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The psychological impact of non-responsiveness to antidepressants on patients with depression and the role of pharmacogenomics-based drug therapy

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ABSTRACT

Depression is a common and crippling condition that is not easily ameliorated with conventional antidepressant medications due to a lack of drug response. Patients are significantly impacted by this non-responsiveness, which causes emotional anguish, decreased mental health, and a higher risk of suicide. This article examines the psychological implications of antidepressant non-response, underscoring the emotional toll on patients and the detrimental impact on their general well-being. It also emphasizes the difficulties of forecasting treatment outcomes using current prescription practices as well as the link between non-responsiveness and a higher risk of suicide. Pharmacogenomics (PGx)-based drug therapy emerges as a potential solution to address non-responsive depression. By analyzing an individual's genetic profile, health-care providers can personalize therapeutic plans, selecting medications and dosages that are more likely to be safe and effective for individual patients. This approach offers several benefits, including enhanced treatment effectiveness, individualized dosing, the avoidance of treatment resistance, cost-effectiveness, and improved safety profile. Our work primarily highlights the potential of PGx to revolutionize depression treatment by providing a more tailored and effective approach. We present evidence from studies supporting the clinical benefits of PGx-guided medication management, highlighting improved depression outcomes and higher remission rates compared to standard care.

Keywords: Pharmacogenomics, Depression, Non-responsiveness, Mental health, Antidepressants

INTRODUCTION

Depression is a frequently occurring, severe, and recurrent condition that has been linked to decreased quality of life and role functioning as well as medical morbidity and death.[1,2] According to the World Health Organization, depression was the 3rd leading cause of disease burden globally in 2008 and is expected to surpass all other diseases by 2030.[3] With a 15–18% lifetime risk of

depression,[4] depression is a prevalent condition, with nearly 1 in 5 people experiencing an episode at some point in their lives.[5] Antidepressants are used as first-line treatment in patients diagnosed with moderate-to-severe depression, of which only 50% will respond to antidepressant treatment.[6] Antidepressants come in different classes and the class that is currently most frequently prescribed as first-line therapy are the selective serotonin reuptake inhibitors (SSRIs).[7] Being that one-third of patients treated for a major depressive episode do not experience remission after two or more attempts with first-line agents,[8] it follows that individuals can be non-responsive to even the mostly prescribed SSRIs. More so, a study by Casarotto *et al*. suggests that the common mechanism for antidepressant activity is through allosteric enhancement of brain-derived neurotrophic factor signaling, which may explain why most antidepressants act slowly.[9]

Patients resistant to multi-regimen approaches are defined as having treatment-resistant depression (TRD). According to a study by Binder, TRD was shown to double the risk of hospitalizations, increasing the length of stay by 36%, and was 7 times more likely to result in suicidal thoughts than treatment-responsive depression[10] where treatment-responsive patients are defined as those with adequate therapeutic responses at approximately 6 weeks.

Some studies[11-13] have shown evidence of improved efficacy and response in pharmacogenomic (PGx)-based antidepressant therapy with defined drug cost savings reported with combinatorial PGx testing.[14] Our review aims to emphasize the potential psychological effects of non-responsiveness or resistance to antidepressants in patients with depression and the utility of PGx in prescription practices for such patients.

THE PSYCHOLOGICAL IMPACT OF NON-RESPONSIVENESS TO ANTIDEPRESSANTS

Different emotional responses are associated with non-responsiveness to antidepressants. It has been found that frustration is the most frequently reported emotion linked with non-responsiveness to antidepressants.[15] In a survey of health-care professionals' (HCPs) perceptions on the emotional impact of non-responsiveness to antidepressants on their patients, HCPs revealed that 11% of their patients were frustrated with their medications compared with the self-reported frustration by 30% of the patients;[15] impact on daily life (53%), and treatment issues (lack of efficacy and side effects; 50%) were also identified as the primary causes of the patients' frustration. In addition, HCPs are aware of a variety of unfavorable feelings that may be connected to treatment failure and chronic depression symptoms. Aside from these emotional effects, it has also been shown that antidepressants show different effects on individuals and varying conditions.[16] The most prevalent side effects associated with the use of antidepressants include gastrointestinal issues, weight gain, appetite, xerostomia, insomnia, sexual problems, spasticity, diarrhea, constipation, and dizziness.[16-18] Suicidal tendencies and withdrawal effects are also connected with the use of antidepressants due to the reduction in positive feelings.[19] The side effects, non-responsiveness, and the general impact on patients' well-being are reported to be the cause of frustration in patients.[15]

Relationship between non-responsiveness and increased risk of suicide

Most antidepressants do not provide instant relief of symptoms, taking an average of 3–4 weeks of treatment for the effect to be fully noticed.[20] In addition, studies indicate that traditional antidepressant therapy only works for 60–70% of patients[21] whereas between 10% and 30% of individuals experience limited or no improvement, along with functional difficulties, a diminished quality of life, thoughts of suicide, self-harming tendencies, and a substantial likelihood of relapse.[21] Notable conditions treated by antidepressants include anxiety, panic disorders, and Obsessive-Compulsive Disorder.[22] These conditions and other mood disorders are sometimes accompanied by suicidal behavior.[23] Since antidepressant therapy is aimed at treating these symptoms in patients, when these symptoms persist or prove resistant to treatment, they can escalate in severity. This heightened level of depression is linked to an elevated risk of suicidal thoughts and attempts when not treated, or if a patient is resistant to treatment this can lead to increased severity, and this increase in depression severity has been associated with an increased risk of suicidal ideation and suicide attempts.[24] Such suicide attempts were 8 times more likely for those with severe depression symptoms.[25] According to the 2014 study by Courtet *et al*., non-improvement of depression following the use of antidepressants results in suicidal ideations in patients who initially were not expressing such ideation before the treatment, it was also observed in patients who initially had a history of suicide attempts and alcohol misuse.[26] Likewise, in a recent study, patients who did not respond to treatment, according to observation, expressed feelings of hopelessness or pessimism, and approximately 80% reported experiencing feelings of guilt, worthlessness, or helplessness which increased suicide attempts and suicidal thoughts.[24]

PGx-BASED THERAPY (PGx-BT)

Benefits of PGx-BT

In clinical practice, it is widely recognized that patients exhibit diverse reactions to medications. This implies that while a specific drug and/or dosage may be effective for some patients, it might not be effective or may even result in adverse reactions in other patients. To explore the connection

between individual genetic variations and medication response, PGx research has focused on investigating genes that influence clinical outcomes.[27] The field of genetics has been extensively applied in precision medicine, and one of its emerging applications is in the analysis of genetic features.[28] Genetic testing analyzes an individual's DNA to identify specific genetic variations known as single nucleotide polymorphisms and other structural variants. These variants can influence the activity and expression of key enzymes and receptors, determining an individual's response to therapeutic drugs like antidepressants. By detecting these genetic variants, health-care providers can gain a deeper understanding of an individual's unique drug metabolism and response profile. It has been suggested that the response to antidepressant medications is a polygenic trait, with common genetic variants playing a significant role in determining the variability in response.[29] Key genes often analyzed include cytochrome P450 genes (such as *CYP2D6*, *CYP2C19*, *CYP2C9*, and *CYP1A2*), which encode enzymes responsible for metabolizing medications, resulting in different levels of enzyme activity,[30] as well as genes such as serotonin transporters (*SLC6A4* and *5HTR2A*) which are involved in neurotransmitter transport and receptor function.[31,32] Consequently, these gene variants have been hypothesized to be predictive of individual variations in antidepressant drug metabolism, therapeutic responses, and the risk of drug-related toxicities.

Several studies have identified the clinical benefits of PGx-guided medication therapy management in patients with depression [Figure 1] but the applicability of these findings in real-world settings for validity is still limited.

Enhanced treatment efficacy

The use of PGx in health-care settings will enable health-care providers to tailor pharmacological treatment plans based on an individual's genetic makeup leading to an improved effective response with reduced risk of adverse side effects and an overall reduction in medicine cost. By analyzing specific genes involved in drug metabolism, transporters, and targets, researchers can identify particular genetic variants associated with various health conditions to enable treatment. This approach increases the chances of achieving better treatment outcomes and optimizing drug selection. Studies[11,33] provided evidence that patients with moderate-to-severe depression who had combinatorial PGx testing had substantial improvements in their depression outcomes.

Personalized dosing

The current methods of determining doses based on weight and age will be replaced by dosing based on a person's genetics, the body's ability to handle the medication, and the amount of time it takes for the drug to be metabolized.[34] PGx-testing helps identify genetic markers associated with drug metabolism, enabling health-care providers to adjust medication dosages based on an individual's genetic profile. Evidence[35] suggests that among patients with depression, the application of PGx in predicting and monitoring drug-gene interactions reduced the prescription of medications with predicted drug-gene interactions compared with usual care. This approach ensures that patients receive optimal amounts of medication, improves efficacy, and reduces the likelihood of overdose.

Better drug selection

All antidepressants have the drawback of having a significant delay between the start of treatment and clinical improvement that can last up to several weeks or months.[10] PGx-BT offers the opportunity to make better drug selection ensuring therapeutic response of the patients.

Avoidance of treatment resistance

PGx can identify genetic markers associated with poor treatment outcomes. The known incidence of TRD in 10–30% of patients with depression appears as refractoriness to standard antidepressant therapy[21] which may, in part, be due to genetic factors. To find appropriate treatments and cut down on patients' protracted suffering, genetic testing for individuals with early TRD symptoms might be viewed as an element of the management approach.[36]

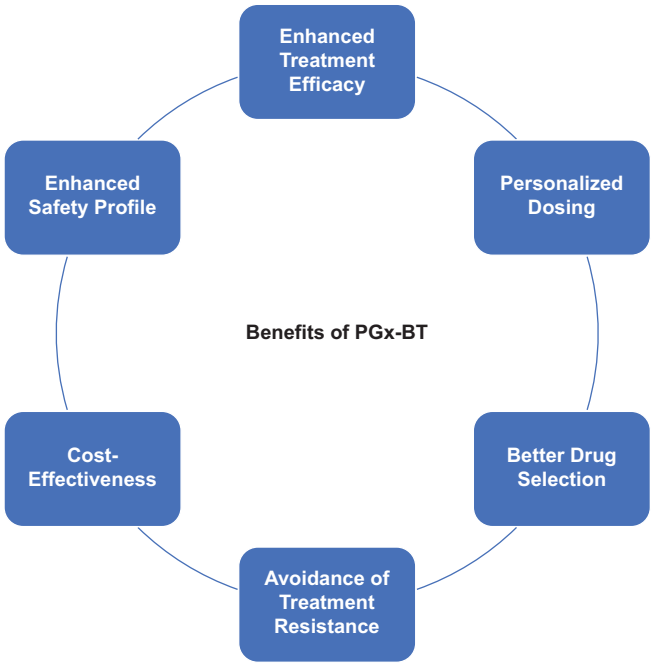

Figure 1: Benefits of PGx-BT in the treatment of TRD. PGx-BT: Pharmacogenomics based therapy, TRD: Treatment-resistant depression.

Cost-effectiveness

PGx offers the potential for significant economic benefits, both in the short term through the avoidance of potentially unsafe or ineffective medications in specific patients and the long term because patients on targeted drug treatments are more likely to experience improved health outcomes.[37] It has the potential to lower costs associated with inappropriate or expensive treatment of depression and/or serious adverse drug reactions that may require hospitalization. In a systematic review evaluating the cost-effectiveness of pharmacogenetic and PGx screening, its application was found to be mostly cost-effective or cost-saving.[14]

Enhanced safety profile

Genetic factors account for more than 60% of the variability in pharmacological response and side effects for various types of antidepressant drugs.[38] Results from a systematic review[38] suggest that drug therapy based on individuals' genetic makeups may result in a clinically important reduction in adverse outcomes. PGx-testing helps identify genetic variants associated with a higher risk of adverse reactions. With this information, health-care providers can avoid prescribing medications that are likely to cause severe adverse effects in certain patients, thereby minimizing potential harm and improving patient safety.

Comparison of PGx-BT to traditional antidepressant therapy

PGx-BT allows for a personalized approach to antidepressant treatment by considering an individual's genetic profile. Genetic testing helps identify specific genetic markers associated with drug metabolism and response, enabling clinicians to select medications and dosages that are more likely to be therapeutically effective for individual patients. In contrast, traditional antidepressant therapy relies on a trial-and-error process,[39,40] where patients are often placed on multiple medications initially before finding out those that work for them. PGx-BT will lead to a decrease in the time taken for clinical effects to be observed in patients compared to the traditional approach leading to a reduction of emotional toll which arises due to the delay in the onset of the antidepressant effect. The concept of PGx provides insights into how an individual's genetic variations may impact the metabolism and response to specific antidepressant medications.[30] This information enables clinicians to make informed decisions about which antidepressant to prescribe and avoid medications that are likely to be less effective or cause adverse reactions. In traditional antidepressant therapy, medication selection is typically based on clinical guidelines, trial data, and the clinician's experience, without considering an individual's genetic factors.[41] While PGx-BT holds promise, its implementation in routine clinical practice is still evolving.[12] Challenges such as accessibility to genetic testing, and interpretation of genetic results need to be addressed for widespread adoption while further research is needed to validate the utility and refine the applications of PGx-based drug therapy in depression treatment.

THE ROLE OF PGx IN TREATMENT-RESISTANT DEPRESSION

Highlighting success rates

Pharmacogenetics can enhance the effectiveness of depression treatment by adjusting drug selection to a given patient's genetic profile.[42] Hence, clinicians can choose the best drug, dose, and length of treatment for each patient by learning about the hereditary factors that affect the variety of antidepressant responses.[43] In a large-scale genome-wide association study, several genetic loci associated with depression were examined[44] and current knowledge of peripheral biomarkers associated with depression highlights their potential role in predicting treatment response thus aiding in the diagnosis of depression and guiding personalized treatment strategies.[45] Identification of blood-based biomarkers for TRD which explores gene expression patterns in peripheral blood samples exemplifies potential molecular signatures that may distinguish individuals with TRD from those who respond well to treatment.[46] In addition, in a 213-participant randomized controlled trial,[12] where 105 patients were randomly assigned to PGx-based antidepressant medication while 108 received standard care. Participants with depression or Generalized Anxiety Disorder who were randomly assigned to receive pharmacist-led PGx-BT at 6 months had less severe depressive symptoms than those assigned to standard care. In comparison to participants on standard care, those receiving PGx-BT also reported higher improvements in generalized anxiety and impairment. For the PGx-BT group, 36% of the baseline depression severity had improved compared to the control group (18%). Another study[35] showed that patients whose care was guided by PGx-testing experienced greater remission rates over 24 weeks than patients receiving standard care. It also showed that patients under PGx-BT had a lower likelihood of receiving medications with drug-gene interactions. Similar findings from other research[11,13,27] support the role of PBT in enhancing antidepressant response and minimizing adverse effects.

CONCLUSION

By tailoring medicine selection based on a person's genetic profile, PGx-based pharmacotherapy has the potential to improve the treatment of non-responsive depression. The trial-and-error nature of traditional antidepressant therapy frequently leads to extended morbidity and an

elevated risk of adverse responses. PGx, however, has several clinical advantages, such as improved treatment effectiveness, personalized dosing, the identification of superior antidepressants, prevention of drug resistance, cost-effectiveness, and improved safety profile. HCPs can select an appropriate dose, and prolong the duration of treatments by analyzing individual genes involved in drug metabolism and response, which improves outcomes and lowers risks. Studies have shown that PGx-guided treatment is successful in lowering depressive symptoms, increasing remission rates, and reducing the prescription of drugs that may interact negatively with genes. However, more research is required to enable PGx to become part of mainstream treatment in healthcare settings globally.

Authors' contributions

CEA and UEC developed the concept for the paper. All the authors were involved in drafting the full manuscript.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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