Relationship between Oxytocin level and Major Depressive disorder

AThesis

Submitted for The partial fulfillment of M.D Degree in Psychiatry

By

Fairouz Ahmed Abdel moneim Tawfik

M.Sc in Neuropsychiatry
Faculty of Medicine – Ain Shams University

Under Supervision of

Prof. Abd El Nasr Mahmoud Omar

Professor of Neuropsychiatry Department Faculty of Medicine – Ain Shams University

Prof. Heba Hamed Mahmoud Alshahawy

Professor of Neuropsychiatry Department Faculty of Medicine – Ain Shams University

Prof. Doaa Hamed Mostafa Hewedi

Professor of Neuropsychiatry Department Faculty of Medicine – Ain Shams University

Ass.Prof. Reem El Sayed Mohamed Hashem

Assistant professor of Neuropsychiatry Department Faculty of Medicine – Ain Shams University

Faculty of Medicine Ain-Shams University CAIRO, 2018



Acknowledgments

First, I wish to express my deep thanks, sincere gratitude to Allah, who always helps me, care for me and grunted me the ability to accomplish this thesis.

I would like to express my deepest gratitude, thanks and gratefulness to **Prof. Abd El Nasr Mahmoud Omar,** Professor of Neurology and Psychiatry, Ain Shams University, for his enthusiastic support, continuous encouragement, valuable scientific advices, and great help through out of the accomplishment of this work. It would be impossible to count all the ways that he has helped me to complete this work and throughout my career path.

I am very grateful to **Prof. Heba Hamed Mahmoud Alshahawy**, Professor of Neurology and Psychiatry, Ain Shams University, for her kind supervision, support, indispensable suggestion, and great help through out of course of my thesis.

I am profoundly grateful to **Prof. Doaa Hamed Mostafa Hewedi**, Professor of Neurology and Psychiatry, Ain Shams University for her guidance.

My sincere thanks to Ass. Prof. Reem El Sayed Mohamed Hashem, Assistant professor of Neurology and Psychiatry, Ain Shams University, for her kind and meticulous supervision, support, help, valuable supervision all through the work.

Words can never express my sincere thanks to my family and my loving husband for their generous emotional support and continuous encouragement which brought the best out of me. I owe them all every achievement throughout my life. I can't miss my Sweet Unique Beloved Son Whose love and smile gives meaning to life and the power to carry on.

I would like to express my overlasting gratitude to all my all my professors, colleagues and friends, so many of them influenced, encouraged and inspired me throughout the years and wishing them the best of all.

I would like also to thank the **patients** who agreed willingly to be part of my study and without them I wouldn't have been able to accomplish this work.

📜 Fairouz Ahmed Abdel Moneim Tawfik

List of Contents

| Subject I | Page No. |
|-----------------------------------------------|----------|
| List of Abbreviations | i |
| List of Tables | iv |
| List of Figures | vi |
| Abstract | X |
| Introduction | 1 |
| Aim of the Work | 5 |
| Review of Literature | |
| Pathophysiology of Depression | 6 |
| Oxytocin and Psychiatric disorders | 25 |
| Oxytocin and management of Psychiatric disord | ers 51 |
| Patients and Methods | 64 |
| Results | 73 |
| Discussion | 104 |
| Strength of the study | 115 |
| Limitations of the study | 116 |
| Conclusion | 117 |
| Recommendations | 119 |
| Summary | 120 |
| References | 126 |
| Arabic Summary | |

List of Abbreviations

Full-term

ACTH : Adrenocorticotropic hormone

ASD : Autism spectrum disorders

BDNF : Brain derived neurotrophic factor

BMI : Body mass index

Abbr.

CNS : Central nervous system

CRH : Corticotropin-releasing hormone

CSF : Cerebrospinal fluid

ECT : Electroconvulsive therapy

FST : Forced swimming test

GABA : Gamma-aminobutyric acid

GAD : Generalized Anxiety disorder

GRs : Glucocorticoid receptors

HPA : Hypothalamic-pituitary-adrenal

HRSD : Hamilton Rating Scale for Depression

i.p : Intraperitoneal

ICV : Intra-cerebroventricular

IQR : Interquartile range

LHA : Lifetime History of Aggression

LH-RH : Luteinizing hormone-releasing hormone gene

M : Mean

MAOA : Monoamine oxidase Type A

MBTs : Mind–body therapies

MDD : Major Depressive Disorder

MnR : Median raphe nuclei

MPFC: Medial prefrontal cortex

NMDA : N-methyl-D-aspartate

NPV : Negative predictive value

OCD : Obsessive-compulsive disorder

OTRs : Oxytocin receptors

OXT : Oxytocin

OXTR : OXT receptor

P : Probability

PPV : Positive predictive value

PTSD : Post-traumatic stress disorder

PVN: Paraventricular nucleus

r : Correlation coefficient

RCTs : Randomized controlled trials

ROC : Receiver operator curve

SCID-I: Structured Clinical Interview for DSM-IV-TR

Axis I Disorders

SD : Standard deviation

SNRI : Selective norepinephrine reuptake inhibitor

SON : Supraoptic nucleus

SPSS : Statistical Package for Social Sciences

SSRIs : Selective serotonin reuptake inhibitors

STAI : State trait anxiety inventory

TCA : Tricyclic antidepressant

TGOT: Thr4, Gly7-oxytocin

WHO: World Health Organization

List of Tables

| Table No | . Title Page | No. |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------|-----|
| Table (1): | Comparison between the patients group and the controls group regarding their gender | 74 |
| Table (2): | Comparison between the patients group and the controls group regarding their age | 75 |
| Table (3): | Diagnosis of the Patients according to SCID -I | 77 |
| Table (4): | Descriptive Statistics of the patients group regarding Hamilton Rating Scale for Depression and State trait anxiety inventory | 78 |
| Table (5): | Range of age of onset of illness among the patient group | 78 |
| Table (6): | Clinical characteristics of the patients group according to the duration of illness | 79 |
| Table (7): | Clinical characteristics of the patients group according to the number of episodes . | 80 |
| Table (8): | Clinical characteristics of the patients group according to the presence of suicidal and psychotic symptoms | 81 |
| Table (9): | Clinical characteristics of the patients group according to the current status of receiving medications or not | 83 |
| Table (10): | Concomitant psychiatric medications for the patients group | 84 |
| Table (11): | Clinical characteristics of the patients group according to Electroconvulsive therapy | 85 |

| Table (12): | Comparison between the patients and the |
|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | controls group regarding the oxytocin level86 |
| Table (13): | ROC curve between Patients group and Controls group87 |
| Table (14): | Comparison between the patients group and the controls group regarding the cutoff point of the oxytocin level |
| Table (15a): | Comparison between the patients group and the controls group regarding the Body mass index91 |
| Table (15b): | Comparison between the patients group and the controls group regarding the Body mass index |
| Table (16): | Comparison between the gender difference in the patients group and the controls group regarding the oxytocin level |
| Table (17): | Relation between the patients who experienced suicidal symptoms and the patients who didn't experience suicidal symptoms regarding the oxytocin level 94 |
| Table (18): | Relation between the patients who experienced psychotic symptoms and the patients who didn't experience psychotic symptoms regarding the oxytocin level 95 |
| Table (19): | Relation between the patients who experienced both suicidal and psychotic symptoms and the patients who didn't experience these symptoms regarding the oxytocin level |

| Table (20): | Correlations between the ages of the patients, age of onset of illness, BMI, Hamilton score and STAI (state and trait) with the oxytocin level |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Table (21): | Relation between gender differences, living area, current status of receiving medication, SCID-I diagnosis and ECT therapy in the patients group with the oxytocin level |
| Table (22): | Relation between occupation, marital status, Education, severity of depressive symptoms, duration of illness, No. of episodes and Type of treatment in the patients group with the oxytocin level 100 |
| Table (23): | Comparison between Group A1 and Group A2 regarding Hamilton score, STAI (state and trait), ages of the patients and age of onset of illness with the oxytocin level |
| Table (24): | Comparison between Group A1 and Group A2 regarding gender, occupation, marital status, BMI, Education, living area, medication and SCID diagnosis 102 |
| Table (25): | Comparison between Group A1 and Group A2 regarding Duration of illness, Severity of depressive symptoms, No. of episodes, ECT and Type of medications 103 |

List of Figures

| Figure No. | Citle Page T | No. |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Figure (1): | Neural systems of relevance to major depressive disorder | 7 |
| Figure (2): | Major integrated pathway pathologies in depression | . 19 |
| Figure (3): | The dual role of activated microglia | . 21 |
| Figure (4): | The inflammation as a key mediator for the development of depression | . 24 |
| Figure (5): | A schematic depiction of the hypothesized interactions between oxytocin and other neurochemical and hormonal systems in response to an acute stressor | . 36 |
| Figure (6): | Physiological function of OXT | . 50 |
| Figure (7): | Modulation of the fear response by oxytocin ("fear system") | |
| Figure (8): | Comparison between the patients group and the controls group regarding their gender | . 74 |
| Figure (9): | Comparison between the patients group and the controls group regarding their age | . 75 |
| Figure (10): | Diagnosis of the Patients according to SCID- I | |
| Figure (11): | Clinical characteristics of the patients group according to the duration of illness | . 79 |

| Figure (12): | Clinical characteristics of the patients group according to the number of episodes |
|---------------------|----------------------------------------------------------------------------------------------------------------------|
| Figure (13): | Clinical characteristics of the patients group according to the presence of suicidal and psychotic symptoms |
| Figure (14): | Clinical characteristics of the patients group according to the current status of receiving medications or not |
| Figure (15): | Concomitant psychiatric medications for the patients group |
| Figure (16): | Clinical characteristics of the patients group according to Electro-convulsive therapy85 |
| Figure (17): | Comparison between the patients and the controls group regarding the oxytocin level |
| Figure (18): | ROC curve between Patients group and Controls group |
| Figure (19): | Comparison between the patients group and the controls group regarding the cutoff point of the oxytocin level |
| Figure (20a): | Comparison between the patients group and the controls group regarding the Body mass index91 |
| Figure (20b): | Comparison between the patients groups and the controls group regarding the Body mass index |
| Figure (21): | Comparison between the gender difference in the patients group and the controls group regarding the oxytocin level93 |

| Figure (22): | Relation between the patients who experienced suicidal symptoms and the patients who didn't experience suicidal symptoms regarding the oxytocin level94 |
|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Figure (23): | Relation between the patients who experienced psychotic symptoms and the patients who didn't experience psychotic symptoms regarding the oxytocin level 95 |
| Figure (24): | Relation between the patients who experienced both suicidal and psychotic symptoms and the patients who didn't experience these symptoms regarding the oxytocin level |

ABSTRACT

Background: major depressive disorder is one of the most common medical disorders worldwide, having huge impact on physical and mental health in the society and is considered an extended lifedisorder. threatening psychiatric **Abnormalities** in the neurohypophyseal system, neuroendocrine, and immune systems have been reported in depression. Aim of the Work: this study was carried out to identify the relationship between plasma oxytocin level and the severity of major depressive disorder. Patients and Methods: this case control observational study was started from July 2016 till March 2018. The subjects were selected from inpatient and outpatient clinics of Institute of Psychiatry, Faculty of medicine, Ain Shams University. Twenty two female patients were enrolled and fourteen female healthy subjects were considered as controls. Both groups were subjected to Arabic version of Structured Clinical Interview for DSM-IV-TR Axis I Disorders and sampling of serum Oxytocin. Moreover the female patients were subjected to Hamilton rating scale for depression and state trait anxiety inventory to assess the presence of anxiety symptoms. **Results:** our study revealed reduced serum oxytocin levels in depressed female patients with cutoff point \(\le 25.6 \) denoting that below this level shows probability for major depressive disorder in females. **Conclusion:** our study revealed reduced serum oxytocin levels in depressed female patients. Consistently with the hypothesis of dysregulated OXT biology may serve as a biomarker for major depression.

Keywords: Oxytocin, major depressive disorder, Hamilton Rating Scale for Depression, state trait anxiety inventory.

Introduction

ajor depressive disorder (MDD), is associated with substantial deficits in quality of life, considered to be the leading cause of disability globally as it affects nearly 350 million people worldwide (Rapaport et al., 2005; Ishak et al., 2013).

Importantly, the quality of life deficits revealed to persist beyond the clinical resolution of symptoms. Placing patients at an increased risk for relapse and rising direct and indirect costs (Ishak et al., 2015).

In the last decades several neuropeptide families were discovered having modulatory roles on neurotransmission in synapses. This in turn evoked the interest of psychoneuro-endocrinologists predicting potential significant clinical relevance in the treatment of stress-related mood disorders (Paschos et al., 2009).

Oxytocin (OXT) is a neuropeptide produced in the hypothalamus, involved in a broad range of physiological and behavioral processes (McQuaid et al., 2013).

A few data suggest a link between Oxytocin and neuropsychiatric disorders, especially obsessive-compulsive disorder, eating disorders, addiction, post-traumatic stress