EFFECTIVENESS OF THE COMBINED ANTIPSYCHOTIC AND BRAIN SYNCHRONIZATION THERAPY IN FIRST EPISODE PSYCHOSIS

Thesis

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By

MOSTAFA MOHAMMED ALY SHOHDY

M.B. B.Ch. Faculty of Medicine – Cairo University

Supervised by

PROF. DR. NAHLA AL SAYED NAGY

Professor of Psychiatry,

Faculty of Medicine, Ain Shams University

PROF. DR. HANAN M. EZZ EL DIN AZZAM

Professor of Psychiatry,

Faculty of Medicine, Ain Shams University

DR. HANAN HANY ELRASSAS

Lecturer of Psychiatry,

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

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عن رسالـــــة :

دكتـــــوراة

في :.....الطب.....النفسي.....

المقدمة من الطالب/.....مصطفى محمد على سعد.....

بحث عنوان باللغة العربية فعالية العلاج بالمزج بين الأدوية المضادة للذهان وجلسات تنظيم ايقاع المخ في أول نوبة ذهانية

باللغة الانجليزية Effectiveness of the Combined Anti Psychotic and Brain Synchronization therapy in first Episode Psychosis

بناء على موافقة الجامعة بتاريخ / / تم تشكيل لجنة الفحـــص

والمناقشة للرسالة المقدمة من الطالب: مصطفى محمد على سعد

بعنوان : .....فعالية المزج بين الأدوية المضادة للذهان وجلسات تنظيم ايقاع المخ في أول نوبة ذهانية

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ABBREVIATIONS

(18) F-DOPA	Fluoro-dopa-F-18.
5-HIAA	5-Hydroxy-Indole Acetic Acid
5HT	5-Hydroxytryptamine
ACTH	Adrenocorticotropic
ARMS	At Risk Mental Status
ASUIP	Institute of Psychiatry Ain Shams University
BDNF	Brain Derived Neurotrophic Factor
BPRS	Brief Psychiatric Rating Scale
BST	Brain Synchronization Therapy
CGI	Clinical Global Impression
CNS	Central Nervous System
COMT	Catechol-O-methyltransferase
CRP	C Reactive Protein
CSF	Cerebrospinal Fluid
D1R	Dopamine 1 Receptors
D2R	Dopamine 2 Receptors
D3R	Dopamine 3 Receptors
DA	Dopamine
DISC	Disruption in Schizophrenia
DNMT1	DNA Methyltransferase 1
DSM IV	The Diagnostic and Statistical Manual of Mental Disorders IV
DTNBP1	Dystrobrevin binding protein 1
DUP	Duration of untreated Psychosis
ECS	Electro Compulsive Shock
FEP	First Episode Psychosis
FGAs	First Generation Antipsychotics

GABA	gamma-Aminobutyric acid
HPA	hypothalamic–pituitary–adrenal
HVA	Homovanillic acid
ICV	Intracranial Volume
IFN-γ	Interferon Gamma
IL-12	Interleukin 12
IL-1B	Interleukin 1B
IL-6	Interleukin 6
MRS	Magnetic Resonance Spectroscopy
NGF	Nerve Growth Factor
NIH	National Institutes of Health
NMDAr	N-Methyl D-Aspartate receptors
NRG1	Neuregulin-1
PANSS	Positive and Negative Syndrome Scale
PET	Positron emission tomography
PRODH	Proline Dehydrogenase
RGS4	Regulator Of G-Protein Signaling 4
SCID	Structured Clinical Interview for DSM Disorders
SGAs	Second Generation Antipsychotics
SIL-2R	Soluble Interleukin 2 Receptors
TGF-B	Tumor Growth Factor Beta
TNF α	Tumor Necrosis Factor Alpha
VEGF	Vascular endothelial growth factor
VGKC	Voltage Gated Potassium Channel

INTRODUCTION

INTRODUCTION

Psychotic disorders are among the most disabling and costly medical conditions with a lifetime prevalence of almost 3% **(Perala *et al.*, 2007)**. It is defined as the prominent presence of delusions and/or hallucinations and/or disorganized speech and/or disorganized behavior (including catatonia) with no insight concerning the nature of these symptoms, denoting a broad impairment in one's capacity to perform critical judgments of reality **(Del-Bem *et al.*, 2010)**.

Definition of First Episode Psychosis (FEP) is controversial in regard to the limits of the duration of symptoms and the inclusion of the prodromal symptoms which are alterations in mental state or behavior that appear before the onset of the full-blown psychotic symptoms described above **(Singh *et al.*, 2005)**. Unfortunately, the typical first psychotic episode goes undiagnosed and untreated for 1 to 2 years, which some studies suggest may allow schizophrenia to progress **(Correll and Mendelowitz, 2003)**.

However, the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-V) defined the FEP as the first manifestation of the disorder meeting the defining diagnostic symptom and time criteria **(Tandon and Carpenter, 2013)**.

Patients with a FEP have inflammatory like immunological function during early phases of the illness that it is independent of the antipsychotic treatment used **(Benedicto *et al.*, 2006)**. Several markers of neurobiological changes including dynamic changes in brain structure in the frontal and temporal regions, neurochemical alterations in dopamine and glutamate and evidence for neuro-inflammation through microglial activation **(Cropley *et al.*, 2013)**.

Clinical studies show reductions in brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in schizophrenic patients as compared to normal control subjects **(Martinotti *et al.*, 2012)**. Moreover, low BDNF levels in subjects with FEP in comparison with normal healthy controls suggest that it may contribute to the pathogenesis of schizophrenia and/or perhaps could be a helpful neurobiological marker for possible early treatment intervention **(Buckley *et al.*, 2008)**.

In FEP, early treatment with antipsychotic drugs is associated with significant symptom reduction, and the results of several studies suggest that there are no significant short-term efficacy differences between FGAs and SGAs **(Schoolar *et al.*, 2005)**. Antipsychotic medications had also been shown to affect pro-inflammatory cytokine network and immune function in schizophrenia **(Drzyzga *et al.*, 2006)**, perhaps provide an aspect of disease modification and prevention to the known therapeutic index on dopamine regulation **(Kristen and Sandoval, 2012)**.

Brain Synchronization Therapy (BST) exhibits demonstrable effectiveness for psychotic symptoms associated with a broad range of neuropsychiatric conditions. However, the mechanism remains poorly understood particularly with regard to antipsychotic effects **(Rosenquist, 2014)**. Moreover, BST is an effective and safe intervention used in patients with first-episode psychosis and can be considered an early psychosis intervention **(Zhang *et al.,* 2012)**.

The exact therapeutic mechanism of action of BST remains unresolved. BST has been proven to have numerous reproducible effects on brain chemistry, regional brain activity, electroencephalographic sleep stages, and neurogenesis. Clinically, BST has been shown to have antidepressant, antipsychotic, antimanic. It is possible that different biological effects of BST are responsible for different clinical effects or that several biological effects in concert work together to produce a given clinical effect **(McCall *et al.,* 2014)**.

Acute BST increases the production of the cytokines IL-6, TNF-α, Cortisol and ACTH, therefore BST is associated with transient immunological and neuro-endocrine changes **(Fluitmana *et al.,* 2011)**. Moreover, it was found that BST enhances serotonergic neurotransmission and activation of the mesocorticolimbic dopamine system. Furthermore, it seems that these effects are evident at various levels, including neurotransmitter release, receptor binding, and overall neurotransmission **(Baldinger *et al.,* 2014)**.

A comparison of the neurophysiologic and molecular properties of antipsychotic drugs and BST reveals some overlap, but there are also distinctive differences; and the significance of these findings remains uncertain **(Rosenquist *et al.,* 2014)**.

RATIONALE OF THE STUDY

Almost two fifths of all FEP patients are prescribed drug treatment that does not meet current recommendations **(Robinson, 2014)**.

FEP is a traumatic experience for patients and families. Treating patients with FEP is challenging, early detection and the pursuit of integrative treatment give patients and their families hope for better course and outcome **(Martin *et al.*, 2009)**.

BST had been used to treat schizophrenia since its introduction but was less utilized after the introduction of effective pharmacological agents. Later, identification of a group of patients with schizophrenia, who were either unresponsive to, or unable to tolerate to pharmacological treatment, resulted in a re-examination of the role of BST in these patients **(Roger and Colleen, 2010)**.

BST-antipsychotic combinations might be better than antipsychotic drugs used alone in the first few weeks of treatment of schizophrenia; the main benefit seemed to be an acceleration of treatment response. Although the evidence was not conclusive because of several methodological difficulties, it does suggest that further research is required to determine the usefulness of the BST-antipsychotic combination in the acute treatment of schizophrenia **(*Painuly et al., 2006)***.

Therefore, early and effective treatment of FEP by different mechanisms by combined antipsychotic-BST may improve the outcome and the quality of life of the patients.