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Understanding the Pharmacogenomics of Anti-depressant Response: Insights from Pharmacy, Laboratory Science, Nursing and Psychology

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ABSTRACT

Introduction: Drug response and side effect development have been shown to vary significantly amongst individuals receiving pharmacotherapy for neuropsychiatric diseases including depression. As a fundamental component of personalized medicine, pharmacogenetics seeks to maximize treatment based on each patient's unique genetic profile by focusing on genetic variants implicated in pharmacokinetic or pharmacodynamic processes. Pharmacodynamic variability is the outcome of an active drug's fluctuating interactions with its target molecules, while pharmacokinetic variability is the consequence of changes in a drug's absorption, distribution, metabolism, and elimination.

Aim of work: To provide a comprehensive assessment of the pharmacogenomics of anti-depressant response.

Methods: Using the following search keywords, we performed a thorough search of the electronic literature in the MEDLINE database: pharmacogenomics, anti-depressant, response,

pharmacy, laboratory, nursing, and psychology. To find relevant literature, the search was limited to articles from 2016 to 2021. I looked through scholarly articles related to my topic by doing a search on Google Scholar. Certain inclusion criteria influenced the articles that were chosen.

Results: The study's analysis included papers that were published between 2015 and 2021. The research was divided up into several parts, each having a header for the discussion portion.

Conclusion: Because pharmacogenetics can precisely predict the clinical outcomes of antidepressant and anxiolytic pharmaceutical usage, it may be able to enhance neuropsychiatric therapy. Genotype-guided therapy decreased unpleasant responses, as shown by the PREPARE trial. Genetic variants that impact transporters, receptors, and metabolizing enzymes are examples of potential pharmacogenetic scenarios. Making educated judgments about prescribing antidepressants may be aided by epigenetic profiles. Nevertheless, further experiments are required to resolve methodological issues and validate current findings. With its potential to improve clinical recommendations, save costs, speed up delivery, and have positive effects on both health and the economy, pharmacogenetics may eventually be used routinely in neuropsychiatric clinical settings.

Keywords: Pharmacogenomics, Anti-depressant, Response, Pharmacy, Laboratory, Nursing and Psychology

INTRODUCTION

Neuropsychiatric diseases, such as anxiety and depression, have been treated with pharmaceutical responses that vary greatly and with significant side effects. This has been acknowledged as a significant issue in clinical practice (Willner et al., 2019). In addition to a range of environmental, physiological, and psychological influences, inherited factors may account for a significant portion of these individual variances. In an attempt to find genetic variations that would indicate which patients would benefit most from certain tailored therapies, many pharmacogenetic studies have been carried out (Xin et al., 2020). Potential genes linked to drug action (pharmacodynamics) and drug metabolism and transport (pharmacokinetics) have been the main focus of pharmacogenetic research. These genes may influence both the effectiveness of therapy and the probability of adverse medication reactions. When it comes to the transportation of medications and their active byproducts to their intended targets or their removal from them, pharmacokinetics examines variations in a drug's absorption, distribution, metabolization, and elimination (ADME) (Shalimova et al., 2021). The ADME processes include the enzymes responsible for drug metabolism as well as the drug transport molecules that aid in drug absorption and elimination. The cytochrome P450 (CYP) and multidrug resistance (MDR) gene families have attracted a lot of attention in this particular setting, according to Pinna et al.'s thorough analysis (2021). The CYP450 enzyme family in the liver is responsible for the metabolism of some medications used to treat mental illness. The genotype of certain CYPs influences drug levels in blood and plasma, which impacts the effectiveness of the treatments and the possibility of adverse effects (Van Westrhenen et al.,

2020). There are four basic CYP phenotypes: ultrarapid metabolizer (UM), extended metabolizer (EM), poor metabolizer (PM), and intermediate metabolizer (IM). These phenotypes are caused by combinations of various alleles with varying degrees of enzyme activity. Pharmacogenetic study indicates that people with poor metabolizer (PM) status often have greater blood levels of the medication; as a result, they may need lower prescription doses to get the desired therapeutic benefits. Ultra-rapid metabolizers (UMs) on the other hand may need larger doses of drugs to have the same therapeutic effects since they eliminate drugs from their bodies more quickly (Shetty, 2019).

Furthermore, the efficacy of psychiatric medications depends on their capacity to enter the brain. While some molecules may passively diffuse across the brain-blood barrier (BBB), most chemicals are actively regulated by a complex network of transporters that affect both the pharmacokinetics (how medications are metabolized in the body) and pharmacodynamics (how they affect the body). If the functional activity or expression of transport proteins in the blood-brain barrier (BBB) decreases for a genetically defined reason, drug clearance from the brain into the circulation is disturbed. This might result in prolonged drug exposure in the brain, drug buildup during long-term treatment, and an increased chance of experiencing severe side effects. (Wyska, 2019).

However, pharmacogenetics is not a complete explanation for all heritable differences in drug reactions. A growing corpus of evidence suggests that a person's epigenetic state might potentially influence a medication's effectiveness (Cascorbi and Schwab, 2016). Pharmacoepigenetics is a new area of study that examines how epigenetic processes—which have the power to regulate gene expression without changing genetic code—may affect people's reactions to medications (Lauschke et al., 2019). Frequently researched epigenetic alterations include DNA methylation, noncoding RNA activity, and histone modifications (Cascorbi and Schwab, 2016). Epigenetic modifications may be inherited by subsequent generations and are caused by a variety of environmental variables, such as diet, stress, and drugs (Tuscher and Day, 2019). Stress, both acute and chronic, may influence the development and progression of a number of neuropsychiatric disorders, such as anxiety and depression. Moreover, stress has the potential to modify the epigenome, which may affect the expression of genes related to target molecules, transport, and drug metabolism. Thus, this could have an impact on the variance in responses to depressive and anxiolytic drugs across individuals (Park et al., 2019). This review summarizes and discusses the key discoveries from pharmacogenetic and pharmacoepigenetic studies on antidepressants, which are often used to treat depression.

AIM OF WORK

To provide a comprehensive assessment of the pharmacogenomics of anti-depressant response.

METHODS

We performed a thorough search using particular keywords like pharmacogenomics, anti-depressant, response, pharmacy, laboratory, nursing, and psychology on reputable scientific platforms like Pubmed and Google Scholar.

The goal was to include every relevant study articles. A set of criteria was used to choose the articles. After a thorough examination of the noteworthy titles and abstracts of every publication, we excluded case studies, duplicate papers, and publications without complete information. The research's reviews were published between 2015 and 2021.

RESULTS

The current investigation concentrated on pharmacogenomics of anti-depressant response between 2015 and 2021. As a result, the review was published under many headlines in the discussion area, including: Pharmacogenetics of Antidepressants, Anti-depressant Pharmacogenomics Evidence Psychiatry

DISCUSSION

1. Pharmacogenetics of Antidepressants

Antidepressants are often prescribed medications for the treatment of depression and anxiety. It's important to keep in mind that only 50% of patients react effectively to these medications, and only 33% of patients fully recover from their symptoms (Helton and Lohoff, 2015). According to Cababelos and Torrellas (2015), genetic factors account for more than 60% of the variance in the response to an adverse effect of various antidepressant medications, such as monoamine oxidase inhibitors (MAOIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic and tetracyclic compounds, monoamine oxidase inhibitors (SSRIs), and noradrenergic and serotonergic modulators. Therefore, it is essential to take into account an individual's genetic profile while selecting an antidepressant and figuring out the appropriate dose. Still, not much is understood about how genetic variations impact the body's capacity to absorb, distribute, metabolize, and excrete antidepressant drugs, as well as how they impact other physiological systems. This is the case even with current research. If medical professionals can determine the hereditary characteristics that influence the spectrum of reactions to antidepressants, it may be simpler for them to choose the appropriate antidepressant, dose, and course of therapy for each patient. As a result, the use of precision medicine may boost antidepressant treatment efficacy while lowering the risk of negative medication responses.

1.1 Pharmacodynamics

Tryptophan Hydroxylase (TPH)

Tryptophan is converted into the amino acid 5-hydroxytryptophan with the help of the enzyme TPH. A neurotransmitter called serotonin controls mood, hunger, sleep cycles, and how the body reacts to stress. Its synthesis begins with this conversion (Kuhn and Hasegawa, 2020). Different genes produce the TPH1 and TPH2 isoforms of the enzyme. TPH1 is mostly expressed in peripheral tissues such the pineal gland, skin, and stomach, while TPH2 is generally expressed in neurons within the central nervous system. The two isoforms show comparable enzymatic activity, despite differences in regulation, tissue distribution, and developmental expression

patterns. Although TPH1's expression in the brain is often lower than that of TPH2, it seems to have a significant impact on mood and stress management and may be implicated in the effects of antidepressant medications (Tao et al., 2018). Variations in serotonin synthesis have been linked to many TPH gene variations. Certain variations of these genetic traits have been associated with an increased chance of developing mental health disorders. Research has examined how TPH gene editing may be used to treat depression, anxiety, and addiction, among other mental health conditions (Kulikova and Kulikov, 2019). On the relationship between TPH polymorphisms and SSRI responsiveness, however, some research has produced conflicting findings (Fabbri and Serretti, 2016).

Monoamine Oxidases (MAO)

The breakdown of monoamine neurotransmitters by the central nervous system depends on a family of enzymes called MAOs (Yeung et al., 2019). The two separate kinds of MAOs, known as MAO-A and MAO-B, are produced by different genes. MAO-A and MAO-B are found in the neurons and astrocytes that make up the central nervous system. MAO-A catabolizes many important monoamine neurotransmitters, including as serotonin, norepinephrine, and dopamine. According to Jones and Raghanti (2021) neurotransmitters are essential for controlling behavior, emotion, and cognitive functions. Numerous genetic variations of the MAOA gene have been linked to variations in enzyme activity and monoamine metabolism. Furthermore, a higher risk of mental health issues has been associated with some genetic variations (Jones and Raghanti, 2021). The connection between the many MAOA gene variations and mental illnesses is unknown, however. Variations in the MAO gene have also been studied to determine whether they may influence a person's sensitivity to antidepressants. Several studies have shown that certain genetic variations in MAO genes may influence the metabolism of antidepressants, hence influencing the effectiveness and side effects of the drugs. For instance, those with a particular type of the MAOA gene responded better to fluvoxamine than people without this mutation (RASHMI et al., 2020). Furthermore, a different research found that the gender-specific polymorphisms of the MAOA rs979605 may affect an individual's response to antidepressant medication (Kang et al., 2020).

Catechol-O-Methyltransferase (COMT)

The breakdown of catecholamines, including dopamine, epinephrine, and norepinephrine, requires the enzyme COMT. The COMT gene has several variations, the most well-studied of which is the rs4680 polymorphism, sometimes referred to as Val158Met (Srivastava et al., 2021). The enzyme catechol-O-methyltransferase (COMT) has valine (Val) at position 158 rather than methionine (Met) due to a single nucleotide polymorphism (SNP). Higher levels of the Val allele and lower levels of the Met allele are correlated with COMT activity. As so, the Met/Met genotype is associated with the lowest degree of COMT activity, the Val/Met genotype with intermediate activity, and the Val/Val genotype with the greatest level of activity. The COMT Val158Met polymorphism has been connected to a number of mental diseases, such as depression, anxiety, and schizophrenia (Srivastava et al., 2021). Additionally, research has connected the COMT Val158Met polymorphism to the reaction to selective serotonin reuptake

inhibitors (SSRIs), such fluoxetine and paroxetine. According to a research by He et al. (2020), the Val/Met genotype significantly affects fluvoxamine responsiveness. Furthermore, there is a suggestion that the way the COMT genotype influences the response to antidepressants may be influenced by other variables, including the specific medicine used, the severity and duration of depression, and other genetic and environmental factors. However, Brunoni et al. (2020) found no evidence of a significant correlation between COMT mutations and the effectiveness of escitalopram therapy.

1.2 Pharmacokinetics

The broad family of enzymes known as CYP450 breaks down and processes a wide range of medicines and xenobiotics, including those used to treat depression. The CYP450 enzymes CYP2D6, CYP2C19, CYP3A4, CYP1A2, CYP2B6, CYP2C8, and CYP2C9 are critical for the metabolism of several psychiatric drugs (He et al., 2020). Several CYP enzymes may digest a single medicine, and distinct CYP450 enzymes may metabolize various pharmaceuticals (Van Westrhenen et al., 2020). Individual variances in the metabolism and responsiveness to antidepressant medications may arise from genetic variants that affect the activity of these enzymes. The bulk of the genes encoding cytochrome P450 enzymes (CYPs) exhibit significant genetic variability (Samardzic et al., 2017). It is crucial to do research on how CYP polymorphisms affect medication metabolism in the field of personalized medicine. Despite the discovery of approximately 2000 mutations in CYP genes, only a small number of Single Nucleotide Polymorphisms (SNPs) are known to impact CYP enzymatic function (Van Westrhenen et al., 2020). Individuals may be categorized into four main CYP phenotypes: ultrarapid metabolizers, moderate metabolizers, extensive metabolizers (considered usual), and poor metabolizers, depending on the genetic variations that impact enzyme activity (Shetty, 2019). The CYP enzyme is either completely absent in IMs or very weakly active in PMs due to genetic differences. Due to a slower rate of drug breakdown, those classified as poor metabolizers (PMs) or intermediate metabolizers (IMs) may be more vulnerable to negative pharmacological effects from antidepressant drugs. Patients may thus need to reduce the amount of their antidepressant prescriptions or change their dosing schedule less often. NMs do, however, exhibit conventional drug metabolism rates and enzyme activity. On the other hand, UMs' elevated enzymatic activity quickens the digestion of medications. People with depression may thus need greater antidepressant dosages or more frequent medication administration in order to achieve the intended therapeutic effect (Shetty, 2019).

2. Anti-depressant Pharmacogenomics Evidence Psychiatry

Research on major depressive illness accounts for the majority of the information about the effects of antidepressants on hereditary factors. Most of these studies have concentrated on the physiological pathways that antidepressants employ to metabolize; these subjects have been extensively discussed in earlier works (Hicks et al., 2015). In conclusion, research has linked genetic variations in CYP2C19 and CYP2D6 to blood levels of antidepressants, adverse drug responses, and, to a lesser degree, treatment outcomes including halting or improving symptoms (Hicks et al., 2015). The Munich Antidepressant Response Signature (MARS) (Probst-

Schendzielorz et al., 2015), the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study Pigott, H. E. (2015), the Genome-based Therapeutic Drugs for Depression (GENDEP) project (Lin and Lane, 2015), and the International SSRI Pharmacogenomics Consortium GWAS analysis (Biernacka et al., 2015) have all consistently failed to identify a specific gene variant related to pharmacodynamic effects that can accurately predict the response to antidepressant treatment. The Pharmacogenomics Knowledgebase (PharmGKB) contains clinical annotations that describe associations between the effectiveness of antidepressants and potentially relevant genes, including glutamate ionotropic receptor kainate 4 (GRIK4), FKBP5 (FK506 binding protein 5), serotonin transporter SLC6A4, and serotonin 2A receptor HTR2A. On the other hand, the evidence for the links is merely moderate to weak. (2020, Singh).

Opinions vary on the role that PGx testing plays in the prescribing of antidepressants. The US Food and Drug Administration (FDA) has released a safety statement cautioning against using PGx testing to guide antidepressant prescription due to a lack of evidence (FDA, 2019). However, as we previously said, published PGx-based prescription recommendations or product labeling have included 17 antidepressants due to correlations with CYP2C19 and/or CYP2D6. According to the Clinical Pharmacogenetic Implementation Consortium (CPIC) recommendations for CYP2C19 PMs, citalopram, escitalopram, sertraline, and tertiary amine tricyclic antidepressants (like amitriptyline) should be started at a 50% lower dosage. Nevertheless, owing to insufficient blood levels of the antidepressants in circulation, RMs/UMs treated with citalopram, escitalopram, and tertiary amine tricyclic antidepressants would probably not respond well to therapy (Hicks et al., 2017). As a result, they could benefit from switching to a different antidepressant. PMs with CYP2D6 should cut their doses of most tricyclic antidepressants, fluvoxamine, and paroxetine by up to 50%, while CPIC encourages UMs to choose an alternative antidepressant that is not largely metabolized by CYP2D6. Additionally, according to Van Schaik et al. (2020), the Dutch Pharmacogenetics Working Group (DPWG) recommends a lower dosage of venlafaxine (amount unknown) for CYP2D6 PMs and an increase of up to 150% for UMs.

CONCLUSION

Because pharmacogenetics can precisely predict the clinical outcomes of antidepressant and anxiolytic pharmaceutical usage, it may improve the treatment of neuropsychiatric disorders. This entails assessing the therapy's efficacy and locating any possible side effects. The large-scale PREPARE trial showed that the use of genotype-guided therapy with a 12-gene pharmacogenetic panel dramatically decreased the incidence of major adverse drug responses. The findings of this research demonstrate that, in order to increase the safety of pharmacological treatment on a broad scale, it is both feasible and advantageous to use a panel-based pharmacogenetic testing approach.

Genetic variants that affect the P-glycoprotein ABC transporter, the metabolizing cytochrome CYP450 and UGT enzymes, as well as the transporters, receptors, and enzymes involved in the metabolism of monoamines and GABA, are the most promising pharmacogenetic candidates for antidepressant medication. A number of gene candidates—some of which are among them—

have shown modified stress responses as a result of epigenetic modifications. This raises the possibility of utilizing epigenetic profiles to guide clinically meaningful antidepressant prescription choices.

While pharmacogenetic research has shown that using antidepressants and anxiolytics more safely and effectively when treatment decisions are made based on genotype, more carefully planned trials are required to address a number of methodological issues and validate the pharmacogenetic findings that have already been made. The high expense of molecular testing, their scarcity, and the difficulties in interpreting the results are the primary obstacles to pharmacogenetic research that examines both pharmacokinetic and pharmacodynamic variability. In neuropsychiatric clinical settings, pharmacogenetics—a crucial component of personalized medicine—has the potential to become standard procedure. More proof of its financial and health advantages, better clinical guidelines, lower prices, and faster delivery times are some ways to accomplish this. Nevertheless, pharmacoepigenetics is still in its infancy, despite the fact that pharmacogenetic research has advanced significantly. Therefore, greater study on the relationship between pharmacological responses and epigenetic alterations is needed in order to tailor antidepressant therapy.

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