. *Br J Psychiatry.* 2001;178(S40):s18-24. DOI: [10.1192/bjp.178.40.s18](#).
6. Hooten WM, Townsend C, Sletten C. The triallelic serotonin transporter gene polymorphism is associated with depressive symptoms in adults with chronic pain. *J Pain Res.* 2017;10:1071-8. DOI: [10.2147/JPR.S134231](#). PubMed PMID: [28533695](#); PubMed Central PMCID: [PMC5431744](#).
7. Pettitt A. Genetic variations in the serotonergic system mediate a combined, weakened response to SSRI treatment: a proposed model. *eNeuro.* 2015;2(3):ENEURO.0032-14.2015. DOI: [10.1523/ENEURO.0032-14.2015](#). PubMed PMID: [26464988](#); PubMed Central PMCID: [PMC4586934](#).
8. Goh LL, Lim CW, Sim WC, Toh LX, Leong KP. Analysis of genetic variation in CYP450 genes for clinical implementation. *PLoS One.* 2017;12(1):e0169233. DOI: [10.1371/journal.pone.0169233](#). PubMed PMID: [28046094](#); PubMed Central PMCID: [PMC5207784](#).
9. Anil Yağcıoğlu AE, Yoca G, Ayhan Y, Karaca R, Çevik L, Müderrisoğlu A, et al. Relation of the allelic variants of multidrug resistance gene to agranulocytosis associated with clozapine. *J Clin Psychopharmacol.* 2016;36(3):257-61. DOI: [10.1097/JCP.0000000000000495](#). PubMed PMID: [27043126](#).
10. Vasudev K, Choi Y-H, Norman R, Kim RB, Schwarz UI. Genetic determinants of clozapine-induced metabolic side effects. *Can J*

- Psychiatry. 2017;62(2):138-49. DOI: [10.1177/0706743716670128](https://doi.org/10.1177/0706743716670128). PubMed PMID: [27681143](https://pubmed.ncbi.nlm.nih.gov/27681143/); PubMed Central PMCID: [PMC5298525](https://pubmed.ncbi.nlm.nih.gov/PMC5298525/).
11. Genotype and phenotype [Internet]. Hamilton (New Zealand): Science and Learning Hub; c2018 [updated 2011 Jun 10; cited 2017 Jul 1]. Available from: <https://www.sciencelearn.org.nz/resources/207-genotype-and-phenotype>
 12. Stelzer G, Rosen R, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, et al. The GeneCards Suite: From gene data mining to disease genome sequence analysis [Internet]. Rehovot (Israel): Weizmann Institute of Science; c2016 [updated 2016 Jun 20; cited 2017 Jul 1]. Available from: www.genecards.org
 13. Daray FM, Thommi SB, Ghaemi SN. The pharmacogenetics of antidepressant-induced mania: a systematic review and meta-analysis. *Bipolar Disord*. 2010;12:702-6. DOI: [10.1111/j.1399-5618.2010.00864.x](https://doi.org/10.1111/j.1399-5618.2010.00864.x). PubMed PMID: [21040287](https://pubmed.ncbi.nlm.nih.gov/21040287/).
 14. Bonvicini C, Faraone SV, Scassellati C. Attention-deficit hyperactivity disorder in adults: a systematic review and meta-analysis of genetic, pharmacogenetic and biochemical studies. *Mol Psychiatry*. 2016;21(7):872-84. DOI: [10.1038/mp.2016.74](https://doi.org/10.1038/mp.2016.74). PubMed PMID: [27217152](https://pubmed.ncbi.nlm.nih.gov/27217152/).
 15. Ramsey TL, Liu Q, Massey BW, Brennan MD. Genotypic variation in the SV2C gene impacts response to atypical antipsychotics the CATIE study. *Schizophr Res*. 2013;149(1-3):21-5. DOI: [10.1016/j.schres.2013.07.008](https://doi.org/10.1016/j.schres.2013.07.008). PubMed PMID: [23886675](https://pubmed.ncbi.nlm.nih.gov/23886675/).
 16. Zhang J-P, Lencz T, Geisler S, DeRosse P, Bromet EJ, Malhotra AK. Genetic variation in BDNF is associated with antipsychotic treatment resistance in patients with schizophrenia. *Schizophr Res*. 2013;146(1-3):285-8. DOI: [10.1016/j.schres.2013.01.020](https://doi.org/10.1016/j.schres.2013.01.020). PubMed PMID: [23433505](https://pubmed.ncbi.nlm.nih.gov/23433505/).
 17. Kapelski P, Skibińska M, Maciukiewicz M, Zaremba D, Jasiak M, Hauser J. Family association study of Transforming Growth Factor-Beta1 gene polymorphisms in schizophrenia. *Psychiatr Pol*. 2016;50(4):761-70. DOI: [10.12740/PP/61273](https://doi.org/10.12740/PP/61273). PubMed PMID: [27847927](https://pubmed.ncbi.nlm.nih.gov/27847927/).
 18. Blasi G, Selvaggi P, Fazio L, Antonucci LA, Taurisano P, Masellis R, et al. Variation in dopamine D2 and serotonin 5-HT2A receptor genes is associated with working memory processing and response to treatment with antipsychotics. *Neuropsychopharmacology*. 2015;40(7):1600-8. DOI: [10.1038/npp.2015.5](https://doi.org/10.1038/npp.2015.5). PubMed PMID: [25563748](https://pubmed.ncbi.nlm.nih.gov/25563748/).
 19. Tan ML, Dyck BA, Gabriele J, Daya RP, Thomas N, Sookram C, et al. Synapsin II gene expression in the dorsolateral prefrontal cortex of brain specimens from patients with schizophrenia and bipolar disorder: effect of lifetime intake of antipsychotic drugs. *Pharmacogenomics J*. 2014;14(1):63-9. DOI: [10.1038/tpj.2013.6](https://doi.org/10.1038/tpj.2013.6). PubMed PMID: [23529008](https://pubmed.ncbi.nlm.nih.gov/23529008/); PubMed Central PMCID: [PMC3970980](https://pubmed.ncbi.nlm.nih.gov/PMC3970980/).
 20. Almoguera B, Riveiro-Alvarez R, Lopez-Castroman J, Dorado P, Vaquero-Lorenzo C, Fernandez-Piqueras J, et al. Association of common genetic variants with risperidone adverse events in a Spanish schizophrenic population. *Pharmacogenomics J*. 2013;13(2):197-204. DOI: [10.1038/tpj.2011.57](https://doi.org/10.1038/tpj.2011.57). PubMed PMID: [22212732](https://pubmed.ncbi.nlm.nih.gov/22212732/); PubMed Central PMCID: [PMC3619141](https://pubmed.ncbi.nlm.nih.gov/PMC3619141/).
 21. Haerian BS, Baum L, Tan HJ, Kwan P, Raymond AA, Saruwatari J, et al. SCN1A IVS5N+5 polymorphism and response to sodium valproate: a multicenter study. *Pharmacogenomics*. 2012;13(13):1477-85. DOI: [10.2217/pgs.12.127](https://doi.org/10.2217/pgs.12.127). PubMed PMID: [23057548](https://pubmed.ncbi.nlm.nih.gov/23057548/).
 22. Zain MA, Jahan SN, Reynolds GP, Zainal NZ, Kanagasundram S, Mohamed Z. Peripheral PDLIM5 expression in bipolar disorder and the effect of olanzapine administration. *BMC Med Genet*. 2012;13:91. DOI: [10.1186/1471-2350-13-91](https://doi.org/10.1186/1471-2350-13-91). PubMed PMID: [23031404](https://pubmed.ncbi.nlm.nih.gov/23031404/); PubMed Central PMCID: [PMC3502145](https://pubmed.ncbi.nlm.nih.gov/PMC3502145/).
 23. He Y, Zhang W, Chen N, Wang W, He J, Han Z, et al. HLA-A, -B and -DRB1 allele and haplotype frequencies of 8333 Chinese Han from the Zhejiang province, China. *Int J Immunogenet*. 2016;43(2):86-95. DOI: [10.1111/iji.12254](https://doi.org/10.1111/iji.12254). PubMed PMID: [26919533](https://pubmed.ncbi.nlm.nih.gov/26919533/).
 24. Yamanouchi Y, Iwata N, Suzuki T, Kitajima T, Ikeda M, Ozaki N. Effect of DRD2, 5-HT2A and COMT genes on antipsychotic response to risperidone. *Pharmacogenomics J*. 2003;3(6):356-61. DOI: [10.1038/sj.tpj.6500211](https://doi.org/10.1038/sj.tpj.6500211). PubMed PMID: [14610521](https://pubmed.ncbi.nlm.nih.gov/14610521/).
 25. Azuma J, Hasunuma T, Kubo M, Miyatake M, Koue T, Higashi K, et al. The relationship between clinical pharmacokinetics of aripiprazole and CYP2D6 genetic polymorphism: effects of CYP enzyme inhibition by coadministration of paroxetine or fluvoxamine. *Eur J Clin Pharmacol*. 2012;68(1):29-37. DOI: [10.1007/s00228-011-1094-4](https://doi.org/10.1007/s00228-011-1094-4). PubMed PMID: [21739267](https://pubmed.ncbi.nlm.nih.gov/21739267/); PubMed Central PMCID: [PMC3249179](https://pubmed.ncbi.nlm.nih.gov/PMC3249179/).
 26. Zhang WV, D'Esposito F, Edwards RJ, Ramzan I, Murray M. Interindividual variation in relative CYP1A2/3A4 phenotype influences susceptibility of clozapine oxidation to cytochrome P450-specific inhibition in human hepatic microsomes. *Drug Metab Dispos*. 2008;36(12):2547-55. DOI: [10.1124/dmd.108.023671](https://doi.org/10.1124/dmd.108.023671). PubMed PMID: [18809730](https://pubmed.ncbi.nlm.nih.gov/18809730/).
 27. Campbell DB, Ebert PJ, Skelly T, Stroup TS, Lieberman J, Levitt P, et al. Ethnic stratification of the association of RGS4 variants with antipsychotic treatment response in schizophrenia. *Biol Psychiatry*. 2008;63(1):32-41. DOI: [10.1016/j.biopsych.2007.04.018](https://doi.org/10.1016/j.biopsych.2007.04.018). PubMed PMID: [17588543](https://pubmed.ncbi.nlm.nih.gov/17588543/); PubMed Central PMCID: [PMC2194758](https://pubmed.ncbi.nlm.nih.gov/PMC2194758/).
 28. Teh LK, Selvaraj M, Bannur Z, Ismail MIM, Rafia H, Law WC, et al. Coupling genotyping and computational modeling in prediction of anti-epileptic drugs that cause Stevens Johnson Syndrome and toxic epidermal necrolysis for carrier of HLA-B*15:02. *J Pharm Pharm Sci*. 2016;19(1):147-60. DOI: [10.18433/J38G7X](https://doi.org/10.18433/J38G7X). PubMed PMID: [27096699](https://pubmed.ncbi.nlm.nih.gov/27096699/).
 29. Zhang J-P, Robinson DG, Gallego JA, John M, Yu J, Addington J, et al. Association of a schizophrenia risk variant at the DRD2 locus with antipsychotic treatment response in first-episode psychosis. *Schizophr Bull*. 2015;41(6):1248-55. DOI: [10.1093/schbul/sbv116](https://doi.org/10.1093/schbul/sbv116). PubMed PMID: [26320194](https://pubmed.ncbi.nlm.nih.gov/26320194/); PubMed Central PMCID: [PMC4601717](https://pubmed.ncbi.nlm.nih.gov/PMC4601717/).
 30. Bishop JR, Reilly JL, Harris MSH, Patel SR, Kittles R, Badner JA, et al. Pharmacogenetic associations of the type-3 metabotropic glutamate receptor (GRM3) gene with working memory and clinical symptom response to antipsychotics in first-episode schizophrenia. *Psychopharmacol (Berl)*. 2015;232(1):145-54. DOI: [10.1007/s00213-014-3649-4](https://doi.org/10.1007/s00213-014-3649-4). PubMed PMID: [25096017](https://pubmed.ncbi.nlm.nih.gov/25096017/).
 31. McClay JL, Adkins DE, Aberg K, Bukszár J, Khachane AN, Keefe RSE, et al. Genome-wide pharmacogenomic study of neurocognition as an indicator of antipsychotic treatment response in schizophrenia. *Neuropsychopharmacology*. 2011;36(3):616-26. DOI: [10.1038/npp.2010.193](https://doi.org/10.1038/npp.2010.193). PubMed PMID: [21107309](https://pubmed.ncbi.nlm.nih.gov/21107309/); PubMed Central PMCID: [PMC3055694](https://pubmed.ncbi.nlm.nih.gov/PMC3055694/).
 32. Mertens J, Wang Q-W, Kim Y, Yu DX, Pham S, Yang B, et al. Erratum: differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. *Nature*. 2016;530(7589):242. DOI: [10.1038/nature16182](https://doi.org/10.1038/nature16182). PubMed PMID: [26605530](https://pubmed.ncbi.nlm.nih.gov/26605530/).
 33. Novartis Pharmaceuticals Corporation. Tegretol (carbamazepine) chewable tablets, tablets, suspension; package insert. March 2018 [cited 2018 Oct 23]. East Hanover (NJ): Novartis. Available from: <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/tegretol.pdf>
 34. Hu Y, Ehli EA, Nelson K, Bohlen K, Lynch C, Huizenga P, et al. Genotyping performance between saliva and blood-derived genomic DNAs on the DMET array: a comparison. *PLoS One*. 2012;7(3):e33968. DOI: [10.1371/journal.pone.0033968](https://doi.org/10.1371/journal.pone.0033968). PubMed PMID: [22448283](https://pubmed.ncbi.nlm.nih.gov/22448283/); PubMed Central PMCID: [PMC3309006](https://pubmed.ncbi.nlm.nih.gov/PMC3309006/).