

The Impact of Drug and Gene Interaction on the Antipsychotic Medication for Schizophrenia

Michelle Cho¹, Adriana Contreras¹, Ashley Garza¹, Samantha Olvera¹, David Castillo¹, Gabriel de Erausquin² and Chun Xu^{1*}

¹Department of Health and Biomedical Science, University of Texas Rio Grande Valley, Brownsville, Texas, USA

²Department of Neurology and Psychiatry, University of Texas Rio Grande Valley, Brownsville, Texas, USA

Abstract

Objective: Schizophrenia, a neuropsychiatric disorder, is known to be neurodevelopmentally progressive. Due to the extensive interindividual variability found in the responses of patients, management of schizophrenia has proven to be challenging. This interindividual variability to treatment could be justified by the variation of the enzymes in charge of metabolizing medications, especially those associated with cytochrome P450. Since genetic factors influence the phenotypic responses to drugs, researchers are involved in identifying schizophrenic genetic factors, which could impact responses and severe effects for commonly known neuroleptic drugs known as pharmacogenetics. In order to predict drug response at the personal level, genetic variants that determine drug effects need to be identified.

Methods: We have chosen to investigate gene targets for risperidone and clozapine, two commonly administered drugs for the treatment of schizophrenia. The aim of this review is to contribute in the understanding of genetic influences on drug responses of risperidone and clozapine in schizophrenia. We reviewed original primary research articles, meta-analysis, and review publications on drug and gene interaction on the treatment of schizophrenia. Our main findings focused on schizophrenia, pharmacogenetics and cytochrome P450.

Results and conclusion: After filtering our results to human species and English language, a total of 45 scientific articles were used for this review. A promising direction for future research in schizophrenia treatment lies behind the identification of the specific genetic contributors that affect drug response.

Keywords: Schizophrenia; Pharmacogenetics; Cytochrome p450; Treatment; Psychiatric disorders

Introduction

Schizophrenia and/or treatment

The debilitating disease schizophrenia, which affects millions of people, is a chronic, neuropsychiatric disorder, considered neurodevelopmentally progressive, and ranks as one of the 20 major factors for disability in the world [1,2]. Schizophrenia is also considered a complex disorder that cannot be described as a single developmental, degenerative process because of how challenging it is to be diagnosed and treated [1,3]. Statistically, individuals with one immediate family member affected with the disease are usually 10 times more prone to be affected with schizophrenia, while individuals with both parents affected with the disease are around 50 times more likely to also be affected [4]. Moreover, unlike the plaques and tangles that characterize Alzheimer's disease, the brain abnormalities found in schizophrenic patients do not usually contribute to a diagnosis [4]. Today, schizophrenia is usually treated with antipsychotic medications either first generation, also known as typical, or second generation, known as atypical. Although, both categories block dopamine receptors, the second generation drugs also affect serotonin levels. The use of these medications could result in increased morbidity, which includes extrapyramidal-like symptoms, weight gain, and rigidity [5]. Typical antipsychotics generally treat positive symptoms associated with schizophrenia but these types of medications are also found to cause unwelcome motor side effects. In comparison, atypical antipsychotics have the ability to effectively treat both positive and negative symptoms associated with schizophrenia, but may also lead to severe metabolic side effects [6]. Despite the large availability of resources in the medical field, physicians still struggle to produce rational treatment options. Consequently, the trial and error method is utilized and usually results in patient suffering, high cost, and stress on the patient and the patient's family [7]. Previously, a traditional

approach has been used in order to develop drug compounds that exhibit a mean average response from the population, which usually results in large interindividual variation in the way that patients respond to specific drugs [7].

Cytochrome p450 (CYP)

Due to the extensive interindividual variability found in the responses of patients, management of schizophrenia has proven to be challenging [3]. This interindividual variability to treatment could possibly be justified by the variation of the enzymes in charge of metabolizing medications, especially the enzyme system associated with cytochrome P450 (CYP), which is composed of the major enzymes in charge of the entire metabolic process [3,8,9]. This system is made up of a family of isoenzymes, which are located in the inner membrane of the mitochondria or the smooth endoplasmic reticulum of cells, especially in the liver [10]. The major enzymes that have been identified from the CYP family include CYP1A2, CYP2D6, CYP3A4 and CYP2C19. These enzymes are coded by highly polymorphic genes [11]. For instance, CYP2D6 contains over 60 alleles and 130 genetic variations due to combinations of single nucleotide polymorphisms (SNPs) and

***Corresponding author:** Chun Xu, Assistant professor, Department of Health and Biomedical Science, University of Texas Rio Grande Valley, Brownsville, Texas, USA, Tel: 956 882 4193; E-mail: Chun.Xu@utrgv.edu

Received December 21, 2016; **Accepted** February 01, 2017; **Published** February 08, 2017

Citation: Cho M, Contreras A, Garza A, Olvera S, Castillo D, et al. (2017) The Impact of Drug and Gene Interaction on the Antipsychotic Medication for Schizophrenia. *Bipolar Disord* 3: 117. doi: [10.4172/2472-1077.1000117](https://doi.org/10.4172/2472-1077.1000117)

Copyright: © 2017 Cho M, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

copy number variations. This gene is found to be highly polymorphic. CYP2D6, along with the other variants of the CYP family, metabolize different types of antipsychotics [12]. Moreover, out of five main CYP genes, the function of CYP2D6 is to metabolize several existing prescribed antipsychotics as well as antidepressants and anxiolytics. The CYP2D6 is one of the major genes in drug metabolism and it is located on chromosome 22 [6]. Many antipsychotic drugs are considered lipophilic compounds and require extensive metabolic energy in order to be excreted from the body [13]. Approximately 20-25% of clinically used medications are metabolized by the enzyme CYP2D6 [14]. Furthermore, a genetic impairment in CYP2D6 contributes to the development of extrapyramidal side-effects, which usually result from long-term schizophrenic treatment [12]. Additionally, the amount of drug concentration is based on the rate at which enzymes metabolize it, which is affected by genetic polymorphisms. Consequently, lower rates of enzymatic activity will likely result in higher concentrations of the drug and the possibility of adverse drug responses, while a higher rate of enzymatic activity can result in a decrease of plasma levels and diminished drug effects [6].

Pharmacogenetics

Since genetic factors influence the phenotypic responses to drugs, an increasing number of researchers are involved in identifying schizophrenic genetic factors for the disorder and treatment responses for commonly known neuroleptic drugs [15,16]. This is where the field of pharmacogenetics plays a major role. Pharmacogenetics focuses on the relationship between the pharmacokinetic level or the pharmacodynamic level and interindividual differences [15]. The pharmacokinetics focuses on the way drugs being metabolized based on individual genetic differences, while pharmacodynamics is to elucidate the differences in responses among individuals [15]. Pharmacogenetics also focuses on variations found in the human genome and in the different ways in which individuals respond to drugs based on genetic factors [17]. Despite the fact that there is a large variety of available medications, as many as 30-50% of the patients with treatment of antidepressants and antipsychotics will not adequately respond to treatment [16]. In order to predict drug response at the personal level, genetic variants that determine drug effects need to be identified [15]. Therefore, pharmacogenetics is to understand individual differences within humans to help identify potential variants in order to help formulate an individualized care for patients using antipsychotic medications [8]. Recent scientific advancements, such as the Human Genome Project, cutting edge technology and methods of DNA analysis progress, have introduced new tools that aid in the identification of genetic variation focusing on a drug target level. Giving a new perspective for the field of pharmacogenetics [15], a large number of research studies has been conducted. Although a vast amount of genetic variation has been depicted regarding responses to certain pharmaceutical medications, genetic tools are not able to identify the likelihood of an individualized response to treatment. Consequently, there is difficulty in establishing personalized drug therapies with favorable options regarding medication and dosage. Despite the development of expedient and more effective methods in genetic testing, clinical application in the use of pharmacogenetics as a guide for therapy may only be possible through the availability of a reliable predictor for clinical outcomes [16].

Drugs

In order to appropriately select genes to investigate, familiarity with a specific drug's mechanism of action must be known. Consequently, there is an inclination to study well known drug targets [7]. Therefore, we have chosen to investigate gene targets for risperidone and clozapine,

two commonly administered drugs for the treatment of schizophrenia. "Risperidone is a widely prescribed antipsychotic for the treatment of schizophrenia, with a relatively high rate of non-effectiveness or intolerable side effects" [18]. Due to the unwelcoming side effects, there is a high occurrence of risperidone non-compliance [18]. Some common examples of these side effects include "extrapyramidal symptoms (EPS), hyperprolactinemia, hyperlipidemia, weight gain, and metabolic syndrome" [18]. On the other hand, clozapine, compared to the other atypical antipsychotics, has been shown to be effective in 30-60% of schizophrenia patients [6]. "Clozapine is the drug of choice for the management of treatment-resistant schizophrenia (TRS) because of its superior clinical efficacy, its ability to reduce suicidal risk, and its low propensity to produce movement disorders" [19]. In addition, since clozapine is able to interact with various serotonin and dopamine receptors, it is speculated to yield antipsychotic effects. However, the mechanisms are not yet clear [6]. Hence, knowledge and understanding of the behavior of specific genes that affect risperidone and clozapine treatment is of the utmost importance in order to guide the personalization of prescribing the optimal medication for each individual patient afflicted with schizophrenia [8].

The aim of this review is to understand genetic influences on drug responses in schizophrenia. To aid in the development of a pharmacogenetic test that would allow for the personalization of antipsychotic drugs in the hopes of reducing undesirable side effects [7]. Lastly, to provide an updated overview on risperidone and clozapine to guide physicians and clinical scientists in their clinical practice in order to reduce toxicity, increase efficacy and reduce the overall cost based on genotypes of each individual patient.

Methods

The primary aim of this review is to understand genetic influences on drug response in schizophrenia. There were a total of 52 publications with all five keywords (schizophrenia, pharmacogenetics, cytochrome P450, treatment, and psychiatric disorders (Figure 1)). We then filtered for the Human species and the English language and identified a total of 45 publications. After further filtering for free full text, 10 publications were identified. We assessed all 10 publications and identified 25 candidate genes and selected eight of those candidate genes and their polymorphisms. The eight genes selected include Cytochrome P450 2D6 (CYP2D6), Catechol-O-methyltransferase (COMT), 5-Hydroxytryptamine transporter (5HTT), 5-Hydroxytryptamine receptor 6 (5HT6), 5-Hydroxytryptamine receptor 2A (HTR2A), 5-Hydroxytryptamine receptor 2C (HTR2C), Dopamine receptor D2 (DRD2) and Dopamine receptor D3 (DRD3). These genes were selected because they were the most prominent in our search in relation to clozapine and risperidone treatment.

Results

After filtering steps, we were focus on eight genes in association with antipsychotic treatment responses for patients with schizophrenia (Figure 1).

CYP2D6

The P450 enzyme system in the liver is the main system responsible for drug metabolism. CYP2D6, located on chromosome 22q13.1, is one of the major genes used by the system and it metabolizes around 20-25% of all clinically used medications, including risperidone and clozapine [20]. This gene is considered to be highly polymorphic. We discussed four genetic variants involved in differences in treatment responses in various populations (Table 1). Research shows that poor metabolizers

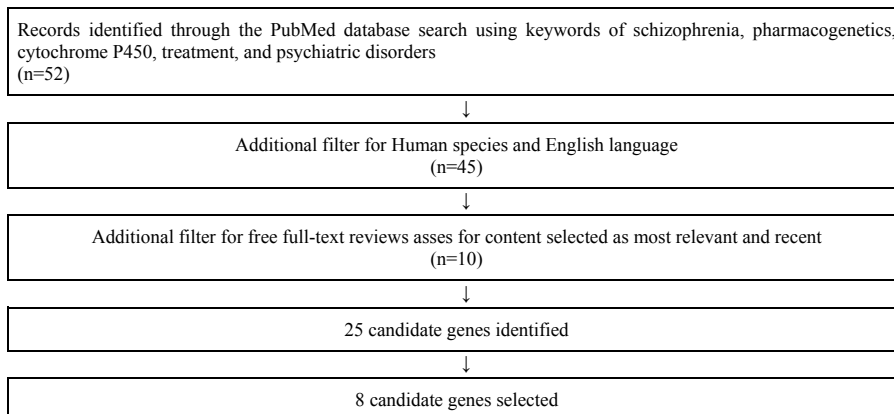


Figure 1: Workflow of publications used for this review paper.

GeneS	Polymorphism	Population	Frequency	Treatment Response	Antipsychotic
CYP2D6	*3B (rs1135824)	A (n=75) C (n=65) H (n=49) AS	0.000 0.000 0.000 N/A	<ul style="list-style-type: none"> • PMs tend to accumulate higher drug levels in blood, and theoretically, require lower doses to achieve therapeutic effects (Kakihara et al. [21], n=136; Riedel et al. [22], n=82) • UMs may require higher doses of an antipsychotic due to faster elimination of the drug (Arranz and de Leon [23]) 	Risperidone
	*3B (rs35742686)	A (n=661) C (n=503) H AS (n=504)	0.002 0.019 N/A 0.000		
	*4 (rs3892097)	A (n=24) C (n=32) H (n=23) AS (n=65)	0.063 0.242 0.065 0.002		
	*6 (rs5030655)	A (n=661) C (n=503) H AS (n=504)	0.001 0.020 N/A 0.000		
COMT	Val108Met (rs4680)	A (n=661) C (n=503) H AS (n=504)	0.281 0.500 N/A 0.280	<ul style="list-style-type: none"> • met/met genotype results in 3-4 fold lower enzyme activity compared with the val/val allele pair (Zhang and Malhotra [20]) • met/val heterozygote results in intermediate enzyme activity (Zhang and Malhotra [20]) • val/val genotypes were less likely to respond to 8 weeks of clozapine treatment (Bertolino et al. [34], n=59) 	First generation Antipsychotics (FGAs) and Clozapine
5HTT	5-HTTLPR (rs25531)	A (n=661) C (n=503) H AS (n=504)	0.220 0.089 N/A 0.132	<ul style="list-style-type: none"> • Short allele is associated with poor response to clozapine and risperidone treatment (Arranz et al. [25], n=200; Wang et al. [26], n=129; Dolzan et al. [27], n=56) 	Clozapine and Risperidone
5HT6	C267T (rs1805054)	A (n=661) C (n=503) H AS (n=504)	0.063 0.283 N/A 0.457	<ul style="list-style-type: none"> • Significant association between the T/T genotype and better treatment response (Yu et al. [28], n=99; Lane et al. [29], n=123; Zhang and Malhotra [20]) 	Clozapine and Risperidone
HTR2A	His452Tyr (rs6314)	A (n=661) C (n=503) H AS (n=504)	0.121 0.079 N/A 0.005	<ul style="list-style-type: none"> • Ca²⁺ mobilization ↓ (Zhang and Malhotra [20]) • Tyr variant is associated with reduced calcium release and reduced ability to activate phospholipases (Zhang and Malhotra [20]) • Tyr variant showed lowered antipsychotic binding affinity and ↓ drug potency (Arranz et al. [35], n=274; Masellis et al. [31], n=185; Arranz et al. [36], n=153) • Tyr allele was significantly associated with poor response to clozapine treatment compared to the His allele (Arranz et al. [35], n=274; Masellis et al. [31], n=185; Arranz et al. [36], n=153) 	Clozapine and Risperidone
	T102C (rs6313)	A (n=661) C (n=503) H AS (n=504)	0.393 0.436 N/A 0.412	<ul style="list-style-type: none"> • C allele of T102C was more prevalent among non-responders for Clozapine (Arranz et al. [35], n=274) • For risperidone response, there is a significant association between the C/C genotype and better response (Lane et al. [37], n=100; Kim et al. [38], n=100) 	
	A-1438G (rs6311)	A (n=661) C (n=503) H AS (n=504)	0.409 0.437 N/A 0.412	<ul style="list-style-type: none"> • G/G genotype was less likely to respond to clozapine (Arranz et al. [35], n=274, Chen et al. [39], n=128) 	
HTR2C	Cys23Ser (rs6318)	A (n=661) C (n=503) H AS (n=504)	0.299 0.117 N/A 0.012	<ul style="list-style-type: none"> • Patients with Ser allele were more likely to respond to clozapine treatment compared to patients who are Cys/Cys homozygotes (n=162) 	Clozapine

DRD2	Ser311Cys (rs1801028)	A (n=661) C (n=503) H AS (n=504)	0.001 0.023 N/A 0.037	<ul style="list-style-type: none"> Inhibition of cAMP synthesis ↓ (Itokawa et al. [50], n=50) Ser/Ser genotype is more likely to respond to risperidone treatment (Lane et al. [29,49], n=123) 	Clozapine and Risperidone
	-141C (rs1799732)	Ins/Del A (n=661) C (n=503) H AS (n=504)	0.430 0.085 N/A 0.137	<ul style="list-style-type: none"> Del allele carriers had poor response to clozapine (Malhotra et al. [43], n=72) and took longer time to respond to risperidone (Lencz et al. [44], n=61) Patients with the Ins/Ins genotype are 54% more likely to respond to antipsychotic drugs than those with at least one copy of the Del allele (Zhang et al. [45], n=687) 	
	Taq1A (rs1800497)	A (n=661) C (n=503) H AS (n=504)	0.385 0.188 N/A 0.406	<ul style="list-style-type: none"> The A1 allele carriers were found to be more responsive to antipsychotic drugs (Suzuki et al. [47], n=25; n=57; Ikeda et al. [30], n=166) 	
	Taq1B (rs1079597)	A (n=661) C (n=503) H AS (n=504)	0.166 0.149 N/A 0.414	<ul style="list-style-type: none"> T allele is associated with a higher response rate in African Americans (Hwang et al. [46], n=232) 	
	A-241G (rs1799978)	A (n=661) C (n=503) H AS (n=504)	0.173 0.060 N/A 0.178	<ul style="list-style-type: none"> In Asian samples, the A allele or A/A genotype was associated with better improvement after risperidone treatment (Xing et al. [51], n=125; Ikeda et al. [30], n=120) but took a long time to respond to risperidone in the American sample (Lencz et al. [44], n=61) 	
DRD3	Ser9Gly (rs6280)	A (n=661) C (n=503) H AS (n=504)	0.181 0.336 N/A 0.306	<ul style="list-style-type: none"> The Gly 9 variant is associated with altered dopamine binding affinity and may ↑ DRD3 densities in some brain areas (Jeanneteau et al. [52], n=276) 	Clozapine and Risperidone

A: African, C: Caucasian and/or European, E: European, H: Hispanic, As: Asian, N/A: Not Available, n: sample size, FGA: First Generation Antipsychotic, PM: Poor Metabolizer, IM: Intermediate Metabolizer, UM: Ultrarapid Metabolizer, EM: Extensive Metabolizer, Del: Deletion, Ins: Insertion

Table 1: Genetic variation of eight genes involved in differences in treatment responses in various populations.

(PMs) typically cause Risperidone build up in the blood. Thus, there is a lower dose requirement to attain a therapeutic effect for PMs [21,22]. In contrast, ultra rapid metabolizers (UMs) are needed in higher doses to produce a therapeutic effect [23]. Moreover, the (Table 1) also shows difference of allele frequencies of CYP2D6-3B (rs35742686) between the Caucasian (19%) and Africa and American population (2%) as well as CYP2D6-4 (rs3892097) between the Caucasian (24%) and Hispanic (6.5%) populations. Because of inter-ethnic heterogeneity, the dosage established in a landmark trial and clinical pharmacogenetics applications for a certain population may not be generalizable to other ethnic populations and a follow-up study is often needed to find the maximum tolerated dose for different populations. This problem even exists in various ethnic sub-populations [24].

5HTT

Actions of antipsychotic medications are believed to be significantly mediated by the serotonin system. Second generation antipsychotics bind to the 2A serotonin receptors relative to the D2 dopamine receptors. Therefore, different genetic variations have been studied in order to examine their associations to drug responses. The gene responsible for the serotonin transporter is known as 5HTT and is located on chromosome 17q11.2. This transporter, an integral membrane protein, allows for the entry of serotonin into presynaptic neurons. As a result, serotonin is recycled in a sodium-dependent method [20]. In three studies, one with a sample composed of 200 Caucasian participants [25], one with a sample of 129 Chinese participants [26] and one with a sample of 56 Caucasian participants [27], a deficient response was associated with the short allele for the 5-HTTLPR polymorphism for Clozapine and Risperidone treatment (Table 1). Again, there are different allele frequencies of the 5-HTTLPR polymorphism among the Africa American (22%), Caucasian (8.9%) and Asia (13%) populations.

5HT6

Other variants of the serotonin system have been associated with drug efficacy, especially the 5HT6 gene. This gene codes for the 5HT6 serotonin receptor [20]. Two studies, one with a sample composed of 99 Chinese participants [28] and one with 123 Chinese participants

[29] have shown a notable association among the T/T genotype and an improved response to Clozapine and Risperidone treatment in Han Chinese participants [28,29]. However, two other studies, one with 120 Japanese participants [30] and one with 173 Caucasian and African American participants [31], did not show any association between the treatment response and genetic variance of the 5HT6 gene (Table 1).

COMT

The COMT gene, located on chromosome 22q11.21, codes for the catechol-O-methyltransferase (COMT) enzyme. Antipsychotic drugs, such as Risperidone and Clozapine employ their effect on the dopaminergic pathways. Because COMT is one of the major enzymes responsible for dopamine clearance, it may be able to control antipsychotic action [20]. Research has shown that there is decreased enzyme activity by 3-4 folds in individuals expressing the met/met genotype as compared to the val/val genotype [20]. When treated with several first generation antipsychotics (FGAs), a case-control study with 94 Caucasian participants showed that the met/met genotype showed a decrease response to the treatment [32]. Furthermore, a study with 86 Caucasian and African American participants confirmed the previous findings and showed that individuals with the met allele were found to exhibit a response to Clozapine and positively influence cognitive functions [33]. Intermediate enzyme function is associated with individuals heterozygous for met/val genotype [20]. However, a study with a small sample size (59 Caucasian participants) showed that individuals with a val/val genotype undergoing an eight-week long treatment regimen were less likely to respond to Clozapine treatment [34] (Table 1). Therefore, future replication and confirmation need to valid these findings. In addition, the findings of COMT-Val108Met (rs4680) also demonstrate ethnic variability in treatment response phenotypes and different allele frequencies among three populations (Table 1).

HTR2A

The gene HTR2A, located on chromosome 13q14-q21, codes for the 5-HT 2A receptor. This receptor is usually found in the cerebral cortex and is often linked to the negative symptoms found in schizophrenia

patients. According to Zhang and Malhotra [20], the polymorphism His452Tyr is associated with a decrease in calcium mobilization, in calcium release, and in activation of phospholipases. In in-vitro data, the Tyr variant demonstrated a smaller drug binding affinity and lowered Clozapine and Risperidone potency. Unlike the His allele, the Tyr allele is correlated to a lowered response to Clozapine treatment in three studies with 153 Caucasian participants [35], 185 Caucasian and African American participants [31], and 274 Caucasian participants [36]. Similarly, in a meta-analysis with 274 Caucasian participants, the Tyr/Tyr genotype was correlated to a lowered response to Clozapine [35]. For the T102C (rs6313) polymorphism, there was a higher predominance of the C allele in non-responders undergoing Clozapine treatment [35]. For Risperidone treatment, individuals with the C/C genotype demonstrated an improved response in two studies with 100 Chinese participants [37] and 100 Korean participants [38]. For the A-1438G (rs6311) polymorphism, individuals with the G/G genotype were shown to exhibit a decreased response to Clozapine treatment in two studies with 274 Caucasian participants [35] and 128 Chinese participants [39] (Table 1).

HTR2C

The gene HTR2C, located on chromosome Xq24, codes for the 5-HT_{2C} receptor. This receptor is usually found in the striatum, prefrontal cortex, and limbic system and it has a role in several pathways including memory, emotional processing, appetite, executive and motor functioning [20]. For the Cys23Ser polymorphism, a study with 162 Caucasian participants found that individuals with the Ser allele, unlike those who were homozygous for the Cys/Cys allele, had a higher rate of response to clozapine treatment [40]. However, three more recent studies one with 152 Caucasian participants [41], one with 185 Caucasian and African American participants [31], and one with 163 Caucasian participants [42] disagreed with this finding (Table 1). The current findings again suggest how complex and heterogeneity of genetics and treatment responses of clozapine among patients with schizophrenia. The contradictory findings might be due to the differences of the technique or genotype methods and the criteria to defined treatment responses used in different studies.

DRD2

The gene DRD2, located on chromosome 11q22, codes for the dopamine D₂ receptor [20]. In the -141C insertion/deletion polymorphism, carriers of the deletion allele exhibited an undesirable response to Clozapine in a study with 72 Caucasian and African American participants [43]. Furthermore, these carriers also exhibited a delayed response to Risperidone in a study with 61 Caucasian and African American participants [44]. On the other hand, individuals with the insertion/insertion genotype are more prone to exhibit a response to antipsychotic medication compared to individuals with one or more copies of the deletion allele in a meta-analysis with 687 participants [45]. The second polymorphism of the gene, the Taq1B polymorphism, particularly the T allele, has been linked to an increased response rate in African Americans in a study with 232 Caucasian and African American participants [46]. Carriers of the third polymorphism, Taq1A, showed a higher response to antipsychotic medications in three different studies, one with 25 Japanese participants [47], one with 57 Caucasian participants [48] and one with 120 Japanese participants [30]. Individuals with the Ser311Cys polymorphism, the fourth polymorphism of the gene, specifically the Ser/Ser genotype, were prone to respond to Risperidone treatment in a study with 123 Chinese participants [49] and demonstrated a decrease in cAMP synthesis inhibition in a study with 50 Japanese participants [50]. For the A-241G

polymorphism, Asian individuals with A allele or A/A genotype showed a positive improvement to Risperidone treatment in a study with 125 Chinese participants [51] and in study with 120 Japanese participants [30]. However, American individuals with the A allele or A/A genotype showed a delayed response to Risperidone treatment in a study with 61 Caucasian and African American participants [44]. Since these studies were conducted with different ethnic populations, slightly contradictory findings may be due to different allele frequencies of the markers in different ethnic populations (Table 1).

DRD3

The DRD3 gene, located on chromosome 3q13.3, codes for the D₃ dopamine receptor. This receptor is usually associated with the limbic system and basal ganglia. Because of its ability to inhibit spontaneous neurotransmitter transcription, this receptor plays a major role in neurotransmitter regulation [20]. For the Ser9Gly polymorphism, in the DRD3 gene, the Gly 9 variant was found to increase the affinity alteration of dopamine binding and seem to increase brain density in areas where DRD3 is found in individuals with this variant in a study with 30 French participants [52] (Table 1), however future study is needed to confirm these findings.

Discussion

Schizophrenia, a neuropsychiatric disorder, is known to be neurodevelopmentally progressive [1]. Due to the extensive interindividual variability found in the responses of patients, management of schizophrenia has proven to be challenging [3]. This interindividual variability to treatment could possibly be justified by the variation of the enzymes in charge of metabolizing medications, especially the enzyme system associated with cytochrome P450 (CYP) [3]. Evidence exists for the critical role genetic factors play in antipsychotic medication treatment response. Decades of investigations and clinical studies are beginning to provide results that may soon be translated into clinical practice. We evaluated over 51 publications including reviews, meta-analyses, and original studies related to clozapine and risperidone antipsychotic treatment for schizophrenia and pharmacogenetics. We identified eight genes (CYP2D6, 5HTT, 5HT6, COMT, HTR2A, HTR2C, DRD2 and DRD3) with likely associations with treatment response that may be good candidates for translation into clinical applications of pharmacogenetics. Moreover, we focused on the frequency of genetic polymorphisms in specific populations such as Caucasian/European, African American, Hispanic and Asian. Both researchers in the field of pharmacogenetics and clinicians could benefit from a greater awareness of genetic polymorphisms associated with antipsychotic treatment response and their frequencies in different populations.

Finally, there is a paucity of pharmacogenetics antipsychotic studies in populations other than Caucasian and Asian. However, there is sufficient evidence demonstrating ethnic variability in antipsychotic response phenotypes with carriers of the identical polymorphisms in the genes we reviewed. We can conclude that this evidence points to polygenic influence with possible linkage disequilibrium affecting treatment outcomes. In order to elucidate the cause of ethnic variability, additional studies with diverse populations are needed and results should be stratified by ethnicity. The potential for pharmacogenetics to improve treatment outcomes in the realm of psychiatric diseases is undoubtedly vast. A greater focus on population specific outcomes may simplify the challenges remaining in the field.

Some of the major difficulties that we encountered for antipsychotic

pharmacogenetic studies were linked to small sample sizes, insufficient information on minority populations, and outdated studies on clozapine and risperidone despite the fact that they are widely prescribed antipsychotic medications for schizophrenia. Therefore, future directions should be aimed towards 1) studies including larger sample sizes, 2) studies including a larger sample of minority populations, such as the Hispanics and other minorities, 3) studies focused on clozapine and risperidone antipsychotic treatment response.

References

- Gupta S, Kulhara P (2010) What is schizophrenia: A neurodevelopmental or neurodegenerative disorder or a combination of both? A critical analysis. *Indian J Psychiatry* 52: 21-27.
- Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, et al. (2013) Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 382: 951-962.
- Fleeman N, McLeod C, Bagust A, Beale S, Boland A, et al. (2010) The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics: A systematic review and economic evaluation. *Health Technol Assess* 14: 1-157.
- Mortensen PB, Pedersen CB, Westergaard T, Wohlfahrt J, Ewald H, et al. (1999) Effects of family history and place and season of birth on the risk of schizophrenia. *N Engl J Med* 340: 603-608.
- Naumovska Z, Nestorovska AK, Filipce A, Sterjev Z, Brezovska K, et al. (2015) Pharmacogenetics and antipsychotic treatment response. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)* 36: 53-67.
- Mackenzie B, Souza R, Likhodi O, Tiwari A, Zai C, et al. (2010) Pharmacogenetics of antipsychotic treatment response and side effects. *Therapy* 7: 191-198.
- Adam GI, Reneland R, Andersson M, Risinger C, Nilsson M, et al. (2000) Pharmacogenomics to predict drug response. *Pharmacogenomics* 1: 5-14.
- Clark SL, Souza RP, Adkins DE, Aberg K, Bukszar J, et al. (2013) Genome-wide association study of patient-rated and clinician-rated global impression of severity during antipsychotic treatment. *Pharmacogenet Genomics* 23: 69-77.
- Guengerich FP (2008) Cytochrome p450 and chemical toxicology. *Chem Res Toxicol* 21: 70-83.
- Scordo MG, Spina E (2002) Cytochrome P450 polymorphisms and response to antipsychotic therapy. *Pharmacogenomics* 3: 201-218.
- Brandl EJ, Kennedy JL, Müller DJ (2014) Pharmacogenetics of antipsychotics. *Can J Psychiatry* 59: 76-88.
- Andreassen OA, MacEwan T, Gulbrandsen AK, McCreddie RG, Steen VM (1997) Non-functional CYP2D6 alleles and risk for neuroleptic-induced movement disorders in schizophrenic patients. *Psychopharmacology (Berl)* 131: 174-179.
- Dahl ML (2002) Cytochrome p450 phenotyping/genotyping in patients receiving antipsychotics: Useful aid to prescribing? *Clin Pharmacokinet* 41: 453-470.
- Ingelman-Sundberg M (2005) Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): Clinical consequences, evolutionary aspects and functional diversity. *Pharmacogenomics* 5: 6-13.
- Cichon S, Nöthen MM, Rietschel M, Propping P (2000) Pharmacogenetics of schizophrenia. *Am J Med Genet* 97: 98-106.
- Kirchheiner J, Nickchen K, Bauer M, Wong ML, Licinio J, et al. (2004) Pharmacogenetics of antidepressants and antipsychotics: The contribution of allelic variations to the phenotype of drug response. *Mol Psychiatry* 9: 442-473.
- Mroziewicz M, Tyndale RF (2010) Pharmacogenetics: A tool for identifying genetic factors in drug dependence and response to treatment. *Addict Sci Clin Pract* 5: 17-29.
- Almoguera B, Riveiro-Alvarez R, Lopez-Castroman J, Dorado P, Vaquero-Lorenzo C, et al. (2013) Association of common genetic variants with risperidone adverse events in a Spanish schizophrenic population. *Pharmacogenomics* 13: 197-204.
- Rajkumar AP, Poonkuzhali B, Kuruvilla A, Srivastava A, Jacob M, et al. (2012) Outcome definitions and clinical predictors influence pharmacogenetic associations between HTR3A gene polymorphisms and response to clozapine in patients with schizophrenia. *Psychopharmacology (Berl)* 224: 441-449.
- Zhang JP, Malhotra AK (2011) Pharmacogenetics and antipsychotics: Therapeutic efficacy and side effects prediction. *Expert Opin Drug Metab Toxicol* 7: 9-37.
- Kakihara S, Yoshimura R, Shinkai K, Matsumoto C, Goto M, et al. (2005) Prediction of response to risperidone treatment with respect to plasma concentrations of risperidone, catecholamine metabolites, and polymorphism of cytochrome P450 2D6. *Int Clin Psychopharmacol* 20: 71-78.
- Riedel M, Schwarz MJ, Strassnig M, Spellmann I, Muller-Arends A, et al. (2005) Risperidone plasma levels, clinical response and side-effects. *Eur Arch Psychiatry Clin Neurosci* 255: 261-268.
- Arranz MJ, de Leon J (2007) Pharmacogenetics and pharmacogenomics of schizophrenia: A review of last decade of research. *Mol Psychiatry* 12: 707-747.
- Drozda K, Müller DJ, Bishop JR (2014) Pharmacogenomic testing for neuropsychiatric drugs: Current status of drug labeling, guidelines for using genetic information, and test options. *Pharmacotherapy* 34: 166-184.
- Arranz MJ, Munro J, Birkett J, Bolonna A, Mancama D, et al. (2000) Pharmacogenetic prediction of clozapine response. *Lancet* 355: 1615-1616.
- Wang L, Yu L, He G, Zhang J, Zhang AP, et al. (2007) Response of risperidone treatment may be associated with polymorphisms of HTT gene in Chinese schizophrenia patients. *Neurosci Lett* 414: 1-4.
- Dolzan V, Serretti A, Mandelli L, Koprivsek J, Kastelic M, et al. (2008) Acute antipsychotic efficacy and side effects in schizophrenia: Association with serotonin transporter promoter genotypes. *Prog Neuropsychopharmacol Biol Psychiatry* 32: 1562-1566.
- Yu YW, Tsai SJ, Lin CH, Hsu CP, Yang KH, et al. (1999) Serotonin-6 receptor variant (C267T) and clinical response to clozapine. *Neuroreport* 10: 1231-1233.
- Lane HY, Lin CC, Huang CH, Chang YC, Hsu SK, et al. (2004) Risperidone response and 5-HT6 receptor gene variance: Genetic association analysis with adjustment for non-genetic confounders. *Schizophr Res* 67: 63-70.
- Ikeda M, Yamanouchi Y, Kinoshita Y, Kitajima T, Yoshimura R, et al. (2008) Variants of dopamine and serotonin candidate genes as predictors of response to risperidone treatment in first-episode schizophrenia. *Pharmacogenomics* 9: 1437-1443.
- Maselli M, Basile V, Meltzer HY, Lieberman JA, Sevy S, et al. (1998) Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. *Neuropsychopharmacology* 19: 123-132.
- Illi A, Mattila KM, Kampman O, Anttila S, Roivas M, et al. (2003) Catechol-O-methyltransferase and monoamine oxidase A genotypes and drug response to conventional neuroleptics in schizophrenia. *J Clin Psychopharmacol* 23: 429-434.
- Woodward ND, Jayatilake K, Meltzer HY (2007) COMT val108/158met genotype, cognitive function and cognitive improvement with clozapine in schizophrenia. *Schizophr Res* 90: 86-96.
- Bertolino A, Caforio G, Blasi G, Rampino A, Nardini M, et al. (2007) COMT Val158Met polymorphism predicts negative symptoms response to treatment with olanzapine in schizophrenia. *Schizophr Res* 95: 253-255.
- Arranz MJ, Munro J, Owen MJ, Spurlock G, Sham PC, et al. (1998) Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT2A receptor gene and response to clozapine. *Mol Psychiatry* 3: 61-66.
- Arranz MJ, Collier DA, Munro J, Sham P, Kirov G, et al. (1996) Analysis of a structural polymorphism in the 5-HT2A receptor and clinical response to clozapine. *Neurosci Lett* 217: 177-178.
- Lane HY, Chang YC, Chiu CC, Chen ML, Hsieh MH, et al. (2002) Association of risperidone treatment response with a polymorphism in the 5-HT(2A) receptor gene. *Am J Psychiatry* 159: 1593-1595.
- Kim B, Choi EY, Kim CY, Song K, Joo YH (2008) Could HTR2A T102C and DRD3 Ser9Gly predict clinical improvement in patients with acutely exacerbated schizophrenia? Results from treatment responses to risperidone in a naturalistic setting. *Hum Psychopharmacol* 23: 61-67.
- Chen SF, Shen YC, Chen CH (2009) HTR2A A-1438G/T102C polymorphisms predict negative symptoms performance upon aripiprazole treatment in schizophrenic patients. *Psychopharmacology (Berl)* 205: 285-292.
- Sodhi MS, Arranz MJ, Curtis D, Ball DM, Sham P, et al. (1995) Association between clozapine response and allelic variation in the 5-HT2C receptor gene. *Neuroreport* 7: 169-172.

41. Rietschel M, Naber D, Fimmers R, Moller HJ, Propping P, et al. (1997) Efficacy and side-effects of clozapine not associated with variation in the 5-HT_{2C} receptor. *Neuroreport* 8: 1999-2003.
42. Schumacher J, Schulze TG, Wienker TF, Rietschel M, Nöthen MM (2000) Pharmacogenetics of the clozapine response. *Lancet* 356: 506-507.
43. Malhotra AK, Buchanan RW, Kim S, Kestler L, Breier A, et al. (1999) Allelic variation in the promoter region of the dopamine D-2 receptor gene and clozapine response. *Schizophrenia research* 36: 92-93.
44. Lencz T, Robinson DG, Xu K, Ekholm J, Sevy S, et al. (2006) DRD2 promoter region variation as a predictor of sustained response to antipsychotic medication in first-episode schizophrenia patients. *The Am J Psychiatry* 163: 529-531.
45. Zhang JP, Lencz T, Malhotra AK (2010) D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis. *Am J Psychiatry* 167: 763-772.
46. Hwang R, Shinkai T, De Luca V, Müller DJ, Ni X, et al. (2005) Association study of 12 polymorphisms spanning the dopamine D(2) receptor gene and clozapine treatment response in two treatment refractory/intolerant populations. *Psychopharmacology (Berl)* 181: 179-187.
47. Suzuki A, Mihara K, Kondo T, Tanaka O, Nagashima U, et al. (2000) The relationship between dopamine D2 receptor polymorphism at the Taq1 A locus and therapeutic response to nemonapride, a selective dopamine antagonist, in schizophrenic patients. *Pharmacogenetics* 10: 335-341.
48. Schäfer M, Rujescu D, Giegling I, Guntermann A, Erfurth A, et al. (2001) Association of short-term response to haloperidol treatment with a polymorphism in the dopamine D(2) receptor gene. *Am J Psychiatry* 158: 802-804.
49. Lane HY, Lee CC, Chang YC, Lu CT, Huang CH, et al. (2004) Effects of dopamine D2 receptor Ser311Cys polymorphism and clinical factors on risperidone efficacy for positive and negative symptoms and social function. *Int J Neuropsychopharmacol* 7: 461-470.
50. Itokawa M, Arinami T, Futamura N, Hamaguchi H, Toru M (1993) A structural polymorphism of human dopamine D2 receptor, D2(Ser311-->Cys). *Biochem Biophys Res Commun* 196: 1369-1375.
51. Xing Q, Qian X, Li H, Wong S, Wu S, et al. (2007) The relationship between the therapeutic response to risperidone and the dopamine D2 receptor polymorphism in Chinese schizophrenia patients. *Int J Neuropsychopharmacol* 10: 631-637.
52. Jeanneteau F, Funalot B, Jankovic J, Deng H, Lagarde JP, et al. (2006) A functional variant of the dopamine D3 receptor is associated with risk and age-at-onset of essential tremor. *Proc Natl Acad Sci U S A* 103: 10753-10758.

Citation: Cho M, Contreras A, Garza A, Olvera S, Castillo D, et al. (2017) The Impact of Drug and Gene Interaction on the Antipsychotic Medication for Schizophrenia. *Bipolar Disord* 3: 117. doi: [10.4172/2472-1077.1000117](https://doi.org/10.4172/2472-1077.1000117)