Pharmacogenetics related to classical antidepressants.

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Abstract. Pharmacogenetics represents an important field to be considered in the search for personalized medical treatments, gaining prominence in the response to antidepressants due to the remarkable variability in patient reactions and the high resistance rate to these classic treatments. Pharmacogenetics analyzes the effects of specific genes on drug response. In the case of antidepressants, pharmacogenetics looks at how particular genes can influence how the body processes these medications. Variations in genes related to drug metabolism are identified in people using classic antidepressants, such as in the CYP450 enzymatic system, which plays a crucial role in the metabolization of antidepressants. CYP450 genetic variations can control the speed and efficiency of metabolization, affecting the effective concentration in the blood and, thus, the response to treatment. Genetic variations in neurotransmitters and their transporters influence different reactions in each individual, especially serotonin and noradrenaline, which are closely related to mood regulation and the main targets of classic antidepressants. Genetic variations in the genes of these neurotransmitters and their transporters can impact the response to pharmacological treatment. Despite the promises of pharmacogenetics in personalized medicines, ethical issues and ongoing research are essential for practical and responsible application. This review addresses pharmacogenetics in the effect of classical antidepressants, focusing on variations in the CYP450 system and neurotransmitters and their transporters.

Keywords. Pharmacogenetics, antidepressants, depression, genes.

1. Introduction

Pharmacogenetics has emerged as an essential field in the search for personalized and effective medical treatments. In particular, the application of pharmacogenetics to the response to classical antidepressants has attracted considerable attention because of the significant variability in patient responses to these medications [1].

Classical antidepressants are widely used to treat depression and other mood-related disorders. However, the effectiveness of these medications can vary considerably from person to person. Some patients respond well and experience significant improvement in their symptoms, while others may not respond or even experience intolerable side effects [2].

The variability in response to classical antidepressants is attributed to genetic and environmental factors. However, genetic factors play an essential role in this variability. Differences in metabolic enzymes, neurotransmitter transport systems, neurotransmitter receptors, and other proteins related to the central nervous system can be influenced by genetic variants [3].

Pharmacogenetics has the potential to help clinicians choose the most appropriate antidepressant for each patient based on their genetic makeup. This can lead to more personalized and effective treatments, reducing ineffective treatment attempts' time and side effects. Genetic testing can be performed to identify relevant genetic variants that may influence response to classic antidepressants, helping to guide treatment decisions [4].

This article explores how pharmacogenetics is crucial in understanding individual responses to classic antidepressants.

2. Pharmacogenetics and Pharmacogenomics

It is essential to understand the distinction between the terms pharmacogenetics and pharmacogenomics. Both fields are concerned with genetic influence on drug response but differ in scope and approach [5].

Pharmacogenetics studies individual genetic variations that affect how a person responds to medications. It focuses on specific genes influencing patients' responses to certain treatments, considering factors such as drug metabolism, effectiveness, and possible side effects [6].

Pharmacogenetics seeks to understand how genetic differences between individuals can explain why some people can process drugs more effectively while others can have adverse reactions [6].

On the other hand, pharmacogenomics broadens this scope by considering multiple genes and their interactions [5].

3. Variation in response to classic antidepressants

Classic antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs) have been used for decades to treat depressive disorders [1].

However, the variability in patient responses to these medications has been a persistent challenge. Some patients experience relief of symptoms with remarkable efficacy, while about 30% do not see significant improvements even after two or more treatment trials of classical antidepressants [2].

The ineffectiveness of classic antidepressants represents a significant challenge in psychopharmacology, leaving many individuals with depressive disorders without adequate relief, resulting in persistent distress, functional decline, and a negative impact on quality of life, often known as antidepressant resistance [7].

This scenario has driven continuous research in search of innovative and personalized therapeutic approaches for depression, encompassing new drugs, combination therapies, and interventions based on a deeper understanding of the underlying neurobiology [8].

4. Influence of individual genes on response to antidepressants

Variation in response to antidepressants has been partly linked to genetic diversity among individuals. The expression and function of specific genes are crucial in determining how a person will respond to these medications [9].

Genes that encode enzymes responsible for the metabolism of antidepressants can influence the speed at which the drug is processed and eliminated from the body, thus affecting its effectiveness and potential side effects [10].

In addition, genes related to the transmission of neurotransmitter signals, such as those encoding serotonin and norepinephrine receptors, may influence how the brain responds to the effects of antidepressants [11].

It is also important to highlight that genes involved in regulating gene expression in brain areas associated with mood control may play a crucial role in the effectiveness of antidepressants since they influence neuronal plasticity and emotional regulation circuits [10].

5. CYP450 and antidepressant metabolism

Different plasma concentrations of antidepressant medications are identified in individuals who received the same dose, and a significant part of this variation can be attributed to the activity of cytochrome P450 (CYP450) enzymes. The CYP450 enzyme system metabolizes many drugs, including antidepressants [12].

Specific genetic variants within the CYP450 enzyme genes can result in variations in the speed and efficiency with which antidepressants are metabolized. This can lead to differences in the effective concentration of the antidepressant in the body, which can influence the response to treatment [13].

Individuals who metabolize antidepressants too quickly may experience inadequate drug levels, reducing effectiveness. In contrast, those who metabolize them slowly may have higher drug levels and a greater risk of side effects [13].

6. Neurotransmitter transporters and individual sensitivity

Another determining factor in the individual response to antidepressants is related to neurotransmitter transporters, which play a crucial role in regulating the reuptake of substances such as serotonin and noradrenaline. These neurotransmitters are closely linked to mood regulation and are among the main targets of antidepressants. Genetic variations in the genes encoding these transporters can significantly impact individual sensitivity to antidepressants that act on these systems [1].

In particular, the serotonin (SERT) and noradrenaline (NET) transporters are relevant. Studies have shown that genetic polymorphisms in the genes responsible for encoding SERT and NET can influence the rate of reuptake of these neurotransmitters, thus affecting the availability of

these chemical signals in the synaptic space [14]. This altered availability can directly influence the effectiveness of antidepressants that aim to increase the concentration of these neurotransmitters in the brain. For example, individuals with genetic variations that result in lower levels of serotonin transport may be more sensitive to the effects of antidepressants that increase the activity of this neurotransmitter [14].

A relevant study examined how genetic variations in the serotonin transporter gene-linked polymorphic region (5-HTTLPR) affect response to antidepressant treatment. It was found that patients with the genotype associated with lower serotonin transporter expression had lower response rates to selective serotonin reuptake inhibitor (SSRI) antidepressants [15, 16].

In the context of noradrenaline, one study investigated the influence of polymorphisms in the NET gene on the response to antidepressant treatment in patients with major depression. The results indicated that specific polymorphisms were associated with different levels of response to antidepressants that affect noradrenaline, suggesting that genetic variations in NET may influence the effectiveness of these drugs [17].

7. Ethical considerations and the future of pharmacogenetics

The application of pharmacogenetics in clinical practice has the potential to revolutionize the approach to treating depression and other psychiatric disorders, offering the promise of personalized and more effective therapies [18].

By considering individual genetic profiles, clinicians can gain a more accurate view of how each patient is likely to respond to different antidepressants, thereby minimizing the trial-and-error process that often occurs in selecting treatments. This can reduce the time required to achieve an adequate therapeutic response and improve the patient's quality of life [18].

However, this approach also raises important ethical issues that must be addressed. Genetic privacy is crucial, as genetic analysis can reveal sensitive information about genetic predisposition to mental disorders and other medical conditions. Ensuring that patients' genetic information is protected and its use is consented to is crucial to preventing abuse and preserving trust in personalized medicine [19].

In addition, equity in access to treatment is also a concern, as the implementation of pharmacogenetics may be more straightforward in some regions or population groups than others, widening health disparities. Furthermore, pharmacogenetics is an ever-evolving field, with research continuing to reveal new associations between genes and drug response [19].

8. Conclusions

Pharmacogenetics plays a vital role in understanding variability in response to classical antidepressants. By studying the effects of individual genes, it is possible to identify genetic patterns that influence the effectiveness and side effects of antidepressants. Also, integrating pharmacogenetics into clinical practice could revolutionize the treatment of depression, allowing for more precise and personalized interventions for patients. However, it is crucial to continue research and address ethical issues to ensure that pharmacogenetics benefits everyone fairly and responsibly.

9. References

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