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PHD THESIS

**THE CONTRIBUTION OF GENETIC TESTING IN OPTIMIZING
THERAPY OF PATIENTS WITH TREATMENT-RESISTANT
MAJOR DEPRESSIVE DISORDER**

- A B S T R A C T -

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Major depressive disorder (MDD), with its large spectrum of clinical manifestations, represents an important public health concern due to its increased prevalence and high recurrence tendency, resulting in disability and a reduced quality of life, in addition to its subsequent elevated socioeconomic costs.

Currently, MDD constitutes one of the principal domains of clinical psychiatry and mental health research, attracting high levels of interest from mental health professionals and the wider medical community. This attitude is explained by the epidemiological reality, considering the increased prevalence and incidence of MDD in the adult population, as also confirmed by official World Health Organization (WHO) reports stating that, in the year 2020, MDD represented the second-leading cause of disability among all potentially invalidating diseases worldwide. Additionally, MDD implies increased costs (direct, but especially indirect) determined by its treatments, considering that MDD represents one of the most treatable mental disorders. Direct medical costs are related to diagnosis, evaluation, hospitalization, and both medical and nonmedical treatment, including prevention and rehabilitation of patients with MDD, while the indirect costs result from the incapacity of people suffering from MDD to perform properly their profession, frequently resulting in impaired quality and productivity of their work, or even unemployment. Other indirect costs are consequences of their temporary or long-term disability, sometimes resulting in premature mortality due to healthcare neglect and increased suicide rates encountered in patients with MDD, and frequently with economic consequences on their families, who have to take care of these patients. Moreover, MDD is frequently associated with other medical conditions that could potentially aggravate depressive symptoms and prolong the duration of hospitalization and disability related to depression in these patients. On the other hand, MDD negatively impacts the evolution and therapy of other diseases, especially cardiovascular diseases, even facilitating the development of some cardiovascular dysfunctions. Unfortunately, the prophylaxis and precocious diagnosis of MDD in the general population, especially at the level of primary medical assistance, is still strongly influenced by the patient's socioeconomic level.

Frequently, MDD is accompanied by symptoms of anxiety, especially in the elderly, among whom depression must be treated as a priority. If MDD occurs in a patient already diagnosed with an anxious disorder, this pathology needs to be treated first.

It is well known that MDD manifests a high tendency towards recurrence, so the term recurrent depressive disorder (RDD) defines MDD by recurrent episodes, characterized by the occurrence of two or more episodes of depressive symptoms separated by periods of remission

within a year. Another term, resistant depression (RD) or treatment-resistant depression (TRD), established by the European Medicines Agency (EMA), is considered if an adequate therapeutic response has not been achieved after therapy with at least two antidepressants from different pharmacological classes, in appropriate therapeutic doses, and for a sufficient period of time (minimum of 6 weeks). It is considered that approximately 40% of all patients with MDD manifest RDD, with persistent depressive symptoms, sleep disorders, fatigue, and recurrent thoughts about death. It has been observed that the elderly, women, and people with other pathologies are more vulnerable to developing RDD.

To quantify the intensity of depressive symptoms, the severity of accompanying anxious elements, and their evolution under therapy, several instruments have been developed, such as the Hamilton Depression/ Anxiety Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A), created by Hamilton in 1960, which was one of the first, but is still among the most used scales, both in clinical practice and in research. Its initial purpose was to assess the severity of MDD episodes. Although it was not designed for diagnostic purposes, it is frequently used in this sense in clinical research that employs threshold scores to indicate the presence of a depressive episode. Other scales, such as the Clinical Global Impressions Scale with its two domains (Severity and Improvement (CGI-S, CGI-I)), are clinical instruments developed by the National Institute of Mental Health (1976) to follow up the evolution of MDD.

Several antidepressant drugs have been developed starting from the hypothesis of the hypofunction of aminergic brain transmission, e.g. serotonergic, noradrenergic, and dopaminergic. From this perspective, some drugs act selectively on one neurotransmission system, while others act more or less selectively on several neurotransmission systems (new-generation antidepressants versus classical antidepressants). Depending on the clinical effectiveness, costs, and implementation factors, the Nice Guidelines 2022 recommend combining antidepressant treatment with cognitive behavioural therapy (CBT), group exercise or guided self-help, interpersonal psychotherapy (IPT), short-term psychodynamic psychotherapy (STPP), or individual behavioural activation (BA). The choice of treatment takes into account the specific effects of the drugs, the risk of suicide, and the history of response to antidepressant drugs. For first-line therapy, selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), or tricyclic antidepressants (TCAs) are recommended. Other antidepressants could be indicated based on the patient's clinical history and previous treatment. SSRIs are generally well tolerated, have a good safety profile, and

should be considered the first choice for most people. Antidepressant treatment should be taken for at least 6 months, and the benefits should be felt in 4 weeks.

Since RDD and TRD are quite frequent, and therapeutic failure or partial recovery is not unusual, new methods to assess the mechanisms and causes of impaired therapeutic response have been elaborated. Genetic testing offers major advantages to healthcare professionals, providing them with genetic information that may help them select appropriate medications for individuals with mental illnesses and other brain disorders. In this direction, the Genomind Professional PGx genetic test has been developed to provide data that may help healthcare professionals to optimize the drug therapy of patients with mental health disorders. This genetic test provides important information about the patient's genetic profile by analysing 24 genes involved in the patient's response to 130 drugs employed in the treatment of depression, anxiety, bipolar disorder, schizophrenia, autism, attention deficit hyperactivity disorder, post-traumatic stress, obsessive-compulsive disorder, addiction and substance abuse, and chronic pain. Developed in May 2022, the new updated version of the Genomind genetic test offers a personalized approach to the management of mental disorders, recognizing the variation in treatment effectiveness and the sensitivity of mental health disorders induced by genetic changes. Thus, the pharmacogenetic test improves the therapeutic results for patients through a more precise selection of the drugs suitable for the patient according to their genetic material.

A limited number of studies are available in the specialized literature concerning the clinical impact of genetic testing on the selection of an adequate antidepressant therapy according to the patient's pharmacogenetic profile. Therefore, according to the more recent data debated in the medical literature, we strongly consider that further clinical studies are required concerning the possibilities offered by genetic testing for an appropriate pharmacogenetic-guided therapy in patients with depression and anxiety.

The aim of this study was to analyse the differences concerning the 12-month evolution of the intensity of RDD symptoms in patients whose treatment was optimized in accordance with information offered by genetic testing, in comparison to a control group of subjects who did not benefit from this testing.

All the studies adhered to the principles outlined in the Declaration of Helsinki – Ethical Principles for Medical Research. All studies were conducted in compliance with the Ethical protocol, the Data Protection Act and other regulatory requirements as appropriate. All studies were initiated after the Ethical protocol was reviewed, and received favorable opinion from the

responsible Independent Ethics Committees. Ethical approval for this research was obtained from the PsihoNeuro Mag Clinic, Oradea, Romania (22/12.03.2019) and by Ethics Committee of University of Medicine and Pharmacy “Victor Babeş” Timișoara (71/19.12.2018).

LIST OF PUBLISHED SCIENTIFIC PAPERS

1. **Platona RI**, Voiță-Mekeres F, Tudoran C, Tudoran M, Enătescu VR. The Contribution of Genetic Testing in Optimizing Therapy for Patients with Recurrent Depressive Disorder. Clinics and Practice. 2024; 14(3):703-717. <https://doi.org/10.3390/clinpract14030056>. ISI, IF 2.3, Pubmed
2. **Platona RI**, Voiță-Mekereș F, Enătescu VR. Depression Rating Scales – Benefits and Limitations. A Literature Review. Journal of Psychological and Educational Research. 2023 Nov 1;31(2):138-52. ISI, IF 0.7
3. **Platona RI**, Căiță GA, Voiță-Mekereș F, Peia AO, Enătescu RV. The Impact of Psychiatric Comorbidities Associated with Depression: A Literature Review. Medicine and Pharmacy Reports. 2024 Feb 7. BDI, Pubmed
4. **Platona RI**, Căiță GA, Manole A, Szilagyi G, Enătescu RV. Assessment of Functional Improvement after Pharmacogenomically Guided Antidepressant Therapy in Patients with Recurrent Depressive Disorder. Journal of Psychological and Educational Research. 2024 2024, 32 (1), May, 109-122. ISI, IF 0.7
5. Fodor R, Voiță-Mekeres F, Cheregi CD, Indrieș M, Noor H, Pop NO, Marian P, **Platona RI**, Lascu CF, Marcu OA. Epidemiological Study on Spinal Cord Injuries in a Hospital from North-West of Romania. Pharmacophore. 2023 Jan 1;14(1):80-6 ISI, IF 0.5

MDD is a complex disorder that has been considered for more than two decades to have a background of increased heritability, reaching as high as 37% according to the estimates of two twin studies. Despite strong evidence for a genetic component, identifying the specific gene variants responsible for the development of this disorder has always constituted a major challenge. Genome-wide association studies have tested the existence of differences in the allele frequencies between patients with MDD and control groups, with millions of common single-nucleotide polymorphisms throughout the genome. These differences may be functionally relevant for this disease, or they may indicate loci that are transmitted in a linkage disequilibrium with a causative polymorphism.

In the domain of psychiatric nosology and therapy, depressive disorder and anxiety have a long and close common history. Analyses of large-scale epidemiological surveys have identified major patterns of phenomenological overlap between these two conditions. Over time, the hypothesis of a common genetic background has been tested as a potential basis for this relationship. A previous family study by Hettrema et al. debated evidence concerning the co-occurrence of anxiety and MDD, while twin studies indicate shared genetic risk factors that could potentially explain these comorbidities. Therefore, studying the molecular genetics of these pathologies can provide potential support for specific genetic loci that could influence individuals' susceptibility to developing a spectrum of depressive and/ or anxious symptoms.

The aim of our first study was to analyse the differences concerning the 12-month evolution of the intensity of RDD symptoms in patients whose treatment was optimized in accordance with information offered by genetic testing, in comparison to a control group of subjects who did not benefit from this testing. Methods: This prospective longitudinal study was conducted between 2019 and 2022, and the patients were evaluated by employing the Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A) and the Clinical Global Impressions Scale: Severity and Improvement. We followed them up at 1, 3, 6, and 12 months. Results: Of the 76 patients with RDD, 37 were tested genetically (Group A) and 39 were not (Group B). Although the patients from Group A had statistically significantly more severe MDD at baseline than those from Group B ($p < 0.001$), by adjusting their therapy according to the genetic testing, they had a progressive and more substantial reduction in the severity of RDD symptoms [$F = 74.334$; $\eta^2 = 0.674$; $p < 0.001$], indicating a substantial association with the results provided by the genetic testing (67.4%). Conclusions: In patients with RDD and a poor response to antidepressant therapy, pharmacogenetic testing allows for treatment adjustment, resulting in a constant and superior reduction in the intensity of depression and anxiety symptoms.

The objective of the second research was to compare the functionality of patients diagnosed with RDD measured by the GAF score after the treatment optimizing according to the genetic testing versus treatment as usual patients over a period of one year. The functional outcome has become in the last decades of interest for cross-sectional diagnosis in psychiatric genetics. It is essential to know the clinical, demographic, and psychosocial variables that are associated with long-term functioning. The present study is a prospective clinical trial analysing the clinical impact of pharmacogenomics on the management of patients with RDD. Applying a longitudinal model of analysis to samples of patients with RDD genetically tested as well as

to patients who did not benefit from genetic testing, we compared the improvement of functionality measured by the Global Assessment of Functioning (GAF) score. The results indicate an improvement in function in genetically tested patients after three months and up to one year of treatment compared to non-genetically tested patients. One of the main qualities of our research is the longitudinal design that allows the follow-up of patients over a year by using the GAF to assess the functionality of patients at five specific intervals, starting from baseline and after treatment optimization. The information provided by our research could be used to develop an algorithm to personalize the management of patients with RDD according to the results of genetic tests.

The aim of the third study was to identify the variations of 5 genes, 3 pharmacokinetic (CYP2B6, CYP2C19, CYP2D6) and 2 pharmacodynamic (SLC6A4, HTRA2), used to optimize therapy in patients with treatment-resistant depression (TRD) using pharmacogenomic testing (PGx) and monitoring clinical evolution by using the psychometric scales HAM-D and CGI-S in the initial stage (T1) and later HAM-D at 1 month (T2), 3 months (T3), 6 months (T4) and 12 months (T5). In this longitudinal prospective study, we included 128 patients from the outpatient clinic of the PsihoNeuro Mag Clinic in Oradea, Romania, diagnosed with TRD. The age of the patients was between 18 and 73 years, over a period of 5 years, respectively, March 2019 – March 2024. All patients selected in the study were diagnosed with TRD, they were applied at the initial moment (T1) the scales for depression (HAM-D). Following the medical history, it was known that these patients did not respond to antidepressant treatment and they were proposed pharmacogenomic testing (PGx). Thus, 2 groups of patients were formed: assay-guided treatment (AGT, N = 63) and treatment as usual (TAU, N = 65). The average age of genetically tested patients was 36.14, and of those not genetically tested was 50.15, thus there were significant differences between the two groups, which indicates a greater receptivity of the participants of the genetically tested group to modern techniques diagnostic. The onset age of the patients in the AGT group is younger, but significant differences were indicated in the case of gender, the environment of origin and the number of recorded relapses. The evaluation by HAM-D-17 and CGI-S of the participants in the baseline stage indicated a significant severity of AGT patients compared to TAU.

This study has some limitations, particularly resulting from the fact that it was a single-center study conducted on a limited number of patients. Finally, we cannot forget that this study was conducted during the COVID-19 pandemic, when individuals were more prone to depressive disorders and had higher anxiety levels.

Conclusions and Personal Contributions

Final Conclusions

Since the introduction of antidepressants into psychopharmacology in the 1960s, the HAM-D and BDI have been the most commonly used depression rating scales. Many of the scales presented, when used as tools for predicting the outcome of antidepressant treatment, revealed that the scores obtained have limited relevance for the diagnosis of MDD.

The importance of comorbidity with anxiety disorders has profound adverse implications on the evolution, prognosis and therapeutic responsiveness of depression, it will prolong the time required to achieve remission of the depressive episode, and patients in treatment will tend to drop out of treatment faster than those with depression but without anxious comorbidity. The presence of major depression is in itself a predictive factor for a later onset of generalized anxiety disorder. The comorbidity of depression in those with substance abuse or addiction has profound implications on their clinical prognosis. The association of personality disorder has a significant impact on the suicidal behaviour of patients with major depression.

The effectiveness of genetic testing in optimizing treatment for patients with mental health disorders highlighted that over 80% of patients who benefited from genetic testing reported significant improvements, reduced adverse effects of drugs, improved quality of life, and significantly lower treatment failure rates.

The employment of pharmacogenetic tests to guide therapeutic choices is recommendable and even mandatory to guide treatment for RDD and/ or anxiety, especially when the patient's previous treatment has failed.

After the analysis of the CYP2B6, CYP2C19, CYP2D6, SLC6A4, HTR2A genes, whose results were used to optimize the post-genetic testing treatment, we note that the most frequent change of drug class was indicated in combination with neuroleptics or thymostabilizers.

Comparing the clinical evolution using HAM-D-17, between the baseline treatment and after PGx guided therapy, the assay-guided therapy group obtained clinical improvements to a greater extent compared to the treatment as usual group.

Personal contributions

Our study refers to a current topic, the treatment of patients with TRD, a subset of RDD, for whom the pharmacogenetic-guided antidepressant therapy offers the perspective of a personalized prescription, which is more efficient and has fewer adverse effects.

This study is a prospective clinical study, one of the first in our country that analyses the clinical impact of PGx on the management of patients with TRD.

One of the main qualities of our research is the longitudinal design allowing the follow-up of patients' evolution for a year by using several psychometric scales to evaluate the intensity of depression and anxiety symptoms at five specific intervals starting from baseline and after optimizing the treatment.

The information offered by our research could be employed to elaborate an algorithm for personalizing the management of patients with TRD according to the results of the genetic testing.