Efficacy and Safety of Repetitive Transcranial Magnetic Stimulation in Egyptian Subjects with Medications Resistant Major Depressive Disorder

Thesis

Submitted for Partial Fulfillment of Doctorate Degree in Psychiatry

By

Rania Elsayed Hassan Elsayed Kasem

M.B.,B.Ch

M.B., B. Ch., M.Sc.; Psychiatry

Under Supervision of

Prof. Mohammed Refaat Elfiky

Professor of Psychiatry

Faculty of Medicine-Ain Shams University

Prof. Tarek Asaad Abdou

Professor of Psychiatry

Faculty of Medicine-Ain Shams University

Assistant Prof. Marwa Abd-ElRahman Sultan

Assistant Professor of Psychiatry

Faculty of Medicine-Ain Shams University

Faculty of Medicine

Ain Shams University

2018

ACKNOWLEDGEMENT

First of all, I am very grateful to **Allah**, *the most gracious and merciful for blessing me with all the people who helped me to accomplish this piece of work.*

I would like to express my profound gratitude to my respectful **Professor Doctor / Mohamed Refaat ElFiky** *Professor of Neuropsychiatry, faculty of medicine,Ain Shams University, for his continuous support, inspiring guidance, meticulous supervision and most valuable suggestions.*

In addition, I would like deeply and sincerely to thank **Professor Doctor/ Tarek Assad Abdo** *Professor of Neuropsychiatry,faculty of medicine, Ain Shams University, for his valuable ideas, helpful suggestions, and for his endless support .*

I wish to express my gratefulness and appreciation to **Doctor/ Marwa Sultan ,** *Assistant professor of Neuropsychiatry,faculty of medicine, Ain Shams University, for her generous patience and permanent support. Her great cooperation and guidance were essential for this work.*

I would like to express my sincere gratitude to **Prof. Ahmed Saad,** *Professor of Neuropsychiatry and the head of the Psychiatry Department, Faculty of Medicine, Ain Shams University, for his guidance and endless support through the past years.*

My thanks also go to my entire Professors of Neuropsychiatry department, Faculty of Medicine, Ain Shams University & for all who helped me in this work.

I wish to express my sincere gratitude to the cooperative patients who agreed to participate in this research.

Great love and many thanks to my dear friends and colleagues for helping me pass hard times and for their cooperation that gave me the opportunity to work in a convenient way.

No words can express my genuine gratitude and deep appreciation and great love to my supportive parents , loving husband , my beloved kids (Abd El-Rahman & Marian) for their encouragement and constant support. I can never forget what they have done to me and I will always owe to them a lot as long as I live.

Rania ElSayed Hassan ElSayed Kasem

Contents

List of Abbreviations

Abbrev.	Meaning
AMPAr	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
AD	Alzheimer's disease
BDNF	Brain Derived Neurotrophic Factor
B-rTMS	Bilateral Transcranial Magnetic Stimulation
cAMP	Cyclic Adenosine Monophosphate
CDK 5	Cyclin Dependent Kinase 5
CEN	Central Executive Network
CREB	cAMP responsive element binding protein
cTBS	Continuous Theta Burst Stimulation
dACC	Dorsal Anterior Cingulate Cortex
DLPFC	DorsoLateral Prefrontal Cortex
DMN	Default Mode Network
DMPFC	DorsoMedial Prefrontal Cortex
ELF-MFs	Extremely Low Frequency Magnetic Fields
FA	Fractional Anisotropy
FDI	First Dorsal Interosseous
fMRI	Functional Magnetic Resonance Imaging
GAD	Glutamate Adenyl Decarboxylase
GLUR1	Glutamate receptor 1
HDRS	Hamilton Depression Rating Scale

HF	High Frequency
HFL	High Frequency Left
HFMS	High Frequency Magnetic Stimulation
HPA	Hypo-Thalamus- Pituitary Adrenal
HVA	HomoVanillic Acid
ICNs	Intrinsic Connectivity Networks
IEGs	Immediate Early Genes
ISI	Inter Stimulus Interval
iTBS	Intermittent Theta Burst Stimulation
LF	Low Frequency
LFMS	Low Frequency Magnetic Stimulation
LFR	Low Frequency Right
LI-rMS	Low Intensity repetitive Magnetic Stimulation
LTD	Long Term Depression
LTP	Long Term Potentiation
MAO	MonoAmine Oxidase
MDD	Major Depressive Disorder
MEP	Motor Evoked Potential
MPFC	Medial Prefrontal Cortex
MS	Magnetic Stimulation
MT	Motor Threshold
NaSSA	Noradrenergic and specific serotonergic antidepressants
NDRI	Norepinephrine dopamine reuptake inhibitor
NIBS	Non-Invasive Brain Stimulation

NMDAr	N Methy D Aspartate receptor
PAS	Paired Associative Stimulation
PCC	Posterior Cingulate Cortex
PPD	Pulse Per Day
PSD95	Synaptic Density Protein 95
QIDS-SR	Quick Inventory of Depressive Symptoms, Self-Report
rCBF	Regional Cerebral Blood Flow
RMT	Resting Motor Threshold
rTMS	Repetitive Transcranial Magnetic Stimulation
SARIS	Serotonine antagonist and reuptake inhibitors
SCG	Subgenual Cingulate Gyrus
SDS	Small Dendritic Spines
SgACC	Subgenual Anterior Cingulate Cortex
SN	Salience Network
SNRIs	Sereotonin –norepinephrine reuptake inhibitor
SSRIs	Selective Serotonin Reuptake Inhibitors
TBS	Theta Burst Stimulation
TCAs	TriCyclic Antidepressants
TDM	Therapeutic Drug Monitoring
TEM	Treatment Emergent Mania
TRD	Treatment Resistant Depression
VMPFC	Ventro Medial PreFrontal Cortex
VS	Ventral Striatum

List of Figures

List of Tables

Introduction

Major depression is a common debilitating disorder affecting 10%–15% of the population per year. Despite advances in the understanding of the psychopharmacology and biomarkers of major depression and the introduction of several novel classes of antidepressants, only 60%–70% of patients with depression respond to antidepressant therapy ***(Sakolsky et al., 2011).***

Of those who do not respond, 10%–30% exhibit treatment-resistant symptoms coupled with difficulties in social and occupational function, decline of physical health, suicidal thoughts, and increased health care utilization. Major depression with a poor or unsatisfactory response to two adequate (optimal dosage and duration) trials of two different classes of antidepressants has been proposed as an operational definition of treatment-resistant depression ***(Ward & Irazoqui ., 2010).***

Treatment-resistant depression (TRD) typically refers to an inadequate response to at least 1 antidepressant trial of adequate dose and duration among patients suffering from major depressive disorder (MDD). Adequate duration is often defined as a minimum of 6 weeks of treatment ***(Fava ., 2003)***, but mental health experts agree that it should only be diagnosed in patients who have not

been helped by two or more antidepressant treatment trials of adequate dose and duration ***(Huynh & McIntyre., 2008).***

Transcranial magnetic stimulation (TMS) was introduced in 1985 as a technique to stimulate the cerebral cortex non-invasively. A TMS device generates a strong magnetic field, inducing an electric current in a specific area, and this in turn induces intracerebral currents in associated neural circuits ***(Ruhe et al., 2012).***

The "single pulse TMS" has been utilized in research on localization of brain functions, while "repetitive TMS" (rTMS) has been used for treatment related studies. It is called "high frequency rTMS" if the stimulus frequency is above 1 Hz, or "low frequency rTM" if stimulus frequency is below 1 Hz. Low frequency rTMS is thought to inhibit cortical firing, while high frequency rTMS is thought to activate it ***(Barrett et al., 2004).***

The physical principles of TMS were discovered in 1881 by English physicist Michael Faraday, who observed that a pulse of electric current passing through a wire coil generates a magnetic field. The rate of change of this magnetic field determines the induction of a secondary current in a nearby conductor. During TMS, the stimulating coil is held over a subject's head and produces an electric current in the subject's brain via electro-magnetic

induction. This current in turn depolarises neurons and can generate various physiological and behavioural effects depending on the targeted brain area. Because magnetic fields can pass the skull with almost no resistance, TMS can induce relatively large currents in targeted cortical areas ***(Horvath et al., 2011).***

The design of magnetic stimulators is relatively straightforward, consisting of a main unit and a stimulating coil. The main unit is composed of a charging system, one or more energy storage capacitors, a discharge switch and circuitry used to control pulse-shape, energy recovery and other variable functions. The factors essential to the effectiveness of a magnetic stimulator are the speed of magnetic field rise time and the maximisation of the peak coil energy. Therefore, large energy storage capacitors and efficient energy transfer from the capacitor to the coil are important (typically energy storage capacity is around 2000J with a 500J transfer from the capacitor to the stimulating coil in less than 100 microseconds via a thyristor, an electrical device capable of switching large currents in a short time). The peak discharge current needs to be several thousand amperes in order to induce currents in the brain of sufficient magnitude to depolarise neural elements i.e. about 10 mA/cm^2 ***(Horvath et al., 2011).***

Several meta-analyses of rTMS in resistant depression have been published in the past ten years, with mixed results ***(Januel et al., 2006*)**. The majority of TMS trials targeted the Left Dorsolateral Prefrontal Cortex with high frequency stimulation, while only a few targeted the Right Dorso lateral Prefrontal Cortex with either low-frequency stimulation ***(Salva et al., 2006)*** or both ***(Stern et al., 2007)***.

In 2008, the U.S. FDA approved rTMS as a treatment for adults with MDD who "have not responded to a single antidepressant medication in the current episode" ***(Lisanby et al., 2010).***

Rationale of the study:

rTMS is an non invasive technique used for persons who have psychiatric and neurological conditions and who have not benefitted from standardized treatment. Despite it is FDA approved in 2008 for treating resistant depression, it is not widely used in Egypt. Unlike electroconvulsive therapy (ECT) , it does not involve any anesthesia or sedation. It is done while the person is awake and alert. Unlike medications, it does not circulate in the blood so its side effects profile may be more tolerable .The proposed research will highlight it as a relatively safe therapy in the treatment of depression.

Hypothesis:

We hypothized that rTMS may offer a new alternative treatment for depression for those who have not benefitted from prior antidepressant medications and not a candidate for electroconvulsive therapy with minimal affection on memory functions.

Aim of the Work

Is to study the following:

1- The effect of rTMS on improving the symptoms of depression compared with antidepressant drugs in an Egyptian sample.

2- The effect of rTMS therapy on memory functions compared with antidepressants.

3- The correlates of short term clinical responses of rTMS therapy (side of stimulation, number of sessions, frequency of stimulation).