Universitatea Transilvania din Brașov

**INTERDISCIPLINARY DOCTORAL SCHOOL**

**Faculty of Medicine**

**Dan Alexandru CONSTANTIN**

# Evaluating the efficacy and safety of rTMS (repetitive transcranial magnetic stimulation) - An Emerging Public Health Issue in Adjustment and Depressive Disorders.

## SUMMARY

Scientific supervisor

Prof. dr. med. Liliana Marcela ROGOZEA

BRAȘOV, 2024

## Table of Contents

## LIST OF ABBREVIATIONS

| Abbreviation | Description |
|---|---|
| BADI | Internet-based therapy |
| BMS | Mind-body-spirit therapy |
| BNDF | Brain-derived neurotrophic factor |
| CBT | Cognitive-behavioural therapy |
| CNAS | National Health Insurance House |
| DLFPC | Dorsolateral prefrontal cortex |
| DLFPC-Law | Right dorsolateral prefrontal cortex |
| DLFPC-Stâng | Left dorsolateral prefrontal cortex |
| ECT | Electroconvulsive therapy |
| EMG | Electromyography |
| FDA | Food and Drug Administration |
| HAM-A | 14-item Hamilton Anxiety Rating Scale |
| HDRS | Hamilton Depression Rating Scale with 17 items |
| HF rTMS | High-frequency transcranial magnetic stimulation |
| ICER | Incremental cost-effectiveness ratio |
| IMAO | Monoamine oxidase inhibitors |
| LF rTMS | Low frequency transcranial magnetic stimulation |
| MEP | Potential driver for action |
| MT% | Individual motor threshold. |
| WHO | World Health Organization |
| OR | Odds ratio |
| PST | Problem-solving therapy |
| PTSD | Post-traumatic stress disorder |
| QALYs | Quality of life years adjusted |
| rTMS | Repetitive transcranial magnetic stimulation |
| SNRI | Selective serotonin-norepinephrine reuptake inhibitors |
| SSRI | Selective serotonin reuptake inhibitors |
| USA | United States of America |
| tDCS | Direct transcranial electrical stimulation |
| TMS | Transcranial magnetic stimulation |
| VNS | Vagus nerve stimulation |
| YLDs | Years of disability |

## LIST OF SYMBOLS

| Symbol | Description |
|---|---|
| $\chi^2$ | Bivariate Chi-square test |
| $\beta i$ | regression coefficients |

## ABSTRACT

**Introduction:** Globally, due to the increasing prevalence of adjustment and depressive disorders and the impact on the population and public health systems, these two conditions are an emerging public health problem. Reducing the impact of these psychiatric conditions requires public health interventions aimed at prevention, treatment of illness and promotion of mental wellbeing in the population. Although there are many therapeutic drug interventions that address these conditions, a large proportion of patients are resistant or experience adverse effects following their administration. Thus, new innovative somatic treatments such as Repetitive Transcranial Magnetic Stimulation (rTMS) could play an important role in both patient treatment and public health policy.

**Aims:** This PhD thesis aimed to examine the possibility of integrating rTMS into public health strategies, addressing its feasibility as a treatment option, an alternative to existing conventional pharmacological therapies.

**Materials and methods:** The PhD thesis, comprised three separate research studies, two of which were quantitative and one qualitative. The research studies received the ethics committee approval with no. 1.3 dated 21/05/2018, issued by the Ethics Committee for Medical Scientific Research of the Faculty of Medicine of Transylvania University. The first quantitative, pilot, interventional, non-randomized study explored the efficacy and safety of rTMS in the treatment of adjustment disorder patients with mixed anxiety-depressive mood on a group of 60 patients. In the second study, the focus was on rTMS as adjunctive therapy for patients with major depressive disorder. A pilot, interventional, non-randomised study was conducted on a sample of 40 patients, comparing the therapeutic outcomes of standard pharmacological treatments with those augmented with rTMS as well as the safety of magnetic stimulation administration. The third qualitative study, used semi-structured interview to assess the perceptions and experiences of patients treated with rTMS for adjustment and major depressive disorder on a sample of 20 patients. The results of the first two studies were statistically analysed using IBM SPSS software version 26.0, and the results of the third study were analysed using NVivo software version 14.

**RESULTS: The** results of the first study showed that rTMS is an effective method in the treatment of patients with adjustment disorder with mixed anxiety-depressive mood, especially when not associated with concomitant pharmacological treatment. The therapy was safe and well tolerated by patients, thus the study provides sufficient arguments for the potential use of rTMS in public mental health policies targeting adjustment disorder. The second study revealed the lack of efficacy of rTMS as an adjunctive treatment for major depressive disorder contrary to existing information in the literature. Although in the group of patients treated concomitantly with rTMS and psychotropic medication, the remission rate was the lowest, it was nevertheless observed that the decrease in symptoms on the anxiety and depression scales were statistically significant. These findings are important and highlight that public health professionals, need to be cautious and allocate funds to research this method before its widespread use is adopted. The results of the semi-structured interviews in the third study revealed that patients have a positive perception of their experience and indicated that their mental health has improved and most of them prefer rTMS over pharmacological options due to reduced side effects. However, challenges such as frequency of treatment sessions and other potential barriers were noted along with widespread adoption of rTMS. The results of the thesis showed that the adoption of rTMS in a wider context in specialist outpatient settings provides sufficient arguments for the potential to transform the treatment of mental disorders in public health by continuing and standardising the application of rTMS. Addressing social factors and improving access to rTMS may also be an efficient and effective way to make it a standard treatment option for patients with mental disorders globally.

**DISCUSSION: This** paper provides a comprehensive investigation of the efficacy and safety of rTMS, as well as exploring the perceptions and experiences of patients who have been treated with magnetic stimulation in three studies, which provide significant insights into the potential of rTMS for the treatment of major depressive disorder and adjustment disorder with mixed anxiety-depressive mood. In all three studies, rTMS demonstrated a response in relieving the symptoms of patients who either did not fully respond to conventional pharmacological treatments or sought a non-pharmacological option due to reduced side effects, particularly in a non-invasive manner, especially in cases where there was some

patient resistance to treatment of these conditions. The addition and adoption of rTMS in the treatment of patients statistically significantly improved anxiety and depressive symptoms, and demonstrated a higher likelihood of achieving remission of adjustment disorder when not combined with psychotropic pharmacological treatment. This indicates that rTMS may fill a critical gap in the current mental health treatment scenario. The safety profile of rTMS, marked by minor and transient side effects, fully supports its adaptability as a standard treatment modality with the potential to improve patient adherence and satisfaction. The qualitative insights, which were one of the main aspects of the PhD thesis, into patients' experiences and their perceptions, provide insights into the importance of considering patients' views in the adoption of any new technology. The appreciation gathered from participants' views of rTMS due to its non-invasiveness and lack of side effects, which are usually associated with pharmacological treatments, provides support that rTMS is a possible treatment for mental disorders alongside conventional treatments. However, some challenges were noted by participants in the qualitative study, mainly related to logistical issues or non-coverage in the standard package by CNAS. As mental health treatment evolves, rTMS stands out as a promising method aligned with public health goals to improve the effectiveness, safety and acceptability of mental health interventions, ultimately resulting in a reduction in the overall burden of mental health disorders.

**Conclusions:** The combined results from all three studies of the PhD thesis show that rTMS has significant potential as an effective and safe treatment for mixed anxiety-depressive mood adjustment disorder. For major depressive disorder, the lack of efficacy of rTMS in the group of participants receiving combined treatment highlights that more research studies are needed to standardize optimal stimulation parameters that could lead to increased efficacy of rTMS. Integrating rTMS into standard mental health care practices can lead to substantial advances in public health strategies to combat mental health disorders. By providing a non-invasive treatment option with minimal or no side effects, rTMS addresses major barriers in treatment adherence and satisfaction, potentially improving patient outcomes and reducing the overall burden on the healthcare system. The ability of rTMS to serve as both a stand-alone and adjuvant treatment enriches the therapeutic arsenal available to clinicians, and is particularly beneficial for patients who are resistant or have adverse reactions to traditional pharmacological approaches. Overall, expanding rTMS applications in clinical settings could significantly improve the accessibility and quality of mental health care. This provides alignment with broader public health goals for mitigating the impact that mental health has on society in a global context.

**The research results were disseminated through two ISI articles and one BDI article according to the contractual terms of the 2016 registration year.**

## INTRODUCTION. MOTIVATION FOR THE CHOICE OF THEME

Mental disorders are of particular interest to public health professionals, and this interest has increased significantly since 2016 with the encouragement of the development of population-oriented public health approaches. This development coincides with the need to treat mental health on a par with physical health, which has increased the attention paid to this area. (Campion, 2018; Mental Health Foundation, 2016). Globally, the prevalence of mental disorders is increasing, affecting 13.04% of the general population and 11.89% of the Romanian population, which highlights their importance in the context of public health (Global Burden of Disease Collaborative Network, 2019). Major depression is a severe psychiatric condition and globally is considered one of the leading causes of disability (James et al., 2018). Adjustment disorder is also responsible for significant disability and increased rates of suicide, and is frequently seen in emergency departments, putting pressure on health systems (American Psychiatric Association, 2013).

The present study addresses two mental health conditions that are emerging public health issues both globally and nationally, with a significant negative impact on the population. This impact is amplified by the inadequacy of support networks, appropriate mental health policies, interventions and initiatives to promote mental wellbeing. In the context of rapid technological change and the frequent ineffectiveness of traditional treatments, which often have significant adverse effects, there is growing interest in exploring new treatments. These novel treatments include non-invasive, effective and safe somatic interventions that include repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS) and direct transcranial electrical stimulation (tDCS).

The paper contains two prospective, longitudinal, interventional, non-randomised pilot studies aimed at evaluating the efficacy and safety of rTMS in the treatment of mixed anxiety-depressive mood adjustment disorder, major depressive disorder and a qualitative research. The qualitative research aims to explore the perceptions and experiences of patients who have been treated with rTMS in Romanian outpatient clinics for the two conditions, positioning this intervention in the broader context of public health concerns. This research arises from the growing need to address mental health disorders, which constitute a significant burden on health systems globally, and to evaluate new therapeutic interventions that promise fewer side effects and are non-invasive compared to traditional treatments.

This thesis provides a solid evidence base for the use of rTMS in mixed anxiety-depressive and major depressive mood adjustment disorder, addressing a significant gap in the literature and providing guidance for clinicians, health policy makers and others. By presenting the benefits and limitations of using rTMS, the present research aims to contribute to the development of more effective, accessible and patient-centred mental health services. The data provided in the paper can be used by clinicians in specialist outpatient clinics in Romania or other countries, providing concrete data on the viability of rTMS in the treatment of mixed mood adjustment disorder and major depressive disorder.

# CHAPTER 1 - GENERAL PART

## 1.1 Mental health - a public health issue

### *1.1.1 Introduction*

Today, public mental health plays a very important role in our society due to the need for population-based approaches and the interest in achieving parity between physical and mental health. (Mental Health Foundation, 2016). The World Health Organisation defines mental health as a condition of well-being in which a person can recognise their own potential, manage everyday stressors, work effectively, and contribute to their community (WHO, 2022). This is a key aspect of people's lives and is necessary for economic and social development. The concept is directly related to quality of life and well-being. (OECD, 2015). Public mental health aims to promote mental wellbeing, treatment, prevention of mental disorders and their associated impact in the general and specific population (patients already suffering from mental illness). These interventions can result in a wide range of population outcomes and can be associated with short and long-term financial savings. Although these interventions exist, few individuals really benefit from them, both in high and low income countries.

### *1.1.2 Impact of mental disorders and population well-being*

Overall, the burden caused by mental disorders, self-harm is measured in years lived with disability, is 14.59%, and nationally 12.05%. (Global Burden of Disease Collaborative Network, 2019). The high prevalence of psychiatric conditions, relapses occurring across the lifespan cause direct effects that have a major impact on both the population and public health systems. The impact caused by the high prevalence and identified gaps in public health policies can be reduced by implementing effective public health interventions that target both prevention, effective treatment of psychiatric conditions and promotion of mental wellbeing in the population.

### *1.1.3 Public mental health interventions*

There are a number of effective public health interventions, such as effective treatment of mental disorders, their prevention and mental well-being promotion in the population. Once implemented, these interventions can significantly reduce the costs associated with these illnesses, as well as reducing their associated impact on the population. (Campion et al., 2012). Interventions can be primary, secondary and tertiary and can be implemented at the population level by family doctors, specialists in outpatient clinics, hospitals as well as public health specialists. Promoting mental well-being also involves interventions at three levels. Primary promotion vation involves the promotion of factors that contribute to the maintenance of mental well-being such as: physical activity, education, employment, adequate housing and meaningful activities. Secondary promotion interventions target people with low mental well-being and tertiary interventions designed for people with low level long-term well-being. (Campion, 2018; Campion et al., 2012).

### *1.1.4 Public mental health policies*

Awareness of the growing impact of psychiatric disorders on the population and public health systems, together with increased interest from mental health professionals, has led to the

creation of mental health policies. Many of these policies take a public health approach. One example is the UK's 2011 national mental health strategy, which includes the prevention of psychiatric conditions and the promotion of mental wellbeing. (HMG, 2011). Similarly, WHO (2013), the United Nations (2016) and the Biden administration have implemented some of the most important mental public health strategies (NBCC, 2023; UN, 2016; WHO, 2013).

#### *1.1.5 Challenges in public mental health management*

Many countries lack a mental health policy even in present times (WHO, 2015), and where such policies exist, they are not being implemented at the desired scale. The lack of health policies, or their poor implementation, means that the specific interventions described above cannot be put into practice, thus the impact of mental illness on the population is increasing. Another reason for the lack of implementation of interventions may include the lack of human, financial resources and services for mental health. (WHO, 2015).

### 1.2 Adjustment and depressive disorders - a public health problem

#### *1.2.1 Epidemiology*

##### *1.2.1.1 Prevalence of adjustment and major depressive disorders*

Globally, the prevalence of mental disorders is 13.04% affecting a total of 970,070,243.21 people and nationally the prevalence is 11.89% affecting a total of 2,197,434.97 people. The impact of these mental disorders on the mental health of the population is very high, so globally 14.59% of patients affected by these diseases have marked disability, compared to Romania where 12.05% of patients with psychiatric disorders have disability. (Global Burden of Disease Collaborative Network, 2019).

The prevalence of adjustment disorders varies widely due to several factors such as: the population studied, the way the samples studied are processed, the diversity of instruments and clear diagnostic criteria (O'Donnell et al., 2019). In general population studies the prevalence of adjustment disorder is around 1% due to diagnostic methods limitations (Gradus, 2017). More recent studies using newer diagnostic methods have shown a prevalence of 2% in the general population. (Glaesmer et al., 2015) In some specific populations the prevalence is much higher, for example in the unemployed population 27% (Perkonigg et al., 2018) or in the population represented by the long-term bereaved 18% (Killikelly et al., 2019).

Globally, major depression is considered a severe psychiatric condition and a leading causes of disability (James et al., 2018). Globally approximately 2.49% of the population suffers from major depressive disorder, affecting over 185 million people, and nationally 2.12%, over 391 thousand people of the total population of the country is diagnosed with major depressive disorder (Global Burden of Disease Collaborative Network, 2019). Of those who suffer a very high percentage are at increased risk of mortality and suicidal behaviour (Briley & Lépine, 2011; Institute of Health Metrics and Evaluation, 2023). Because it is one of the most frequent severe psychiatric illnesses internationaly that causes disability or suicide in the general population makes this condition an emerging public health issue (Yiru Fang, 2019).

#### *1.2.1.2 Risk factors and causes of adjustment and depressive disorders*

The risk factors that mainly cause adjustment disorders are generally environmental factors. People in difficult life situations are usually subject to a much higher number of stressors (American Psychiatric Association, 2013). Thus people who do not have the ability to adapt to these stressors in their lives have an increased risk of developing the condition. The most important risk factors for major depressive disorder are demographic factors. These include age, income, marital status, race, gender, temperament, environmental, physiological and genetic factors. (American Psychiatric Association, 2013; Hasin et al., 2018).

### *1.2.2 Access of patients with adjustment disorder and major depressive disorder to specialist medical services and prevention programmes.*

The healthcare system in Romania is based on the social health insurance model, wherein the state holds a significant role. If a person has health insurance, it enables them to receive the entire package of treatments; if not, it only provides the minimum amount of services. In accordance with national regulations, health services are offered in the nation's capital as well as 41 other regions. Local health service providers (hospitals, main family physicians, specialty outpatient physicians, paraclinical services, home care, etc.) are contracted by each County Health Insurance House (European Observatory on Health Systems; 2023). Additionally, through the various national health programmes, healthcare practitioners may receive payment from the Ministry of Health (European Observatory on Health Systems; 2023).

### *1.2.3 Costs associated with depression and adjustment disorders*

Depending on the prevalence and the degree of development of systems in different countries the average cost per patient per year for the treatment of depression differs from country to country. Spain, according to the Vieta study, has a prevalence of 4.75% and a public cost of €3,255/patient/year. (Vieta et al., 2021). In 2021 the average cost per patient was 3,400 euro/patient/year. (Salvador-Carulla et al., 2011; Vieta et al., 2021). In Eastern and Central Europe we do not have many studies on these costs, and the development of health systems is inefficient (Krupchanka & Winkler, 2016). To assess the cost of depression for the public health system in Romania, we need to consider the sum of direct costs (the cost of resources used to treat the disease) and indirect costs (the number of resources lost due to the condition that can be attributed to the diagnosis), reaching a total of 5553 euro/year (Iordache et al., 2023).

### *1.2.4 Impact of adjustment and depressive disorders on the population*

The profound economic impact of adjustment and depressive disorders underlines the need for effective and affordable treatment interventions in the public health context. Reducing costs, both direct and indirect, through the implementation of effective treatment strategies can have a significant effect on health budgets and overall population well-being. Investment in mental health programmes that promote access to validated and effective treatments, such as psychological therapies, appropriate medication and supportive therapies, can lead to an overall improvement in mental health at community level. These treatments improve individual symptoms, and can also reduce the incidence of severe cases that require costly interventions, such as long-term hospitalisations or frequent use of emergency services. In addition, the adoption of new technologies and innovative treatment methods, such as rTMS, is an important step in diversifying treatment options and increasing response rates to treatments for

adjustment and depressive disorders. The implementation of this therapeutic approach requires a current analysis of the main therapeutic interventions used by clinicians, as well as the identification of their limitations.

### *1.2.5 General treatment principles of adjustment and depressive disorders*

#### *1.2.5.1 Treatment of adjustment disorder*

There is not much data in the literature on the treatment of adjustment disorder (D. Constantin, Dinu, et al., 2020). From the identified data we can say that the most common therapeutic interventions used are pharmacological, psychological and more recently somatic ones such as rTMS. (D. Constantin, Cioriceanu, et al., 2020; Lefaucheur et al., 2020).

#### *1.2.5.2 Treatment of major depressive disorder*

Major depressive disorder treatment can be achieved through pharmacological, psychological and somatic interventions. Depending on the severity of the depressive episode, one or more interventions may be used to achieve clinical response or remission of the depressive episode (D. Constantin, Cioriceanu, et al., 2020; Lefaucheur et al., 2020; NICE, 2020; VA/DoD Clinical Practice Guideline, 2022)..

#### *1.2.5.3 Integrating rTMS in the treatment of adjustment and depressive disorders: a new perspective in public health*

Integrating and exploring emerging technologies such as rTMS in the management of mental health disorders is a significant step forward in improving the therapeutic response to conventional treatments. In a context where traditional pharmacological and psychological treatment options fail to provide effective solutions for all patients, rTMS offers a promising alternative. rTMS is an innovative, non-invasive therapeutic method that is successfully used in clinical practice in several countries around the world and has numerous applications both in psychiatry and in other areas of medicine. This method of treatment as well as its therapeutic applications in adjustment and major depressive disorder are discussed in detail in chapter 1.3 of the PhD thesis.

## 1.3 Repetitive transcranial magnetic stimulation in public health.

### *1.3.1 Introduction*

Researchers have recently gained advantages from sophisticated methods of non-invasive brain stimulation in people. Transcranial magnetic stimulation is a technique that involves delivering electrical stimuli to conscious persons by applying them through the scalp. Typically, single-pulse stimulation is employed to investigate brain function, however recurrent transcranial magnetic stimulation (rTMS) is utilised to elicit enduring alterations in brain activity beyond the duration of stimulation. Applying non-invasive transcranial magnetic stimulation (TMS) to the motor cortex results in the activation of the specific muscle being targeted, causing a motor action potential (MEP) that may be detected by electromyography (EMG). Furthermore, healthcare practitioners have the potential to get compensation from the Ministry of Health via the diverse national health programmes (Klomjai et al., 2015). Repetitive Transcranial Stimulation has proven to be an effective method for treating a diverse range of neuropsychiatric disorders without

the need for intrusive procedures (Aleman et al., 2007; Devlin & Watkins, 2007; Fregni & Pascual-Leone, 2007; George et al., 2007), moreover there has been a significant surge in the number of applications, as several clinical trials are currently being conducted for a wide range of medical issues.

### *1.3.2 Principles and mechanisms of action of transcranial magnetic stimulation*

Several investigations on individuals with depression who had transcranial magnetic stimulation (TMS) targeting the dorsolateral prefrontal cortex (DLFPC) have shown that high-frequency TMS increases blood flow in specific brain regions, while low-frequency TMS decreases blood flow in those regions (Garnaat et al., 2018; Noda et al., 2015). A study conducted on 15 patients with unipolar depression who underwent HF-TMS treatment on the left DLFPC revealed a notable rise in regional cerebral blood flow in the frontal cortex. This increase was found to be correlated with an improvement in clinical symptoms (Shinba et al., 2018).

### *1.3.3 rTMS in the treatment of Adjustment Disorder*

#### rTMS indications and contraindications

rTMS therapy is used in trauma-related disorders, namely PTSD, with a recommendation level B (probable effect) in the international TMS guidelines published in 2020. (Lefaucheur et al., 2020). Patients who have an elevated risk of experiencing epileptic seizures, metallic implants like clips, electrodes, plates, and stimulators (such as vagus nerve stimulators and deep brain stimulators), metallic fragments (such as bullets), cochlear implants, implanted electrical devices like pacemakers, defibrillators, intracardiac lines, and medication pumps, as well as head or neck tattoos made with ferromagnetic ink, should not undergo this procedure. Additionally, individuals with unstable somatic conditions should also avoid it (Loo et al., 2008; McClintock et al., 2018; O'Reardon et al., 2007; Rossi et al., 2009). TMS can safely be used for people with non-ferromagnetic orthodontic components (braces, implants) as well as those with metal implants from the neck down (McClintock et al., 2018).

### *1.3.4 rTMS in the treatment of Major Depressive Disorder*

#### *rTMS indications and contraindications*

rTMS is specifically recommended for patients diagnosed with major depressive disorder who have not shown improvement after receiving at least one course of antidepressant medication. Additionally, it is suggested for patients who have not responded to multiple courses of pharmacological or psychological treatment, as well as for those who have not responded to electroconvulsive therapy (ECT) (Avery et al., 2008). Additional TMS is indicated for patients who have had a favorable response to a previous session of TMS (Perera et al., 2016). TMS may be beneficial for patients suffering from significant depression and concurrent medical comorbidities, as this treatment does not induce systemic side effects (George, 2019). The use of rTMS for treatment-resistant depression is referenced in the American Psychiatric Association treatment guidelines (Gelenberg, 2010), Canadian Anxiety and Mood Treatment Network (Milev et al., 2016), British Association of Psychopharmacology (Cleare et al., 2015), and by the Royal Australian and New Zealand College of Psychiatrists (Malhi et al., 2015). In addition to the general contraindications described in Chapter 1.3.3, specific contraindications for major depressive disorder should be considered. Psychotic symptoms (e.g. delusions, hallucinations) does not represent a contraindication for treatment of major depression with rTMS. (Ray et al., 2011) although most clinical trials have excluded this category of patients (Grunhaus et al., 2003; Huang et al., 2012; McClintock et al., 2018; O'Reardon et al., 2007; Pallanti et

al., 2010). Some best practice guidelines suggest that severe depressive episode with psychotic symptoms be treated with ECT rather than rTMS (McClintock et al., 2018).

### *1.3.5 Safety and adverse effects of rTMS*

TMS is generally a safe and very well tolerated therapeutic method (George et al., 2010; George & Post, 2011; McClintock et al., 2018; O'Reardon et al., 2007; Perera et al., 2016) that does not cause systemic adverse effects (George, 2019). To avoid adverse effects and conduct the studies safely, the paper followed international safety guidelines and took the rTMS screening questionnaire developed by the international committee Rossi et. al (2009) (Rossi et al., 2009).

### *1.3.6 Comparative cost-effectiveness analysis of rTMS therapy with antidepressant and ECT treatments.*

The cost-effectiveness of any treatment is a major factor in patients' decision to opt for a specific treatment when multiple options are available. rTMS is a non-invasive human brain stimulation method that is increasingly accepted and used internationally for both neurological and psychiatric conditions (Lefaucheur et al., 2020)Health insurance programmes in numerous high-income nations provide full or partial coverage for this particular form of therapy. Initially, a number of cost-effectiveness evaluations were carried out to evaluate the efficacy of rTMS with pharmaceutical treatment (Nguyen & Gordon, 2015; Simpson et al., 2009) and with ECT (Kozel et al., 2004; Vallejo-Torres et al., 2015).

### *1.3.7 Public impact of promoting rTMS in the media*

For more than a decade, researchers have observed a growing popularity of TMS as a therapeutic option (Chail et al., 2018; Ruff et al., 2009) as well as in the area of clinical trials and academic research reporting widely varying results (Chipchase et al., 2012). Throughout this time, the rise in academic and therapeutic popularity has been accompanied by a direct, consumer-oriented marketing approach (M. Ad., 2021). Concerns about this media approach derive from the bigger picture of ethical issues surrounding MST and the media's influence on public perception.

### *1.3.8 Perceptions and experiences of patients undergoing rTMS procedures*

Patient acceptability and perception are factors that need to be changed or intervened in by other social factors that can have an impact, such as the media, advertising, workshops, seminars and conferences. However, from the research conducted, it is still evident that due to the availability of rTMS infrastructure, most research is conducted in Europe. There is still a large ethnographic gap for clinicians using rTMS as a treatment for stress-related disorders, major depression and other psychiatric conditions, which is a universal reality globally. Researchers need to invest in and investigate how rTMS performs in other ethnographic settings, such as in Asian regions and other geographic locations where populations are growing at a very rapid rate and mental disorders occur frequently without technological treatments such as rTMS and people have yet to opt for conventional treatment options.

### *1.3.9 Appropriate qualification of medical staff to perform magnetic stimulation procedures.*

In recent decades, the use of TMS in research centres as well as in private clinics and state

facilities has evolved from a few centres to widespread use. In parallel, applications are much more diverse, and growing both in terms of indications and populations studied. All of these issues can lead to less effective TMS use, such as less effective indications, use outside safety norms and lack of quality control. Training guidelines are needed to avoid such uses (Rossi et al., 2021). Thus at international level we find training guidelines for TMS (Fried et al., 2021).

#### *1.3.10 Regulatory and ethical issues*

When considering the ethical aspects of rTMS, it is important to consider its use in non-therapeutic research, therapeutic research on patients, and therapeutic applications in clinical practice (Rossi et al., 2009, 2021).

### 1.4 Conclusions of the General Part

In conclusion, the PhD thesis through the non-randomized, interventional, pilot studies conducted reinforces the position of rTMS as an innovative treatment of adjustment and depressive disorders. The perceptions and experiences of patients who underwent the rTMS procedure provided valuable insight into the real impact of this therapy. Patient feedback highlights the significance of effective clinician-patient communication and reveals the potential benefits of rTMS in improving quality of life. However, further research is essential to optimise treatment protocols, assess long-term effectiveness and integrate rTMS into public mental health policies.

## CHAPTER 2 - PRACTICAL PART

### 2.1 Aim and objectives of the study

This PhD thesis aimed to examine the possibility of integrating rTMS into public health strategies, addressing its feasibility as a treatment option, an alternative to existing conventional pharmacological therapies.

### 2.2 General methodology

The PhD thesis comprises three research studies conducted between April 2018 and August 2023. Two pilot, interventional, non-randomised research studies and one qualitative research study. These studies are important because they provide important insights into the use of rTMS in private specialist outpatient settings in Romania, thus contributing to the literature from a local context and to advancing the understanding of rTMS in the specific context of mental health in Romania.

### 2.3 STUDY 1 - Evaluation of the efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) in the treatment of adjustment disorder with mixed anxiety-depressive mood.

#### *2.3.1 Introduction*

Adjustment disorder is a common condition in both specialist outpatient clinics and emergency departments as well as in healthcare providers treating patients with cancer conditions. (Huyse et al., 2001; Mitchell et al., 2011). Adjustment disorder is not only commonly found in medical units, but it also has significant implications such as increased suicide rates, higher rates of completed suicide, reduced quality of life, and greater levels of disability. Therefore, adjustment disorder might be regarded as a possible precursor to the emergence of significant psychiatric diseases (American Psychiatric Association, 2013).

#### *2.3.2 Aim and objectives of the study*

##### *2.3.2.1 Purpose of the study*

The objective of the study is to evaluate the suitability of using repetitive transcranial magnetic stimulation (rTMS) as a routine therapeutic approach for managing adjustment disorder with mixed anxiety-depressive mood.

##### *2.3.2.2 The research question*

Can repetitive transcranial magnetic stimulation (rTMS) be an effective and safe treatment method for patients with adjustment disorder with mixed anxiety-depressive mood?

##### *2.3.2.3 Research objectives*

**The main objectives of the research were:**

- Evaluating the efficacy and safety of rTMS in the treatment of adjustment disorder with mixed anxiety-depressive mood.
- Identify predictive factors contributing to a positive clinical response or remission of the

condition.

- Identify demographic factors contributing to the decision to opt for rTMS as a therapeutic method.

### *2.3.3 Material and methods*

#### *2.3.3.1 Study design*

The pilot, interventional, non-randomized study was designed to evaluate the efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) in the treatment of mixed anxiety-depressive mood adjustment disorder diagnosed according to DSM-5 criteria (American Psychiatric Association, 2013). The research was carried out at Englober Medical Center SRL, in Brasov, from April 2018 to August 2023.

#### *2.3.3.2 Inclusion criteria*

Participants who met the inclusion criteria were included in the study.

#### *2.3.3.3 Exclusion criteria*

Participants who met at least one of the exclusion criteria were excluded from the research.

#### *2.3.3.4 Study procedures*

***Information on rTMS treatment***

The rTMS treatment was carried out with a certified CE approved equipment registered with the National Agency for Medicines and Medical Devices in Romania. The magnetic stimulation equipment consisted of the following: 100Hz magnetic stimulator equipped with a standard 8-figure coil and an application of the equipment made by the manufacturer. The equipment application contained pre-installed treatment protocols for various psychiatric conditions, including the protocol used in the study. The stimulation site was manually detected using the "5cm rule" method (Herwig et al., 2001; Pascual-Leone et al., 1996).

***Information on drug treatment***

Psychotropic pharmacological treatment used to treat patients with adjustment disorder with mixed anxiety-depressive mood included medication with: antidepressants, mood stabilizers, antipsychotics, benzodiazepines, hypnotics and antimuscarinic agents.

***Study tools***

Depressive symptomatology of study participants was assessed using the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). The 14-item Hamilton Anxiety Rating Scale (HAM-A) was used to assess anxiety symptomatology. (Hamilton, 1959).

#### *2.3.3.5 Data collected*

Patient data were collected from the records of the Englober Medical Center Ltd., anonymized and then manually entered into an Excel database for statistical processing.

#### *2.3.3.6 Statistical analysis*

Results were analysed in the three study groups using descriptive, comparative and associative statistical analysis. Data analysis in this study was performed IBM SPSS software, trial version 26.0, 1 New Orchard Road, Armonk, New York 10504-1722 USA.

#### *2.3.3.7 Safety and Ethical Issues, Informed Consent*

The study has received the ethics committee's opinion with no. 1.3/21.05.2018, issued by the Ethics Committee for Scientific Medical Research of the Faculty of Medicine of Transylvania University**.**

### *2.3.4 Study results*

A total of 60 patients diagnosed with adjustment disorder with mixed anxiety-depressive mood were enrolled in the study, and they were allocated according to the methodology into three study groups, namely: the group that was treated with rTMS treatment only (n=20, 33.3%), the group that was treated with rTMS treatment and pharmacological treatment (n=10, 16.7%) and the group that was treated with pharmacological treatment only (n=30, 50%).

#### *Patient characteristics*

The demographic data studied included age, gender, background, marital status, education, and occupational status. The sample reveals that the mean age of the patients is 40.07 years. The ages vary from the average by a margin of ±13.89 years. The age range was from 20 to 85 years. The study group included subjects of both sexes, with 60% female representatives and 40% male representatives. The majority of patients participating in the study live in urban areas (85%), while 15% live in rural areas. Almost half of the subjects (41.66%) are married, 30% are single, 18.30% are in a consensual relationship, 6.66% are divorced, while 3.30% are widowed. In terms of education level, the sample includes people with different levels of education: 20% have a high school education, 61.70% have a bachelor's degree, 1.70% have only 8 grades, 5% have completed vocational school, while 11.70% have a master's degree. Analysis of occupational status showed that three quarters of the subjects are employed (75%), 16.70% are not employed and 8.30% are retired.

#### *Depression and anxiety scale scores*

Analysed were the HDRS scores (day 1 and day 30) for depressive symptoms and the HAM-A (day 1 and day 30) for anxiety measures to undertake a descriptive analysis of disease severity at baseline and at the end of the trial. The HDRS score at baseline averaged 18.67. Score values deviate from the mean by plus or minus 6.37. The minimum value was 6, while the maximum value was 34. On day 30, the mean HDRS score value was at an average of 9.35, with a standard deviation of 5.27. The minimum score was 2, while the maximum score was 24. Analysing the sample according to the HAM-A score, the mean value at baseline was 23.02. The minimum value found was 10 and the maximum was 30. The HAM-A score values deviated from the mean value by plus or minus 5.02. On day 30, the mean HAM-A score value was 11.28 with a standard deviation of 5.36.

**Stressors involved in the etiology of adjustment disorder in the sample studied**

The most frequent acute stressors encountered in the study group were: stress at work, relationship tensions, break-ups, deaths in the family, job absence and/or job loss. In one participant, a chronic stressor (complicated divorce in court) was identified that caused a long-lasting symptomatology, closely related to it.

***Treatment with rTMS***

In this section, a descriptive analysis was made of how many patients performed rTMS out of the total number of subjects and how the individual motor threshold intensity (MT%) varied in which rTMS procedures were performed. Thus 50% of patients underwent rTMS using the protocol from methodology at individually determined MT%. Each individual exhibits their own motor threshold response intensity following the application of a magnetic pulse, which is correlated with the individual stimulation intensity. Descriptive statistics of individual stimulation intensity showed an average level of 39.87%. The values deviated from the mean by plus or minus 10.39. The minimum value was 22%, while the maximum value was 65%.

***Psychotropic pharmacological treatment***

The primary categories of psychotropic pharmaceutical medication utilised for managing adjustment disorder with mixed anxiety-depressive mood in the study participants were: benzodiazepines 40%, hypnotics 26.70%, mood stabilizers 25%, antidepressants 25% and antipsychotics 5%. Furthermore, analysis of the distribution of the medications prescribed shows the marked prevalence of benzodiazepines (40%) and hypnotics (26.70%). This hierarchy indicates a preference by clinicians for medications that address immediate symptoms, such as anxiety and insomnia, in contrast to those used on a long-term basis such as antidepressants and antipsychotics. The implications of this distribution for clinical management are profound. The predominance of benzodiazepines may reflect the need to provide patients with rapid symptom relief, while the lower proportion of antidepressants may indicate reservations about their side effects or delay in onset of therapeutic effect.

***Medication associated with comorbid somatic conditions***

Our research revealed that only 28.33% of participants had associated medication for the management of comorbid somatic conditions. Specific analysis of the types of associated medications used indicates sporadic and highly selective use, with the majority of medications given to a single patient (1.70%), with the exception of Betaloc and Duspatalin which were used by three subjects (5%) and two subjects (3.30%) respectively. This distribution reflects a personalized care, where prescribing decisions are likely guided by individual needs and the unique profile of each patient.

***Associated comorbidities***

Our research investigated the presence of comorbidities in a sample of 60 patients, revealing that 46.70% (n=28) of participants had comorbidities at the time of inclusion in the study. In contrast, 53.30% (n=32) had no associated comorbidities. Among the identified comorbidities hypertension and diabetes were found to be the most common, with incidences

of 15% and 6.70% respectively. On the other hand conditions such as vertigo syndrome and Parkinson's disease were reported in a proportion of 1.70% each.

***Severity of depressive and anxiety symptoms at the end of the study***

The intensity of depressed and anxious symptoms was assessed using the prescribed approach on both day 1 and day 30. On the first day, the average HDRS score was 18.67, and on the 30th day, it achieved an average value of 9.35 during the retest. Similarly, the mean initial (day 1) HAM-A score was 23.02, to reach 11.28 on day 30. To see if the levels of HDRS and HAM-A scores decreased significantly at retest compared to the assessment at baseline, the Wilcoxon test was applied. The results indicate that both HDRS ($z=-6.676$, $p<0.001$) and HAM-A ($z=-6.722$, $p<0.001$) score changes were statistically significant.

**Clinical response and remission**

The results of the research study revealed that 60% (n=30) of the patients achieved a clinical response for their condition, and 25% (n=15) of them went into remission following the therapeutic interventions applied in the three study groups.

***Association between demographic variables and clinical response or remission of the condition***

Statistical analysis shows a lack of statistically significant association between demographic variables and clinical response or remission.

***Predictive factors in the occurrence of positive clinical response and remission.***

**Positive clinical response**

Binomial logistic regression was used to predict positive clinical response based on the predictor variables: age, gender, living environment, marital status, education, occupational status, presence of stressors, baseline HDRS score, baseline HAM-A score, and subject group (created based on pharmacological and rTMS treatment benefit). Using the Wald model of regression elimination, characteristics that differentiate individuals who may achieve a positive clinical response from those who do not achieve a positive clinical response were examined. The final regression model indicates that people in the **rTMS-only** group **are more likely to have a positive clinical response.**

**Remission**

To predict remission we considered the following predictor variables: age, gender, living environment, marital status, education, occupational status, presence of stressors, baseline HDRS score, HAM-A score, and subject group (created based on medication and rTMS benefit). Using the Wald model of regressive elimination, characteristics that differentiate individuals who may achieve remission from those who do not were analyzed. **The final regression model indicates that people on medication only and with a low HAM-A score are more likely to achieve remission.**

***Relationship between demographics and the choice of rTMS treatment***

Patients' choice of magnetic stimulation does not differ significantly by gender, marital status, education level and occupational status. The research explored how the option for rTMS stimulation also differs according to the living environment of the study participants. In this case we observe a higher proportion of urban people who opted for rTMS (56.9%) compared to rural people (11.10%). The difference between the two living environments is statistically significant (p=0.011).

**Adverse reactions encountered during the study to the different types of interventions**

During the study participants did not experience any serious adverse reactions to the different types of treatments used in the study. Following rTMS treatment, four patients experienced pain at the stimulation site during the sessions and two patients experienced transient dizziness immediately after the end of treatment. Regarding antidepressant medication, three patients experienced gastrointestinal side effects, and six patients reported feeling sedated following benzodiazepine administration.

### *2.3.5 Discussion*

The research study included 60 participants who were divided into groups and treated according to the methodology. The results of the study show that 60% of the total number of participants achieved a positive clinical response following the different interventions applied according to the study group, and 25% of the patients achieved remission of the condition. Analysing by study group we can see that **complete remission of depressive symptoms was very high in the rTMS-only group (80%),** compared to the other groups where the proportion of complete remission was significantly lower, 40% in the psychotropic pharmacological treatment only group and 20% in the rTMS and psychotropic medication group. The efficacy ratio of rTMS in our research study is higher than that presented in the literature and international guidelines for stress-related disorders (Lefaucheur et al., 2014, 2020).

### *2.3.6 Conclusions*

The study sample found rTMS to be an effective, innovative, and non-invasive therapy approach for treating adjustment disorder with mixed anxiety-depressive mood. Research emphasises the greater effectiveness of rTMS in alleviating depressed symptoms compared to typical pharmaceutical treatment. Out of all the individuals, a notable 80% who just got rTMS obtained complete remission, while the groups who received pharmacological treatment or a combination of treatments did not achieve the same level of remission. The results suggest that rTMS could be a more efficient alternative for patients who have an inadequate response to medicine, experience negative side effects, or prefer non-pharmacological therapy choices.

Magnetic stimulation therapy is both safe and well tolerated by patients, exhibiting a minimal occurrence of side effects. This discovery is significant for patients who might hesitate to experiment with novel treatment methods due to safety apprehensions.

The study found no statistically significant correlations between demographic variables, such as age, gender, background, or marital status, and positive clinical response or remission of the condition. Repetitive Transcranial Magnetic Stimulation (rTMS) has the capacity to provide benefits to a diverse spectrum of individuals, irrespective of demographic variables.The conclusive binomial regression model shows that persons in the rTMS-only group had a higher

probability of attaining a favourable clinical response, whereas those solely on medicine with a low HAM-A score have a higher likelihood of achieving remission.

The decision of patients in the study sample to perform rTMS procedures was influenced by their urban background. It is notable that the majority of urban patients opted for rTMS, which may reflect better accessibility and awareness of this treatment option in urban areas. This highlights the need to improve access to rTMS in rural areas and to increase awareness of this therapy among the population.

The results of the research can be taken into consideration by public health specialists with a view to introducing rTMS as a standard treatment option, or as an adjunctive treatment for patients diagnosed with adjustment disorder with mixed anxiety-depressive mood, and it is necessary to create public health policies aimed at promotion, increasing patients' accessibility to treatment by creating the necessary infrastructure at national level, as well as introducing rTMS in the list of procedures paid for by CNAS. Adjustment disorders generate significant financial costs, both direct and indirect, and effective treatment methods such as rTMS could reduce the financial burden on the health system and patients.

**Limitations**

The statistically significant beneficial effect obtained at the end of the study (day 30) following the application of the LF rTMS treatment protocol in right DLFPC was not evaluated in terms of its duration. In some studies, the effect of low frequency stimulation can last up to two weeks (Watts et al., 2012) whereas high frequency stimulation can last up to 3 weeks (Cohen et al., 2004). Otherwise, we cannot argue that the protocol used in our study may be superior to the protocol present in high frequency treatment guidelines that present a type B recommendation level for PTSD (Lefaucheur et al., 2020).

## 2.4 STUDY 2 - Evaluation of the Efficacy and Safety of Repetitive Transcranial Magnetic Stimulation (rTMS) as an Adjuvant Treatment for Major Depressive Disorder.

### *2.4.1 Introduction*

Major depressive disorder is a severe mental illness and is one of the leading causes of disability worldwide (James et al., 2018). Of the 3.8% of the global population suffering from major depression, many have high rates of mortality and suicidal behaviour. (Briley & Lépine, 2011; Institute of Health Metrics and Evaluation, 2023). Currently there are many standard treatment approaches for major depressive disorder including psychotropic pharmacological treatment (monotherapy or combined pharmacological treatment), psychological treatment and somatic treatment such as rTMS, or tDCS. (Sinyor et al., 2010; UK ECT Review Group, 2003). Although many therapeutic options exist internationally, they are not available in low- and middle-income countries. (O'Reardon et al., 2007) such as Romania. As for rTMS for the first time it was approved by the FDA in 2008 following studies that proved the efficacy of the therapy for patients with treatment-resistant major depression. (George et al., 2010; O'Reardon et al., 2007). Then guidelines establishing the clinical applications and efficacy of rTMS procedures in major depression in 2014 (Lefaucheur et al., 2014) and 2020 (Lefaucheur et al., 2020) assigned a recommendation level A (safe effect).

### *2.4.2 Aim and objectives of the study*

#### *2.4.3.1 Purpose of the Study*

The study evaluates the efficacy and safety of using rTMS as an adjunct to standard pharmacological treatment for patients with major depressive disorder, in the context of specialist outpatient clinics in Romania.

#### *2.4.3.2 The research question*

Can repetitive transcranial magnetic stimulation (rTMS) be a safe adjunctive treatment for patients with major depressive disorder in Romanian outpatient clinics?

#### *2.4.3.3 Study objectives*

The main objectives of the study were

- Evaluation of the efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) as an adjuvant treatment for patients with major depressive disorder in Romanian outpatient clinics.
- Identify predictive factors contributing to a positive clinical response or remission in patients.
- Identify demographic variables that contribute to the decision to opt for rTMS as an adjunctive treatment to psychotropic medication.

### *2.4.3 Material and methods*

#### *2.4.3.1 Study design*

This pilot, interventional, non-randomized study included patients diagnosed with Major Depressive Disorder according to DSM-5 (American Psychiatric Association, 2013), who were registered in the private specialist outpatient clinic of Englober Medical Center SRL, Brasov. The study period was April 2018 - August 2023. Subjects enrolled in the study were divided into two groups according to the type of treatment received and preferred by patients: the group that was treated with rTMS and pharmacological treatment, the group that was treated with pharmacological treatment only.

#### *2.4.3.2 Inclusion criteria*

All patients included in the research study met inclusion criteria.

#### *2.4.3.3 Exclusion criteria*

Patients who met at least one of the exclusion criteria were excluded from the study.

#### *2.4.3.4 Study procedures*

***Treatment information***

The rTMS treatment was carried out with a CE certified equipment which was composed of the following components: a 100Hz magnetic stimulator equipped with a standard 8-figure coil and an application of the equipment made by the manufacturer with pre-installed protocols for different psychiatric conditions. The specific protocol selected for this study was part of the pre-installed protocols. Each patient completed 20 sessions with the protocol described above over a period of 4 weeks to be included in the study. The stimulation site was determined using the ''5cm rule'' method. (Herwig et al., 2001; Pascual-Leone et al., 1996).. Psychotropic pharmacological treatment used to treat MDD patients included medication with antidepressants, mood stabilizers, antipsychotics, benzodiazepines, hypnotics and antimuscarinic agents.

***Study tools***

The effectiveness of different therapeutic methods in the two study groups was assessed using the Hamilton Depression Rating Scale-17 items (HDRS) (Hamilton, 1960) for depressive symptoms and Hamilton Anxiety Rating Scale-14 items (HAM-A) (Hamilton, 1959) for anxiety symptomatology that were administered to patients by the clinician on Day 1 (baseline) and Day 30 (end of study).

#### *2.4.3.5 Data collected*

All data were anonymised and then manually entered into an Excel database for statistical processing. Patient data were taken from a private specialist outpatient clinic in Romania (Englober Medical Centre SRL).

#### *2.4.3.6 Statistical analysis*

The results were analysed in two study groups (psychotropic pharmacological treatment only group and psychotropic pharmacological treatment and rTMS group) using descriptive, comparative and associative statistical analysis. Analysis of the data in this study was performed IBM SPSS software, trial version 26.0, 1 New Orchard Road, Armonk, New York 10504-1722 USA.

#### *2.4.3.7 Safety and Ethical Issues, Informed Consent*

All study participants signed informed consent and agreement to rTMS procedures prior to inclusion in the study. The study has received the ethics committee approval no. 1.3/21.05.2018, issued by the Ethics Committee for Medical Scientific Research of the Faculty of Medicine of Transylvania University

### *2.4.4 Study results*

Forty patients with major depressive disorder who met the inclusion criteria were enrolled in the second study of the PhD thesis. Patients were assigned according to the methodology into two study groups, namely: the group that was treated with rTMS and psychotropic pharmacological treatment (n=20, 50%) and the group that was treated with psychotropic pharmacological treatment only (n=20, 50%).

#### *Patient characteristics and treatment information.*

The demographic variables analysed were age, gender, background, marital status, education, occupational status. It is found that the average age of the patients in the sample is 40.73 years. The ages deviate from the average by plus or minus 15.57 years. The minimum age was 20 years, while the maximum age was 75 years. The study group includes subjects of both sexes, with 65% female representatives, while 35% male representatives.Analyzing the background we observe that the majority of patients participating in the study (62.50%) live in urban areas, while 37.50% live in rural areas. In terms of marital status we observe that almost half of the subjects (45%) are married, 30% are single, 20% are in a consensual relationship, while 5% are divorced. The sample includes people with different levels of education: 37.50% have a high school education, 27.50% have a bachelor's degree, 15% have only 8 grades, 10% have completed vocational school, 7.50% have a master's degree, while 2.50% have a post-secondary degree. Analysis of occupational status shows that more than half of the subjects (52.50%) are employed, 32.50% are not employed and 15% are retired.

#### **Depression and anxiety scale scores**

Descriptive analysis of disease severity on day 1 and day 30 was performed by analyzing HDRS scores (day 1 and day 30) for depressive symptomatology and HAM-A (day 1 and day 30) for measuring anxiety levels. The HDRS score at baseline averaged 23.75. The score values deviate from the mean by plus or minus 4.93, as shown in the following table. The minimum value was 14, while the maximum value was 32. On day 30, the mean value of the HDRS score averaged 10.83, with a standard deviation of 5.95. The minimum score was 2, while the maximum score was 24. Analysing the sample according to the HAM-A score, the mean value at baseline was 22.93. The minimum value found was 10 and the maximum was 29. The HAM-A score values deviated from the mean value plus or minus 5.10. On day 30, the mean HAM-A score value was 9.98 with a standard deviation of 4.79.

**Adjuvant treatment with rTMS**

The descriptive results of the research regarding the number of patients who underwent adjuvant rTMS treatment and how the individual motor threshold intensity (MT%) varied, revealed that half of the participants underwent this procedure (50%, n=20). The individual stimulation intensity of the patients was identified according to the methodology thus the average stimulation intensity level was 47.55%. The values deviated from the mean plus or minus by 12.17. The minimum value was 30% while the maximum value was 70%.

***Psychotropic pharmacological treatment***

In this study all study participants (100%) also received medication. The main classes of psychotropic medication found in the study were: antidepressants 92.50% (n=37), benzodiazepines 57.50% (n=23), hypnotics 37.50% (n=15), antipsychotics 32.50% (n=13), mood stabilisers 10% (n=4) and antimuscarinic agents 2.50% (n=1).

**Treatment of associated comorbidities**

Out of the individuals who participated in the trial, 25% (n=10) received additional medicine for their comorbidities, whereas 75% (n=30) did not receive any more medication. Out of the total number of patients (n=10), 25% of them had stable comorbid disorders and received medical treatment at the same time as psychotropic pharmaceutical treatment.

**Associated comorbidities**

Of the study sample 40% (n=16) of the study participants had associated comorbidities, while 60% (n=24) had no such conditions. Among the most common associated comorbidities were hypertension (22.50%), gastritis (5%) and hypothyroidism (5%).

***Evolution of the severity of depressive and anxiety symptoms***

At the initial assessment the average HDRS score was 23.75 and at retest it reached an average of 10.83. The average initial HAM-A score was also 22.93, and on day 30 it was 9.98. To see if the levels of HDRS and HAM-A scores decreased significantly at retest compared to the assessment made at baseline, we applied the Wilcoxon test. The results indicate that both the change in HDRS score ($z=-5.515$, $p<0.001$) and HAM-A score ($z=-5.521$, $p<0.001$) were statistically significant.

**Clinical response and remission of depression.**

Study outcomes were expressed by clinical response, defined as a> 50% reduction in depression score at 30 days after baseline assessment, and remission, defined by a score below 7 on the HDRS and below 9 on the HAM-A. Thus, 60% (n=24) of study participants showed a clinical response and 30% (n=12) went into remission.

***Association between demographic variables and clinical response***

The statistical analysis results indicated that there was no statistically significant correlation between the gender, marital status, education level, occupational status of the individuals, and

their positive therapeutic response. A strong correlation was found between the living environment and clinical response, as indicated by the statistical analysis (χ2 =7.111; df=1; p=0.008). Therefore, it is evident that rural individuals exhibit a substantially greater proportion of clinical response (86.70%) in comparison to urban individuals, who only have a clinical response rate of 44%. The group that got solely psychotropic pharmaceutical treatment exhibited a considerably higher clinical response rate (80%) compared to the group that received both rTMS and psychotropic pharmacological treatment (40%). Based on the outcome of the chi-square test (χ2 =6.667; df=1, p=0.010), we can confidently conclude that there is a clear connection between clinical response and the groups mentioned. The medication-only group exhibited a much greater clinical response.

***Association between demographic variables and disease remission***

It is found that the relationship between participants' gender, living environment, marital status, education level, occupational status and remission is not statistically significant. Rural patients, however, show higher weights in achieving remission compared to urban patients. The bivariate Chi-square test ($\chi^2$ ) indicated the presence of a significant association between education and the presence of remission ($\chi^2$ =16.703; df=5; p = 0.005). Thus, from the contingency table (cross tabulated) below, we observe a higher proportion of remissions in people with low education (8 grades - 50%, vocational school - 75%). We observe a higher percentage of remissions in people who received medication only (45%) compared to people who received concurrent TMS and medication (15.0%). The difference between the two groups is statistically significant (p=0.038).

***Predictors of a positive clinical response***

To predict positive clinical response (as defined above) according to the predictor variables: age, gender, living environment, marital status, education, occupational status, baseline HDRS score and subject group (created based on medication and TMS benefit), binomial logistic regression was used. Using the Wald model of regression elimination, characteristics that differentiate individuals who can achieve a positive clinical response from those who do not achieve a positive clinical response were examined. **The final regression model indicates that people in rural areas and with a low HDRS score are more likely to have a positive clinical response.**

***Predictive factors in the occurrence of disease remission***

The study considered the following predictor variables for predicting remission: age, gender, living environment, marital status, education, occupational status, baseline HDRS score, HAM-A score, and subject group (based on receipt of psychotropic pharmacological treatment and rTMS). Using the Wald model of regressive elimination, the research examined characteristics that differentiate individuals who can achieve remission from those who do not. **The final regression model indicates that people receiving psychotropic pharmacological treatment only and with a low HDRS score are more likely to achieve remission.**

***Relationship between demographics and the option to follow adjuvant treatment with rTMS***

There was no statistically significant difference in patients' selection of magnetic

stimulation based on gender, marital status, and occupational status. The study investigated the variations in stimulation choices based on the living environment of the subjects. The study demonstrates that a greater percentage of individuals residing in urban regions chose to undergo transcranial magnetic stimulation (68%) in comparison to those residing in rural areas (20%). The disparity between the two living settings exhibits a statistically significant distinction, as evidenced by a p-value of 0.003. There is a strong and meaningful relationship between the level of education and the preference for magnetic stimulation. This relationship is supported by statistical evidence ($\chi 2$ =13.388; df=5; p=0.020). It is observed that those with a high school and undergraduate education are given more importance when it comes to executing magnetic stimulation. The Cramer's V coefficient, with a value of 0.579, suggests a strong correlation between the two variables.

### *2.4.5 Discussion*

The second research study in the PhD thesis showed a clinical response in 60% (n=24) of patients and 30% (n=12) of participants went into remission. Although the results of the study were promising overall, it should be noted that the study group receiving only psychotropic pharmacological treatment showed a higher percentage of remissions 45% (n=9) compared to those receiving concurrent rTMS and pharmacological treatment 15% (n=3). The difference between the two groups was also statistically significant (p=0.038). These results do not reflect the level of efficacy contained in the international rTMS guidelines for major depressive disorder. (Lefaucheur et al., 2014, 2020). The lack of efficacy of rTMS in the research study may be correlated with the fact that, even for pharmacological treatment, the chances of a patient achieving remission through medication decreases with each failed course of treatment (Brakemeier et al., 2007; Rush et al., 2006b; Sackeim et al., 1996; Sinyor et al., 2010).

### *2.4.6 Conclusions*

The **lack of efficacy of rTMS as an adjunct to pharmacological treatment for patients with major depressive disorder in the study sample** is in contrast to most studies in the literature. The benefits of rTMS may vary depending on specific individual factors or stimulation parameters. It is possible that subgroups of patients who might benefit from rTMS were underrepresented in our sample, or that the methodology of rTMS implementation may require fine-tuning to maximize the effectiveness of the procedure.

Patients undergoing rTMS therapy have seen little and temporary side effects, indicating that the treatment is safe and well-tolerated. The lack of hypomania induction and other severe side effects aligns with the findings in current literature, indicating that rTMS is a therapy option that has a favourable safety profile.

The association between demographic variables and clinical response, or remission, revealed that rural participants are more likely to have a positive clinical response, demonstrating that environmental and lifestyle factors can influence treatment efficacy. Participants with a lower level of education (8th grade - 50%, vocational school - 75%) were more likely to achieve remission of depression. Patients who were treated with medication alone were statistically significantly more likely to achieve both a positive clinical response and remission.

The prevalence of comorbidities in the sample studied highlights the importance and holistic treatment in the management of major depressive disorder, taking into account other somatic conditions that may complicate their treatment and recovery.

Observations on patients' decision to choose rTMS reflect an increased acceptance of this therapy among urban and better educated people, possibly due to better information and accessibility to innovative treatments.

These findings emphasise the significance of continuously evaluating prescribing methods and customising treatments based on the intricate symptom profile and coexisting medical conditions of patients diagnosed with major depressive disorder. Additional evidence regarding the efficacy of the therapy, together with a thorough examination of the cost-effectiveness of these approaches in comparison to conventional pharmacological therapies or psychological interventions, is required in order to incorporate the use of rTMS in public health campaigns.

## Limitations

The trial conducted in the outpatient environment did not have the opportunity to include a placebo rTMS control group. Furthermore, due to rTMS not being utilised as a primary treatment, we were unable to assess its effectiveness without concurrent pharmaceutical intervention. The study group was limited in size due to the minimal availability of patients in Romania for rTMS, so the findings cannot be extrapolated. Due to the study's brief duration, it is not possible to demonstrate the long-term effects of rTMS therapy. Due to the higher number of female participants in the study, the findings may have limited relevance to men. Therefore, additional research is necessary to investigate the variations in response to rTMS between genders.

## 2.5 STUDY 3 - Exploring the perceptions and experiences of patients treated with rTMS for adjustment disorder and major depressive disorder in a private specialist outpatient clinic in Romania

### *2.5.1 Introduction*

Adjustment disorders and major depression are major global public health problems. The impact of these conditions on morbidity and disability rates are very high (Reddy, 2010). Like the global population, Romanians also suffer from multiple conditions and challenges, which have been shown to impact on mental health disparities and their treatment. In terms of mental health conditions pharmacological treatment and psychotherapy are the main approaches for adjustment disorder and major depressive disorder (Brătucu et al., 2022; D. Constantin, Dinu, et al., 2020).

Research has shown that the Romanian health system is somewhat stagnant at present, with gaps and many shortcomings. However, there are many positive aspects of the Romanian health system. To increase the overall accessibility and quality of mental health care, including the availability of rTMS treatment options in private practices, there is a large gap between effective public health interventions and investments to improve the overall scenario. A better public health approach is that not only treatment should be focused, but a preventive approach should be adopted which could lead to an increase in the engagement of Romanians in mental health services (Petre et al., 2023). The effectiveness of rTMS as a treatment option for depression and adjustment disorders is perceived by the patient and this may also influence the patient's decision-making process. Issues such as public health commitments, awareness, education, access to services, reduction of negative perceptions, and effective communication about treatment play a large role in shaping patient decision-making processes when it comes to the use of rTMS for mental health treatment in private practice (Deng et al., 2023). The present study explores the perceptions and experiences of patients who have undergone rTMS procedures for adjustment disorder and major depressive disorder in private practices in Romania.

### *2.5.2 Aim and objectives of the study*

#### *2.5.2.1 Purpose of the Study*

The aim of the study was to investigate the perceptions and experiences of patients treated with rTMS for adjustment disorder with mixed anxiety-depressive mood and major depressive disorder in private specialist outpatient clinics in Romania.

#### *2.5.2.2 Research questions*

- How do patients with adjustment disorder with mixed anxiety-depressive mood and major depressive disorder perceive the efficacy and acceptability of repetitive transcranial magnetic stimulation (rTMS) in the context of private healthcare in Romania?
- What factors influence patients' decision-making processes regarding the use of repetitive transcranial magnetic stimulation (rTMS) for the treatment of adjustment disorder and major depressive disorder in private specialist outpatient clinics in Romania?

#### *2.5.2.3 Study objectives*

- Investigating patient perspectives on repetitive transcranial magnetic stimulation (rTMS) as a treatment option for major depression and adjustment disorder with anxiety-

depressive mood in private specialist outpatient clinics in Romania focusing on their experiences, perceptions and decision-making processes.

### *2.5.3 Material and methods*

#### *2.5.3.1 Study design*

The qualitative research study using semi-structured interview included patients diagnosed with adjustment disorder with mixed anxiety-depressive mood and major depressive disorder according to DSM-5 (American Psychiatric Association, 2013), who were treated with rTMS and were registered in a private specialist outpatient clinic of the Englober Medical Center SRL, Brasov. Semi-structured interviews were applied to patients after the completion of rTMS treatment sessions, the research was conducted between April 2018 and August 2023.

#### *2.5.3.2 Inclusion criteria*

Patients included in the qualitative research study met the following criteria:

1. Be diagnosed with major depressive disorder or adjustment disorder with mixed anxiety-depressive mood according to DSM-5.
2. Have been treated with a full course of rTMS for their condition.
3. Sign the informed consent for the semi-structured interview.

#### *2.5.3.3 Exclusion criteria*

Patients who met one of the criteria below were excluded from the study:

1. They have not completed all rTMS sessions for their condition.
2. They were treated only with psychotropic pharmacological treatment.
3. They refused to participate in the semi-structured interview at the end of the treatment sessions.

#### *2.5.3.4 Study procedures*

***Study instrument***

A semi-structured interview with 11 questions was created for the qualitative research. The questions were specifically designed so that the patients' answers would provide information about their perceptions, experiences and factors that led to their decision to opt for rTMS.

#### *2.5.3.5 Data collected*

***Data recording and preparation for the analysis process***

Qualitative data were collected from the study participants through semi-structured interviews, which were audio-recorded in Romanian, then transcribed into Romanian and translated into English for thematic content analysis. After transcription and translation the data were arranged, organized, cleaned and coded for thematic content analysis. Thematic content analysis is one of the most important and reliable qualitative analysis techniques. Interviews were taken from patients in a private specialist outpatient clinic in Romania (Centro Medical Englober SRL).

#### *2.5.3.6 Data analysis*

The analysis of the initial interview data in Romanian was carried out after transcription. The transcribed material was read several times to identify similarities and patterns in the participants' responses. An open coding process was adopted to identify manual themes and sub-themes in the qualitative data. Manual coding of the transcripts provided information to the researcher and helped to identify themes and sub-themes. The themes and sub-themes identified are presented below. Qualitative data obtained from the semi-structured interviews were analysed thematically using NVivo 14 software, which is a product of QSR International for qualitative analysis, to better understand the issues and arrive at definitive answers to the predefined research questions.

#### *2.5.3.7 Safety and Ethical Issues, Informed Consent*

The study has received the ethics committee's opinion no. 1.3/21.05.2018, issued by the Ethics Committee for Medical Scientific Research of the Faculty of Medicine of Transylvania University.

### *2.5.4 Results and Discussion*

Twenty participants were included in the research study and thus 10 semi-structured interviews were conducted for patients with adjustment disorder and 10 interviews for those diagnosed with major depressive disorder who were treated with rTMS. The demographic information of the study participants with their codes is presented below.

#### *Theme 01: Effectiveness and acceptability of rTMS*

In terms of finding similarities and patterns among the semi-structured interview transcripts, the transcripts were analysed by a word query test, limited to the 20 most frequent words with their associated synonyms for the current topic, to gain a better insight into NVivo 14. The study used the word cloud to visually represent the frequency of words in the semi-structured interview transcripts analysed. The generated word cloud illustrates key terms associated with rTMS and its relevance as an alternative to pharmacological treatment and psychotherapy.

The acceptability of rTMS among people is generally high, especially given its non-invasive nature and lower risk of side effects compared to antidepressant drugs. Common side effects are usually mild and may include headaches, scalp discomfort at the site of stimulation, tingling or dizziness. Because it does not require sedation or anesthesia, individuals can return to their normal activities immediately after each treatment session, which also contributes to its high acceptability. rTMS is seen as a valuable alternative for those seeking options beyond medication and psychotherapy, particularly for treatment-resistant depression and stress-related disorders. The fact that it is a targeted treatment, a treatment with fewer systemic side effects, makes it an attractive option for many. It's also worth noting that as awareness and availability of rTMS has increased, so has its acceptance among both patients and healthcare providers. Individuals' perspectives on rTMS may vary depending on their personal experiences, the information they have received and their attitudes towards non-traditional treatments.

***Sub-theme 01: Acceptance of rTMS***

Repetitive Transcranial Magnetic Stimulation (rTMS), is an innovative and non-invasive treatment modality that is gaining recognition and acceptance due to its effectiveness in the management of depression, certain stress-related disorders and anxiety disorders. For depression, especially treatment-resistant depression, where traditional treatments, medication and psychotherapy have not been effective, rTMS offers a viable alternative. Its acceptance is growing, partly due to the wealth of evidence supporting its effectiveness. Clinical studies have shown that rTMS can lead to a significant reduction in symptoms for many patients, and some even achieve remission. The non-invasive nature of rTMS, along with its relatively mild side-effect profile, usually limited to temporary discomfort at the site of stimulation or mild headaches, contributes to the favourable perception among patients and clinicians. Beyond major depressive disorder, rTMS has also been explored as a treatment for other mental disorders, although its use in these conditions is more investigational and less established. There is also growing interest in applying rTMS to treat certain stress-related disorders, with preliminary studies showing promise.

The attractiveness of rTMS in these areas stems from the same benefits seen in the treatment of depression. A non-pharmacological approach with few side effects and the potential for significant improvements where other treatments have failed. Acceptability of rTMS is relatively high, especially among patients who have had problems with side effects of medication or those who have not achieved satisfactory results from other treatments. Healthcare providers are increasingly recognising rTMS as a valuable tool in the treatment arsenal for depression and potentially for other stress and anxiety disorders. Technological advances and the accumulation of positive clinical outcomes have helped in this regard, although affordability issues and insurance coverage still limit its use for some patients.

***Sub-theme 02: Effectiveness***

Transcranial magnetic stimulation, TMS, has implications for public health, particularly in the context of treating mental health conditions such as major depressive disorder and stress-related disorders, for which it has been most extensively studied and applied. Its effectiveness in this area can influence broader public health outcomes by improving individual well-being, reducing the overall burden of mental illness, and potentially affecting healthcare costs and resource allocation. rTMS has been shown to be effective in reducing symptoms of depression, particularly in people who have not responded to traditional treatments such as antidepressant medication or psychotherapy. For public health, this means offering a viable additional treatment option that can help reduce the overall burden of depression. Depression is a leading cause of disability worldwide, and effective management of this condition is crucial to improving quality of life and reducing health costs associated with untreated mental health conditions. Perceptions provided by study participants are presented here as annotations.

rTMS is being researched for its potential to treat other mental health conditions, including anxiety disorders, PTSD and obsessive-compulsive disorder. Its effectiveness in these areas could further impact public health by providing new avenues of treatment. This is particularly important for conditions that are difficult to treat or for which there are limited treatment options available. Although rTMS is a promising public health tool for mental health treatment, there are challenges to its widespread adoption. These include ensuring quality and consistency in treatment delivery, training providers, and continuing to research and refine treatment protocols for best outcomes.

***Theme 02: Influencing factors in the decision for rTMS***

In terms of identifying similarities and patterns among the semi-structured interview transcripts, the transcripts were subjected to a word search test limited to the 20 most frequent words and their associated synonyms for the current topic in order to gain a clearer perspective in NVivo 14.

The effectiveness of TMS, particularly in cases of treatment-resistant depression, is a significant factor underlying its consideration. People who have navigated through the challenges of conventional treatments without satisfactory results often turn to rTMS with great hope. The non-invasive nature of rTMS, combined with a relatively benign side-effect profile compared to pharmacological interventions, positions it as an appealing option for those wary of the adverse effects associated with traditional drugs.

Affordability issues, including cost of treatment and insurance coverage, are significant barriers to choosing rTMS. The financial implications of rTMS, which can be substantial, are a critical consideration for many, particularly in regions where healthcare costs are predominantly borne directly by the patient or where insurance coverage for rTMS is limited. The geographical availability of rTMS clinics can influence the decision-making process, as the logistical challenges of attending regular treatment sessions may discourage people living far from specialised centres. The influence of healthcare providers in guiding treatment choices is another important factor.

Individual attitudes towards mental health treatment and the problems associated with certain treatments can influence decision-making. Some individuals may see rTMS as a last resort, to be considered only after all other options have been exhausted, while others may see rTMS as a preferable alternative to medication because of concerns about drug dependence or side effects. The decision to pursue rTMS is multi factorial, influenced by efficacy considerations, personal testimonials, accessibility lity, healthcare provider recommendations, and individual beliefs about mental health treatment. As research on rTMS continues to grow and societal attitudes toward mental health evolve, it is likely that more individuals will consider rTMS as a viable treatment option for managing their conditions.

***Theme 03: Comparing rTMS with other treatments***

In terms of identifying similarities and patterns among the semi-structured interview transcripts, the transcripts were subjected to a word search test limited to the 20 most frequent words along with their associated synonyms for the current topic to gain a clearer perspective in NVivo 14.

rTMS represents a significant advance in non-invasive treatment options, offering a distinct alternative to pharmacotherapy and psychotherapy. Its emergence is particularly relevant in public health discussions due to the growing need for diverse and accessible treatment options. One of the main advantages of rTMS from a public health perspective is its ability to provide a treatment option for patients with treatment-resistant depression. This represents a sizable portion of the population that does not respond to traditional antidepressants or psychotherapy.

Integrating rTMS into public health strategies is not without its challenges. The initial cost and resource investment for rTMS equipment and trained staff is significant, which can impact its availability, particularly in lower income areas or in health systems already strained by limited resources. Although rTMS is an effective treatment option for some, it is not universally effective, and determining which patients might benefit most remains an area of ongoing research. Comparing rTMS with other emerging non-invasive brain stimulation techniques, such as

transcranial direct stimulation, TDCS, reveals a rapidly evolving mental health treatment landscape. Each of these modalities offers unique benefits and limitations, and their comparative effectiveness and applicability to different patient populations are central to public health discussions about optimizing mental health care.

rTMS adds value to mental health treatment options, offering a combination of efficacy and safety that is particularly attractive to public health initiatives aimed at addressing treatment-resistant conditions. The ongoing comparison and integration of rTMS with traditional and emerging treatments is vital to the development of comprehensive, accessible and effective public health strategies for mental health care. As research continues to evolve, so will the role of rTMS in public health, potentially expanding its application and accessibility to benefit a broader spectrum of individuals.

### *2.5.5 Conclusions*

Several key findings emerged from this study regarding rTMS efficacy, acceptability, and influential factors affecting individuals' decisions to opt for this treatment. rTMS is a useful treatment modality in various psychiatric disorders, particularly depression, where it has been rigorously evaluated. Its effectiveness is particularly pronounced among populations with treatment-resistant depression, offering a viable alternative where traditional pharmacological interventions and peptide psychotherapy have failed. The acceptability of rTMS among patients and healthcare providers is generally high, attributed to its non-invasive nature, minimal side effects and the absence of the need for anaesthesia. This acceptability is crucial to its integration into standard psychiatric care, promoting a wider understanding and willingness to adopt this modality as part of comprehensive treatment plans. The personal testimonies of those who have experienced substantial improvements in their symptoms contribute to the growing acceptance and demand for this treatment.

The decision to follow rTMS is influenced by a complex of factors. Cost of treatment and insurance coverage are significant barriers, especially in regions where such treatments are not widely covered by health insurance plans. Accessibility also plays a critical role, with the availability of rTMS services varying considerably by geographic location, potentially limiting access for those in rural or underserved areas. Referral of health professionals based on their knowledge and understanding of rTMS is another important factor, highlighting the need for continuing education and training in this area. Personal attitudes towards mental health treatment, influenced by social factors and individual beliefs, can facilitate or hinder the decision to pursue rTMS. The emerging body of research and clinical trials continues to shape perceptions, gradually alleviating concerns and scepticism by highlighting the scientific basis and therapeutic potential of rTMS.

rTMS is emerging as a compelling treatment option in the field of psychiatry, evidenced by its effectiveness in treating certain disorders and high acceptability among both patients and clinicians. Wider implementation and use of rTMS depends on addressing the influential factors governing access and choice. As the body of evidence supporting rTMS continues to expand, along with efforts to improve accessibility and affordability, it can be anticipated that rTMS will occupy a more prominent position in the public health strategy for managing mental health disorders. This development requires an approach that embraces clinical innovation, public health policy and societal attitudes towards mental health treatment to fully realise the potential of rTMS in contributing to mental health care.

Focusing on rTMS in the Romanian context offers a unique perspective, given the country's health infrastructure, public health policy and societal attitudes towards mental health treatment. The effectiveness of rTMS as a treatment option for depression and other mental health disorders is well documented globally, and this extends to its potential application in Romania. The accessibility and acceptability of rTMS in Romania are influenced by specific national factors, including health funding, availability of rTMS-trained medical professionals, and public awareness of mental health treatments. The Romanian health system has faced challenges related to funding, resource allocation and ensuring equitable access to care. These factors may influence the availability of innovative treatments such as rTMS. For rTMS to be widely accepted and used, concerted efforts should be made to invest in the necessary equipment and to train health professionals in this specialised treatment. Public health initiatives could also play a vital role in raising awareness of rTMS among the general population and medical professionals, highlighting its benefits and potential as an alternative to traditional treatments.

Acceptance of rTMS among patients in Romania may be influenced by societal attitudes towards mental health. There is a continuing need to address the issues and promote understanding and openness towards mental health problems and treatment options. Greater awareness and acceptance may lead to increased demand for rTMS, which in turn could improve availability and access. Economic factors, such as the cost of rTMS and insurance coverage, are critical in determining the feasibility of opting for this treatment. In Romania, as in many other countries, the extent to which innovative treatments are covered by public health insurance or require out-of-pocket expenditure can significantly affect their accessibility. Adopting rTMS as part of insurance coverage would greatly facilitate its uptake and integration into mental health care. While the potential for rTMS to improve mental health outcomes is clear, the Romanian context presents specific challenges and opportunities. Addressing these effectively requires a multi-pronged approach involving improving health infrastructure, increasing awareness and acceptance of rTMS among the public and health professionals, and addressing economic barriers to access. Such efforts can significantly contribute to the wider integration of rTMS into Romania's public health strategy for mental health care, ultimately improving the well-being of individuals and the community at large.

## CHAPTER 3 - FINAL CONCLUSIONS, ORIGINAL CONTRIBUTIONS, DISSEMINATION OF RESULTS, FUTURE RESEARCH DIRECTIONS

### 3.1 INTEGRATION OF RTMS REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN PUBLIC HEALTH.

The results of the first study confirm the efficacy of rTMS treatment in patients with adjustment disorder with mixed anxiety-depressive mood. Based on the statistical results, we can observe a very high proportion of complete remissions in the group treated with rTMS alone (80%) compared to the other groups where the proportion of complete remissions was much lower, 40% in the group treated with psychotropic pharmacological treatment alone and 20% in the group treated with rTMS and psychotropic medication. These results are consistent with the literature on the efficacy of rTMS in stress-related disorders (Lefaucheur et al., 2014, 2020).

The results obtained in the second research study, which evaluated the use of rTMS as an adjunctive treatment method for participants with major depressive disorder, contrary to expectations and information from international guidelines (Lefaucheur et al., 2014, 2020), these highlight a lack of efficacy of this therapeutic method in the studied sample. Only 15% of the group of patients who were treated concomitantly with rTMS and psychotropic pharmacological treatment went into remission. These results, although not in line with international guidelines, are in line with other international studies on the lack of efficacy of rTMS. (Constantin et al., 2024; Lam et al., 2008). In addition, the low absolute rates of remission of depressive episodes correlate with evidence from studies showing that patients who do not respond to pharmacological treatment generally show a poor response to subsequent pharmacological or ECT treatments. (McClintock et al., 2018; O'Reardon et al., 2007).

The results of study three, exploring the perception and experience of patients who have been treated with rTMS for adjustment disorder and major depressive disorder, show that although this therapy is generally perceived with reluctance by patients at first due to lack of information, after a few treatment sessions their perception changes positively as the study participants experience its effectiveness. The majority of patients reported that they had a positive experience with this type of therapy, and it significantly improved their quality of life. Following the qualitative analysis of the semi-structured interviews regarding the accessibility and acceptability of rTMS, it is observed that the majority of patients consider that this method is not well enough promoted so that the majority of the population is not aware of its existence. Also, the fact that this method is not reimbursed by the CNAS greatly reduces the accessibility of patients in the view of the study participants.

Treatment with rTMS was safe and well tolerated by patients in both research studies, with isolated and transient adverse effects. Patients returned to daily activities immediately after the stimulation sessions. The safety profile of rTMS identified in this paper is similar to that described in the literature (Rossi et al., 2009, 2021). Thus we can state that rTMS is a safe, non-invasive treatment method with minimal adverse effects that can be used both in adjustment disorder with mixed anxiety-depressive mood and in major depressive disorder.

Access to rTMS is very limited in Romania, as there are few clinics nationwide offering this type of therapy, as they are located in urban areas. The majority of the participants in the studies included in the PhD work were from urban areas, which confirms that the accessibility of rural patients is limited by the lack of equipment and trained medical staff to perform rTMS procedures. Access to such treatments is another problem for public health professionals. In order to increase access to therapy, public health professionals should consider ensuring the availability of equipment and appropriately trained medical staff in both urban and rural areas. Another obstacle

identified in accessing this type of treatment is the fact that rTMS is currently not paid for by the CNAS, with services available in most cases only privately. In other countries such as America, health insurance systems such as Medicare pay for rTMS procedures for major depressive disorder. (Voigt et al., 2017).

### 3.2 FINAL CONCLUSIONS

**Study 1 - of the PhD thesis on Evaluating the efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) in the treatment of adjustment disorder with mixed anxiety-depressive mood, was the first study of its kind in Romania**. The results of the study allowed the following conclusions to be drawn:

1. rTMS is a therapeutic method that has shown superior efficacy compared to psychotropic pharmacological treatment in addressing adjustment disorders with mixed anxiety-depressive mood. Magnetic stimulation could be used as a more effective alternative for patients who do not respond adequately to medication or who seek non-pharmacological treatment options.
2. The safety profile and limited and transient adverse side effects make rTMS a safe and acceptable treatment method.
3. The rTMS-only group was more likely to have a positive clinical response, and the group that received only pharmacological medication and a low HAM-A score was more likely to experience remission of the disease.
4. Patients' decision to opt for rTMS was closely statistically correlated with urban background.

**STUDY 2 - Evaluating the Efficacy and Safety of Repetitive Transcranial Magnetic Stimulation (rTMS) as an Adjuvant Treatment for Major Depressive Disorder, was the first of its kind in Romania.** The results obtained from the research allowed the following conclusions to be drawn:

1. Lack of efficacy of rTMS as an adjunct to psychotropic pharmacological treatment for patients with major depressive disorder in the study sample.
2. The rTMS procedure was safe and well tolerated by patients, with limited and transient side effects. Hypomania was not induced in any participant in the study.
3. Predictors of clinical response were rural background and lower initial HDRS score. This highlights that lifestyle and living environment can influence treatment and recovery from depression. The group of patients who received only medication and a lower HDRS score were more likely to achieve remission.
4. Study participants' decision to opt for rTMS is influenced by their urban background and higher level of education.

**STUDY 3 - Exploring the perceptions and experiences of patients treated with rTMS for adjustment disorder and major depressive disorder in private specialist outpatient clinics in Romania.** The qualitative analysis was the first on this topic in Romania and allowed the formulation of the following conclusions:

1. The experiences of patients who have been treated with rTMS have been positive,

highlighting the effectiveness and safety of this method, as well as its increased acceptability among patients. In the majority of the interview participants the quality of life was considerably improved following magnetic stimulation procedures.

2. The decision to pursue magnetic stimulation treatment is based on patients' unwillingness to resort to conventional treatment methods, the lack of effectiveness of drug treatment in some cases, and the desire for faster recovery in patients treated concomitantly with rTMS and psychotropic medication.
3. Patients' access to rTMS is restricted because the method is not promoted and the population is not aware of it, and because the therapy involves high financial costs, which cannot be paid for by CNAS. Poor distribution of equipment in rural or under-served areas further limits patients' access to such procedures.

**Strategies and public policies aimed at adopting rTMS as an adjunctive or standard treatment method for adjustment and depressive disorders**.

On the basis of the literature review and the results obtained in the studies carried out in the PhD thesis, public health strategies can be developed in the coming period, based on the following benchmarks:

1. rTMS appears to be a safe, effective and cost-effective method for the treatment of adjustment disorder with mixed anxiety-depressive mood, its role in the treatment of major depressive disorder remains unclear, necessitating more research on the types of effective protocols and caution in considering its widespread use by public health policy. By integrating new innovative methods, the impact of these conditions on individuals and public health systems can be reduced.
2. In order to introduce rTMS as a standard or adjunctive treatment in the studied adjustment disorder, it is necessary for specialists to develop public health policies that develop and implement evidence-based clinical guidelines that include this therapy.
3. The correct implementation and use of this therapeutic method on a large scale requires training and certification programmes for researchers, clinicians and TMS technicians.
4. By allocating funds for the settlement of procedures by CNAS and for equipping outpatient clinics and hospitals with stimulation devices, it is possible to increase accessibility to this type of treatment in both rural and urban areas.
5. Information and education campaigns are needed to increase public awareness and acceptance of rTMS as a safe and effective treatment option. These campaigns should target both the general public and health professionals. Promotion should address both the benefits and risks associated with rTMS and be neutral in tone.

### 3.3 ORIGINAL CONTRIBUTIONS

This PhD thesis provides important insights into the efficacy and safety of using rTMS in the treatment of mixed anxiety-depressive mood adjustment disorder and major depressive disorder in a local context. The studies were the first of their kind in Romania. The results provide information from a local context on the efficacy and safety of rTMS in adjustment and depressive

disorders.

The qualitative research study conducted in this thesis is the first of its kind at national level and reflects the perceptions and experiences of patients with adjustment disorder and major depressive disorder who underwent these procedures in private specialist outpatient clinics in Romania.

The information contained in the general and special part provides a solid basis of information for public health professionals in integrating this innovative method for the treatment of adjustment and depressive disorders into public health strategies and policies.

### 3.4 DISSEMINATION OF RESULTS

- Published 3 articles and presented 2 papers as a lecturer at national conferences.
  - **Articles published in extenso in ISI journals**
  - ***a. first author:***
    - ***Constantin D.,*** Dinu E.A., Rogozea L., Burtea V., & Leasu F.-G. (2020). *Therapeutic Interventions for Adjustment Disorder: A Systematic Review*. American Journal of Therapeutics, 2020 27(4), e375-e386. https://doi.org/10.1097/MJT.0000000000001170
    - ***Constantin D.A,*** Monescu V., Ciorîceanu I.H., Leașu F.G., Rogozea L.M*,. Can Medication be a Factor that Can Negatively Affect the Effect of Transcranial Magnetic Stimulation in Depression?*. American Journal of Therapeutics, 2024 31(1), e30-38. https://doi.org/10.1097/mjt.0000000000001700.
  - **Articles published in extenso in journals indexed in databases**
    - ***a. first author:***
      - ***Constantin D.,*** Ciorîceanu I., Dinu E. A., & Burtea V. (2020, February 24). *Transcranial magnetic stimulation (TMS). Therapeutic applications in psychiatry*. Jurnal Medical Brașovean, 2019(2), 4-14. https://doi.org/10.31926/jmb.2019.2.11
  - **Papers presented at national conferences of the society**
    - ***a. first author***
      - ***Constantin D.,*** *Transcranial Magnetic Stimulation.* National Conference Family Doctor's Day - Essential Skills in Family Doctor's Practice. Brasov 06-09.07.2017 (lecturer)
      - ***Constantin D.,*** *Non-invasive, drug-free treatment of depression by Direct Transcranial Electrical Stimulation - DTE.* National Congress for Students and Young Doctors Kronmed 2023 (lecturer)

- To produce scientific research reports in the scientific training programme.
- Completion of PhD thesis.

### 3.5 FUTURE RESEARCH DIRECTIONS

As future research directions I propose to study:

1. Public health research study on the costs associated with adjustment disorders in Romania.

2. Public health research study on the cost-effectiveness of rTMS versus drug treatment for adjustment disorders in Romania.

3. Public health research study on the cost-effectiveness of rTMS compared to antidepressant drug treatment used in major depressive disorder.

4. Research study on how certain classes of psychotropic medications potentiate or decrease the effectiveness of rTMS for patients with adjustment disorder and major depressive disorder.

5. Research study to analyse the impact of rTMS promotion in the media on the Romanian population.

**BIBLIOGRAPHY**

Aleman, A., Sommer, I. E., & Kahn, R. S. (2007) Efficacy of Slow Repetitive Transcranial Magnetic Stimulation in the Treatment of Resistant Auditory Hallucinations in Schizophrenia. *The Journal of Clinical Psychiatry*, *68*(03), 416-421. https://doi.org/10.4088/JCP.v68n0310

American Psychiatric Association (2013) Diagnostic and Statistical Mental Disorders Manual of Fifth Edition DSM-5. *American Psychiatric Publishing*, *17*(7), 461-462.

Avery, D. H., Isenberg, K. E., Sampson, S. M., Janicak, P. G., Lisanby, S. H., Maixner, D. F., Loo, C., Thase, M. E., Demitrack, M. A., & George, M. S. (2008). Transcranial Magnetic Stimulation in the Acute Treatment of Major Depressive Disorder. *The Journal of Clinical Psychiatry*, *69*(3), 441-451. https://doi.org/10.4088/JCP.v69n0315

Brakemeier, E.-L., Luborzewski, A., Danker-Hopfe, H., Kathmann, N., & Bajbouj, M. (2007) Positive predictors for antidepressant response to prefrontal repetitive transcranial magnetic stimulation (rTMS). *Journal of Psychiatric Research*, *41*(5), 395-403. https://doi.org/10.1016/j.jpsychires.2006.01.013

Brătucu, G., Tudor, A. I. M., Litră, A. V., Nichifor, E., Chițu, I. B., & Brătucu, T.-O. (2022). Designing the Well-Being of Romanians by Achieving Mental Health with Digital Methods and Public Health Promotion. *International Journal of Environmental Research and Public Health*, *19*(13), 7868. https://doi.org/10.3390/ijerph19137868

Briley, M., & Lépine. (2011). The increasing burden of depression. *Neuropsychiatric Disease and Treatment*, 3. https://doi.org/10.2147/NDT.S19617

Campion, J. (2018) Public mental health: key challenges and opportunities. *BJPsych International*, *15*(3), 51-54. https://doi.org/10.1192/bji.2017.11

Campion, J., Bhui, K., & Bhugra, D. (2012). European Psychiatric Association (EPA) guidance on prevention of mental disorders. *European Psychiatry*, *27*(2), 68-80. https://doi.org/10.1016/j.eurpsy.2011.10.004

Chail, A., Saini, R., Bhat, P., Srivastava, K., & Chauhan, V. (2018). transcranial magnetic stimulation: A review of its evolution and current applications. *Industrial Psychiatry Journal*, *27*(2), 172. https://doi.org/10.4103/ipj.ipj_88_18

Chipchase, L., Schabrun, S., Cohen, L., Hodges, P., Ridding, M., Rothwell, J., Taylor, J., & Ziemann, U. (2012). A checklist for assessing the methodological quality of studies using transcranial magnetic stimulation to study the motor system: An international consensus study. *Clinical Neurophysiology*, *123*(9), 1698-1704. https://doi.org/10.1016/j.clinph.2012.05.003

Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., Cowen, P., Dickens, C., Ferrier, I., Geddes, J., Gilbody, S., Haddad, P., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R., Ramchandani, P., Scott, J., Taylor, D., & Uher, R. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology*, *29*(5), 459-525. https://doi.org/10.1177/0269881115581093

Cohen, H., Kaplan, Z., Kotler, M., Kouperman, I., Moisa, R., & Grisaru, N. (2004) Repetitive Transcranial Magnetic Stimulation of the Right Dorsolateral Prefrontal Cortex in Posttraumatic Stress Disorder: A Double-Blind, Placebo-Controlled Study. *American Journal of Psychiatry*, *161*(3), 515-524. https://doi.org/10.1176/appi.ajp.161.3.515

Constantin, D. A., Monescu, V., Ciorîceanu, I. H., Leașu, F. G., & Rogozea, L. M. (2024). Can Medication be a Factor that Can Negatively Affect the Effect of Transcranial Magnetic Stimulation in Depression? *American Journal of Therapeutics*, *31*(1), e30-e38. https://doi.org/10.1097/MJT.0000000000001700

Constantin, D., Ciorîceanu, I., Dinu, E. A., & Burtea, V. (2020). Transcranial magnetic stimulation (TMS). Therapeutic applications in psychiatry. *Brasov Medical Journal*, *2019*(2), 4-14. https://doi.org/10.31926/jmb.2019.2.11

Constantin, D., Dinu, E. A., Rogozea, L., Burtea, V., & Leasu, F.-G. (2020). Therapeutic Interventions for Adjustment Disorder: A Systematic Review. *American Journal of Therapeutics*, *27*(4), e375-e386. https://doi.org/10.1097/MJT.0000000000001170

Deng, Y., Li, W., & Zhang, B. (2023). Functional Activity in the Effect of Transcranial Magnetic Stimulation Therapy for Patients with Depression: A Meta-Analysis. *Journal of Personalized Medicine*, *13*(3), 405. https://doi.org/10.3390/jpm13030405.

Devlin, J. T., & Watkins, K. Stimulating language: insights from TMS. *Brain*, *130*(3), 610-622. https://doi.org/10.1093/brain/awl331

European Observatory on Health Systems; (2023). *Slovenia: Country Health Profile 2023*. OECD. https://doi.org/10.1787/0eb17a30-en

Fregni, F., & Pascual-Leone, A. (2007) Technology Insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. *Nature Clinical Practice Neurology*, *3*(7), 383-393. https://doi.org/10.1038/ncpneuro0530

Fried, P. J., Santarnecchi, E., Antal, A., Bartres-Faz, D., Bestmann, S., Carpenter, L. L., Celnik, P., Edwards, D., Farzan, F., Fecteau, S., George, M. S., He, B., Kim, Y.-H., Leocani, L., Lisanby, S. H., Loo, C., Luber, B., Nitsche, M. A., Paulus, W., ... Pascual-Leone, A. (2021). Training in the practice of noninvasive brain stimulation: Recommendations from an IFCN committee. *Clinical Neurophysiology*, *132*(3), 819-837. https://doi.org/10.1016/j.clinph.2020.11.018

Garnaat, S. L., Yuan, S., Wang, H., Philip, N. S., & Carpenter, L. L. (2018) Updates on Transcranial Magnetic Stimulation Therapy for Major Depressive Disorder. *Psychiatric Clinics of North America*, *41*(3), 419-431. https://doi.org/10.1016/j.psc.2018.04.006

Gelenberg, A. J. (2010). The American Psychiatric Association Treatment Guideline for Major Depressive Disorder: process and content. *Annals of General Psychiatry*, *9*(S1), S46. https://doi.org/10.1186/1744-859X-9-S1-S46

George, M. S. (2019) Whither TMS: A One-Trick Pony or the Beginning of a Neuroscientific Revolution? *American Journal of Psychiatry*, *176*(11), 904-910. https://doi.org/10.1176/appi.ajp.2019.19090957

George, M. S., Lisanby, S. H., Avery, D., McDonald, W. M., Durkalski, V., Pavlicova, M., Anderson, B., Nahas, Z., Bulow, P., Zarkowski, P., Holtzheimer, P. E., Schwartz, T., & Sackeim, H. A. (2010). Daily Left Prefrontal Transcranial Magnetic Stimulation Therapy for Major Depressive Disorder. *Archives of General Psychiatry*, *67*(5), 507. https://doi.org/10.1001/archgenpsychiatry.2010.46.

George, M. S., Nahas, Z., Borckardt, J. J., Anderson, B., Foust, M. J., Burns, C., Kose, S., & Short, E. Brain stimulation for the treatment of psychiatric disorders. *Current Opinion in Psychiatry*, *20*(3), 250-254. https://doi.org/10.1097/YCO.0b013e3280ad4698

George, M. S., & Post, R. M. (2011). Daily Left Prefrontal Repetitive Transcranial Magnetic Stimulation for Acute Treatment of Medication-Resistant Depression. *American Journal of Psychiatry*, *168*(4), 356-364. https://doi.org/10.1176/appi.ajp.2010.10060864

Glaesmer, H., Romppel, M., Brähler, E., Hinz, A., & Maercker, A. (2015). Adjustment disorder as proposed for ICD-11: Dimensionality and symptom differentiation. *Psychiatry Research*, *229*(3), 940-948. https://doi.org/10.1016/j.psychres.2015.07.010

Global Burden of Disease Collaborative Network. (2019). *Global Burden of Disease Study 2019 (GBD 2019) Results.* https://www.healthdata.org/research-analysis/gbd. Accesed at 12.01.2024.

Gradus, J. (2017). Prevalence and prognosis of stress disorders: a review of the epidemiologic literature. *Clinical Epidemiology*, *Volume 9*, 251-260. https://doi.org/10.2147/CLEP.S106250

Grunhaus, L., Schreiber, S., Dolberg, O. T., Polak, D., & Dannon, P. N. (2003). A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biological Psychiatry*, *53*(4), 324-331. https://doi.org/10.1016/S0006-3223(02)01499-3

Hamilton, M. (1959). THE ASSESSMENT OF ANXIETY STATES BY RATING. *British Journal of Medical Psychology*, *32*(1), 50-55. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x

Hamilton, M. (1960). A RATING SCALE FOR DEPRESSION. *Journal of Neurology, Neurosurgery & Psychiatry*, *23*(1), 56-62. https://doi.org/10.1136/jnnp.23.1.56

Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018) Epidemiology of Adult *DSM-5* Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry*, *75*(4), 336. https://doi.org/10.1001/jamapsychiatry.2017.4602.

Herwig, U., Padberg, F., Unger, J., Spitzer, M., & Schönfeldt-Lecuona, C. (2001). Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. *Biological Psychiatry*, *50*(1), 58-61. https://doi.org/10.1016/S0006-3223(01)01153-2

HMG (2011). *No health without mental health: A cross-government mental health outcomes strategy for people of all ages. https://assets.publishing.service.gov.uk/media/5a7c348ae5274a25a914129d/dh_124058.pdf Accesed at 12.01.2024.*

Huang, M., Luo, B., Hu, J., Wang, S.-S., Zhou, W., Wei, N., Hu, S., & Xu, Y. (2012). Repetitive transcranial magnetic stimulation in combination with citalopram in young patients with first-episode major depressive disorder: A double-blind, randomized, sham-controlled trial. *Australian & New Zealand Journal of Psychiatry*, *46*(3), 257-264. https://doi.org/10.1177/0004867411433216

Huyse, F. J., Herzog, T., Lobo, A., Malt, U. F., Opmeer, B. C., Stein, B., de Jonge, P., van Dijck, R., Creed, F., Crespo, M. D., Cardoso, G., Guimaraes-Lopes, R., Mayou, R., van Moffaert, M., Rigatelli, M., Sakkas, P., & Tienari, P. (2001). Consultation-Liaison psychiatric service delivery: results from a European study. *General Hospital Psychiatry*, *23*(3), 124-132. https://doi.org/10.1016/S0163-8343(01)00139-6

Institute of Health Metrics and Evaluation (2023) *Global Health Data Exchange (GHDx)* Institute of Health Metrics and Evaluation https://www.healthdata.org/research-analysis/gbd *Accesed at 12.01.2024.*

Iordache, M. M., Sorici, C. O., Aivaz, K. A., Lupu, E. C., Dumitru, A., Tocia, C., & Dumitru, E. (2023). Depression in Central and Eastern Europe: How Much It Costs? Cost of Depression in Romania. *Healthcare*, *11*(6), 921. https://doi.org/10.3390/healthcare11060921

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R. S., Abebe, Z., Abera, S. F., Abil, O. Z., Abraha, H. N., Abu-Raddad, L. J., Abu-Rmeileh, N. M. E., Accrombessi, M. M. K., ... Murray, C. J. L. (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1789-1858. https://doi.org/10.1016/S0140-6736(18)32279-7

Killikelly, C., Lorenz, L., Bauer, S., Mahat-Shamir, M., Ben-Ezra, M., & Maercker, A. (2019). Prolonged grief disorder: Its co-occurrence with adjustment disorder and post-traumatic stress disorder in a bereaved Israeli general-population sample. *Journal of Affective Disorders*, *249*, 307-314. https://doi.org/10.1016/j.jad.2019.02.014.

Klomjai, W., Katz, R., & Lackmy-Vallée, A. (2015). Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Annals of Physical and Rehabilitation Medicine*, *58*(4), 208-213. https://doi.org/10.1016/j.rehab.2015.05.005

Kozel, F. A., George, M. S., & Simpson, K. N. (2004) Decision analysis of the cost-effectiveness of repetitive transcranial magnetic stimulation versus electroconvulsive therapy for treatment of nonpsychotic severe depression. *CNS Spectrums*, *9*(6), 476-482.

Krupchanka, D., & Winkler, P. (2016). State of mental healthcare systems in Eastern Europe: do we really understand what is going on? *BJPsych. International*, *13*(4), 96-99. https://doi.org/10.1192/S2056474000001446

Lam, R. W., Chan, P., Wilkins-Ho, M., & Yatham, L. N. (2008). Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Metaanalysis. *The Canadian Journal of Psychiatry*, *53*(9), 621-631. https://doi.org/10.1177/070674370805300909

Lefaucheur, J.-P., Aleman, A., Baeken, C., Benninger, D. H., Brunelin, J., Di Lazzaro, V., Filipović, S. R., Grefkes, C., Hasan, A., Hummel, F. C., Jääskeläinen, S. K., Langguth, B., Leocani, L., Londero, A., Nardone, R., Nguyen, J.-P., Nyffeler, T., Oliveira-Maia, A. J., Oliviero, A., ... Ziemann, U. (2020). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clinical Neurophysiology*, *131*(2), 474-528. https://doi.org/10.1016/j.clinph.2019.11.002

Lefaucheur, J.-P., André-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., Cantello, R. M., Cincotta, M., de Carvalho, M., De Ridder, D., Devanne, H., Di Lazzaro, V., Filipović, S. R., Hummel, F. C., Jääskeläinen, S. K., Kimiskidis, V. K., Koch, G., Langguth, B., Nyffeler, T., ... Garcia-Larrea, L. (2014). evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology*, *125*(11), 2150-2206. https://doi.org/10.1016/j.clinph.2014.05.021

Loo, C. K., McFarquhar, T. F., & Mitchell, P. B. (2008). A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. *International Journal of Neuropsychopharmacology*, *11*(1), 131-147. https://doi.org/10.1017/S1461145707007717

M. Ad. (2021). *Transcranial magnetic stimulation marketing & advertising.* https://www.medicaladvertising.ca/transcranialmagnetic-stimulation-marketing-advertising/ *Accesed at 12.01.2024.*

Malhi, G. S., Bassett, D., Boyce, P., Bryant, R., Fitzgerald, P. B., Fritz, K., Hopwood, M., Lyndon, B., Mulder, R., Murray, G., Porter, R., & Singh, A. B. (2015). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Australian & New Zealand Journal of Psychiatry*, *49*(12), 1087-1206. https://doi.org/10.1177/0004867415617657

McClintock, S. M., Reti, I. M., Carpenter, L. L., McDonald, W. M., Dubin, M., Taylor, S. F., Cook, I. A., O'Reardon, J., Husain, M. M., Wall, C., Krystal, A. D., Sampson, S. M., Morales, O., Nelson, B. G., Latoussakis, V., George, M. S., & Lisanby, S. H. (2018). Consensus Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression. *The Journal of Clinical Psychiatry*, *79*(1), 35-48. https://doi.org/10.4088/JCP.16cs10905

Mental Health Foundation (2016). *Better Mental Health For All. A Public Health Approach to Mental Health improvement.* Faculty of Public Health and Mental Health Foundation. https://www.mentalhealth.org.uk/explore-mental-health/publications/better-mental-health-for-all. *Accesed at 12.01.2024.*

Milev, R. V., Giacobbe, P., Kennedy, S. H., Blumberger, D. M., Daskalakis, Z. J., Downar, J., Modirrousta, M., Patry, S., Vila-Rodriguez, F., Lam, R. W., MacQueen, G. M., Parikh, S. V., & Ravindran, A. V. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder. *The Canadian Journal of Psychiatry*, *61*(9), 561-575. https://doi.org/10.1177/0706743716660033

Mitchell, A. J., Chan, M., Bhatti, H., Halton, M., Grassi, L., Johansen, C., & Meader, N. (2011). Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *The Lancet Oncology*, *12*(2), 160-174. https://doi.org/10.1016/S1470-2045(11)70002-X

NBCC (2023). *National Board for Certified Counselors & Affiliates.* https://www.nbcc.org/resources/nccs/newsletter/2023-the-year-of-federal-investments. *Accesed at 12.01.2024.*

Nguyen, K.-H., & Gordon, L. G. (2015). Cost-Effectiveness of Repetitive Transcranial Magnetic Stimulation versus Antidepressant Therapy for Treatment-Resistant Depression. *Value in Health*, *18*(5), 597-604. https://doi.org/10.1016/j.jval.2015.04.004.

NICE (2020). *National Institute for Health and Care Excellence. Implanted vagus nerve stimul ation for treatment-resistant depression. Interventional procedures guidance [IPG67 9].* https://www.nice.org.uk/guidance/ipg679. *Accesed at 12.01.2024.*

Noda, Y., Silverstein, W. K., Barr, M. S., Vila-Rodriguez, F., Downar, J., Rajji, T. K., Fitzgerald, P. B., Mulsant, B. H., Vigod, S. N., Daskalakis, Z. J., & Blumberger, D. M. (2015). Neurobiological mechanisms of repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex in depression: a systematic review. *Psychological Medicine*, *45*(16), 3411-3432. https://doi.org/10.1017/S0033291715001609

O'Donnell, M. L., Agathos, J. A., Metcalf, O., Gibson, K., & Lau, W. (2019). Adjustment Disorder: Current Developments and Future Directions. *International Journal of Environmental Research and Public Health*, *16*(14), 2537. https://doi.org/10.3390/ijerph16142537

OECD. (2015). Fit Mind, Fit Job. In *OECD Publishing Paris, France*. OECD. https://doi.org/10.1787/9789264228283-en

O'Reardon, J. P., Solvason, H. B., Janicak, P. G., Sampson, S., Isenberg, K. E., Nahas, Z., McDonald, W. M., Avery, D., Fitzgerald, P. B., Loo, C., Demitrack, M. A., George, M. S., & Sackeim, H. A. (2007) Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial. *Biological Psychiatry*, *62*(11), 1208-1216. https://doi.org/10.1016/j.biopsych.2007.01.018

Pallanti, S., Bernardi, S., Di Rollo, A., Antonini, S., & Quercioli, L. (2010). Unilateral low frequency versus sequential bilateral repetitive transcranial magnetic stimulation: is simpler better for treatment of resistant depression? *Neuroscience*, *167*(2), 323-328. https://doi.org/10.1016/j.neuroscience.2010.01.063

Pascual-Leone, A., Rubio, B., Pallardó, F., & Catalá, M. D. (1996) Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *The Lancet*, *348*(9022), 233-237. https://doi.org/10.1016/S0140-6736(96)01219-6

Perera, T., George, M. S., Grammer, G., Janicak, P. G., Pascual-Leone, A., & Wirecki, T. S. (2016). The Clinical TMS Society Consensus Review and Treatment Recommendations for TMS Therapy for Major Depressive Disorder. *Brain Stimulation*, *9*(3), 336-346. https://doi.org/10.1016/j.brs.2016.03.010

Perkonigg, A., Lorenz, L., & Maercker, A. (2018) Prevalence and correlates of ICD-11 adjustment disorder: Findings from the Zurich Adjustment Disorder Study. *International Journal of Clinical and Health Psychology*, *18*(3), 209-217. https://doi.org/10.1016/j.ijchp.2018.05.001

Petre, I., Barna, F., Gurgus, D., Tomescu, L. C., Apostol, A., Petre, I., Furau, C., Năchescu, M. L., & Bordianu, A. (2023). Analysis of the Healthcare System in Romania: A Brief Review. *Healthcare*, *11*(14), 2069. https://doi.org/10.3390/healthcare11142069

Ray, S., Nizamie, S. H., Akhtar, S., Praharaj, S. K., Mishra, B. R., & Zia-ul-Haq, M. (2011). Efficacy of adjunctive high frequency repetitive transcranial magnetic stimulation of left prefrontal cortex in depression: A randomized sham controlled study. *Journal of Affective Disorders*, *128*(1-2), 153-159. https://doi.org/10.1016/j.jad.2010.06.027

Reddy, M. S. (2010). Depression: The Disorder and the Burden. *Indian Journal of Psychological Medicine*, *32*(1), 1-2. https://doi.org/10.4103/0253-7176.70510

Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., Carpenter, L. L., Cincotta, M., Chen, R., Daskalakis, J. D., Di Lazzaro, V., Fox, M. D., George, M. S., Gilbert, D., Kimiskidis, V. K., Koch, G., Ilmoniemi, R. J., Lefaucheur, J. P., Leocani, L., ...

Hallett, M. (2021). Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clinical Neurophysiology*, *132*(1), 269-306. https://doi.org/10.1016/j.clinph.2020.10.003

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, *120*(12), 2008-2039. https://doi.org/10.1016/j.clinph.2009.08.016

Ruff, C. C., Driver, J., & Bestmann, S. (2009). Combining TMS and fMRI: From 'virtual lesions' to functional-network accounts of cognition. *Cortex*, *45*(9), 1043-1049. https://doi.org/10.1016/j.cortex.2008.10.012

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., Lebowitz, B. D., McGrath, P. J., Rosenbaum, J. F., Sackeim, H. A., Kupfer, D. J., Luther, J., & Fava, M. (2006) Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. *American Journal of Psychiatry*, *163*(11), 1905-1917. https://doi.org/10.1176/ajp.2006.163.11.1905

Sackeim, H. A., Prudic, J., Haskett, R. F., Mulsant, B., & Pettinati, H. (1996). Medication resistance, ECT response and relapse prevention. *European Neuropsychopharmacology*, *6*, 21. https://doi.org/10.1016/0924-977X(96)87393-7

Salvador-Carulla, L., Bendeck, M., Fernández, A., Alberti, C., Sabes-Figuera, R., Molina, C., & Knapp, M. (2011). Costs of depression in Catalonia (Spain). *Journal of Affective Disorders*, *132*(1-2), 130-138. https://doi.org/10.1016/j.jad.2011.02.019

Shinba, T., Kariya, N., Matsuda, S., Matsuda, H., & Obara, Y. (2018) Increase of frontal cerebral blood volume during transcranial magnetic stimulation in depression is related to treatment effectiveness: A pilot study with near-infrared spectroscopy. *Psychiatry and Clinical Neurosciences*, *72*(8), 602-610. https://doi.org/10.1111/pcn.12680

Simpson, K. N., Welch, M. J., Kozel, F. A., Demitrack, M. A., & Nahas, Z. (2009) Cost-effectiveness of transcranial magnetic stimulation in the treatment of major depression: a health economics analysis. *Advances in Therapy*, *26*(3), 346-368. https://doi.org/10.1007/s12325-009-0013-x.

Sinyor, M., Schaffer, A., & Levitt, A. (2010). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial: A Review. *The Canadian Journal of Psychiatry*, *55*(3), 126-135. https://doi.org/10.1177/070674371005500303

UK ECT Review Group (2003) Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *The Lancet*, *361*(9360), 799-808. https://doi.org/10.1016/S0140-6736(03)12705-5

UN. (2016). *Sustainable development agenda.* https://www.un.org/sustainabledevelopment/development-agenda/. *Accesed at 12.01.2024.*

VA/DoD Clinical Practice Guideline. (2022). *The Management of Major Depressive Disorder.* https://www.healthquality.va.gov/guidelines/MH/mdd/VADoDMDDCPGFinal508.pdf. *Accesed at 12.01.2024.*

Vallejo-Torres, L., Castilla, I., González, N., Hunter, R., Serrano-Pérez, P., & Perestelo-Pérez, L. (2015). Cost-effectiveness of electroconvulsive therapy compared to repetitive transcranial magnetic stimulation for treatment-resistant severe depression: a decision model. *Psychological Medicine*, *45*(7), 1459-1470. https://doi.org/10.1017/S0033291714002554

Vieta, E., Alonso, J., Pérez-Sola, V., Roca, M., Hernando, T., Sicras-Mainar, A., Sicras-Navarro, A., Herrera, B., & Gabilondo, A. (2021). Epidemiology and costs of depressive disorder in Spain: the EPICO study. *European Neuropsychopharmacology*, *50*, 93-103. https://doi.org/10.1016/j.euroneuro.2021.04.022.

Voigt, J., Carpenter, L., & Leuchter, A. (2017). Cost effectiveness analysis comparing repetitive transcranial magnetic stimulation to antidepressant medications after a first treatment failure

for major depressive disorder in newly diagnosed patients - A lifetime analysis. *PLOS ONE*, *12*(10), e0186950. https://doi.org/10.1371/journal.pone.0186950

Watts, B. V., Landon, B., Groft, A., & Young-Xu, Y. (2012). A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder. *Brain Stimulation*, *5*(1), 38-43. https://doi.org/10.1016/j.brs.2011.02.002

WHO. (2013). *Mental health action plan 2013-2020.* https://www.who.int/publications/i/item/978924150602. *Accesed at 12.01.2024.*

WHO (2015). *Mental Health Atlas 2014.* https://www.who.int/publications/i/item/mental-health-atlas-2014. *Accesed at 12.01.2024.*

WHO (2022). *Mental Health: Strengthening Our Response.* https://www.who.int/news-room/fact-sheets/detail/mental-health-strengthening-our-response. *Accesed at 12.01.2024.*

Yiru Fang. (2019). *Depressive Disorders: Mechanisms, Measurement and Management* (Vol. 1180). Springer Singapore. https://doi.org/10.1007/978-981-32-9271-0

# ANNEXES

## ANNEX 1 - LIST OF PUBLICATIONS

a) list of papers published in ISI journals and databases

1. **Constantin, D.,** Cioriceanu, I., Dinu, E. A., & Burtea, V. (2020, February 24). Transcranial magnetic stimulation (TMS). Therapeutic applications in psychiatry. Jurnal Medical Brașovean, 2019(2), 4-14. https://doi.org/10.31926/jmb.2019.2.11

2. **Constantin, D**., Dinu, E. A., Rogozea, L., Burtea, V., & Leasu, F.-G. (2020). Therapeutic Interventions for Adjustment Disorder: A Systematic Review. American Journal of Therapeutics, 2020 27(4), e375-e386. https://doi.org/10.1097/MJT.0000000000001170

3. **Constantin , D. A,** Monescu V., Cioriceanu I.H., Leașu F.G., Rogozea L.M,. Can Medication be a Factor that Can Negatively Affect the Effect of Transcranial Magnetic Stimulation in Depression?. American Journal of Therapeutics, 2024 31(1), e30-38. https://doi.org/10.1097/mjt.0000000000001700.

b) list of papers presented at the conferences

1. **Constantin D**., Transcranial Magnetic Stimulation. National Conference Family Doctor's Day Essential Competences in Family Doctor's Practice. Brasov 06-09.07.2017 (lecturer)

2. **Constantin D**., Non-invasive, drug-free treatment of depression by Direct Transcranial Electrical Stimulation - DTE. National Congress for Students and Young Doctors Kronmed 2023 (lecturer).

# DECLARAȚIE DE AUTENTICITATE

Subsemnații: Dan Alexandru CONSTANTIN
*(nume și prenume doctorand)*

în calitate de

student - doctorand al IOSUD: Universitatea Transilvania din Brașov
*(denumire IOSUD)*

autor al tezei de doctorat cu titlul: Evaluarea Eficacității și Siguranței Folosirii rTMS (stimularea magnetică transcraniană repetitivă) – O Problemă Emergentă de Sănătate Publică în Tulburările de Adaptare și Depresive.
*(titlul tezei de doctorat)*

și

Prof. univ. dr. med Liliana Marcela ROGOZEA
*(nume si prenume conducator doctorat)*

în calitate de Conducător de doctorat al autorului tezei

la instituția Universitatea Transilvania din Brașov
*(denumire institutie)*

declarăm pe proprie răspundere că am luat la cunoștință de prevederile art.143 alin (4) si (5)* și art. 170** din Legea educației naționale nr.1/2011, ale art. 65, alin.5 – 7***, art. 66, alin (2)**** din Hotărârea Guvernului nr.681/2011, privind aprobarea Codului Studiilor universitare de doctorat, ale art. I alin. (5) și (7) ***** din Hotărârea nr. 134 privind modificarea Codului studiilor universitare de doctorat, aprobat prin HG nr. 681/2011 și ale Anexei nr. 2 (Soluționarea sesizărilor cu privire la nerespectarea standardelor de calitate sau de etică profesională, inclusiv cu privire la existența plagiatului, în cadrul unei teze de doctorat) din Ordinul MENCS nr. 3482/2016 privind aprobarea Regulamentului de organizare și funcționare a Consiliului Național de Atestare a Titlurilor, Diplomelor și Certificatelor Universitare (CNATDCU) și ne asumăm consecințele nerespectării acestora.

Semnătură
Student doctorand

Semnătură
Conducător de doctorat

*(4) indrumatorii lucrărilor de licență, de diplomă, de disertație, de doctorat răspund solidar cu autorii acestora de asigurarea originalității conținutului acestora

(5) este interzisă comercializarea de lucrări științifice în vederea facilitării falsificării de către cumpărător a calității de autor al unei lucrări de licență, de diplomă, de disertație sau de doctorat.

** (1) În cazul nerespectării standardelor de calitate sau de etică profesională, se aplică prevederile Hotărârii nr. 134 privind modificarea Codului studiilor universitare de doctorat, aprobat prin HG nr. 681/2011.

(2)Reacreditarea școlii doctorale se poate obține după cel puțin 5 ani de la pierderea acestei calități, numai în urma reluării procesului de acreditare, conform art. 158.

(3)Redobândirea calității de conducător de doctorat se poate obține după cel puțin 5 ani de la pierderea acestei calități, la propunerea IOSUD, pe baza unui raport de evaluare internă, ale cărui aprecieri sunt

validate printr-o evaluare externă efectuată de CNATDCU. Rezultatele pozitive ale acestor proceduri sunt condiții necesare pentru aprobare din partea Ministerului Educației, Cercetării, Tineretului și Sportului.
**(4)**Conducătorii de doctorat sunt evaluați o dată la 5 ani. Procedurile de evaluare sunt stabilite de Ministerul Educației, Cercetării, Tineretului și Sportului, la propunerea CNATDCU.
***(5)** teza de doctorat este o lucrare originală, fiind obligatorie mentionarea sursei pentru orice material preluat.
**(6)** studentul - doctorand este autorul tezei de doctorat și își asumă corectitudinea datelor și informațiilor prezentate în teză, precum și a opiniilor și demonstrațiilor exprimate în teză
**(7)** conducătorul de doctorat răspunde împreună cu autorul tezei de respectarea standardelor de calitate sau de etica profesională, inclusiv de asigurarea originalității conținutului, conform art. 170 din Legea nr. 1/2011.
**** protecția drepturilor de proprietate intelectuală asupra tezei de doctorat se asigură în conformitate cu prevederile legii.
*****(5) (6)** În cazul în care membrii CNATDCU din cadrul unei comisii de evaluare a unei teze de doctorat constată nerespectarea standardelor de etică profesională, inclusiv existența plagiatului, în cadrul tezei și/sau al activităților care au dus la realizarea acesteia, aceștia invalideaza teza de doctorat, comunică aceste constatări celorlalți membri ai comisiei de evaluare și sesizează Consiliul general CNATDCU pentru analiza responsabilității conducătorului de doctorat sau a școlii doctorale și pentru aplicarea prevederilor art. 69 alin. (5).
**(7) (3)** În termenul prevăzut la alin. (2), Consiliul general al CNATDCU solicită IOSUD punctul de vedere care trebuie formulat în termen de maximum 30 de zile de la primirea solicitării. În situația în care IOSUD confirmă încălcarea standardelor de calitate sau de etică profesională, va transmite CNATDCU decizia privind propunerea de retragere a titlului, semnată de rector sau, după caz, de președintele Academiei Române, avizată din punct de vedere juridic de universitate sau, după caz, de Academia Română.

**(4)** În termenul prevăzut la alin. (2), Consiliul general al CNATDCU decide dacă au fost sau nu respectate standardele de calitate sau de etică profesională, inclusiv existența plagiatului, iar președintele CNATDCU transmite autorului sesizării, autorului tezei și IOSUD decizia Consiliului general al CNATDCU și motivarea acesteia. Aceștia au la dispoziție 10 zile pentru formularea unei contestații privitoare la procedură, iar Consiliul general al CNATDCU are la dispoziție 10 zile pentru formularea răspunsului la contestație.

**(5)** În cazul în care Consiliul general al CNATDCU decide că nu au fost respectate standardele de calitate sau de etică profesională, inclusiv în ceea ce privește plagiatul, președintele CNATDCU propune Ministerului Educației Naționale și Cercetării Științifice una sau mai multe din următoarele măsuri:

a) retragerea calității de conducător de doctorat;
b) retragerea titlului de doctor;
c) retragerea acreditării școlii doctorale.