



" قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا
عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ "

صدق الله العظيم

سورة البقرة

آية ٣٢

**ULTRASTRUCTURAL AND
IMMUNOHISTCHEMICAL STUDY ON THE
EFFECT OF CERTAIN WIDELY USED
ANTIDEPRESSANTS ON SUBMANDIBULAR
SALIVARY GLAND OF RATS**

Thesis

**Submitted to the Faculty of Oral and Dental Medicine ☯
Cairo University
In Partial Fulfillment of the Requirement for the Doctor
Degree in Oral Biology**

By

**Tahany Abdel Kareem Mohamed Haggag
(B.D.S.) (M.D.S.)**

**Faculty of Oral and Dental Medicine
Cairo University
2011**

Supervisors

Dr. Rabab Tawfik Moubarak

**Associate Professor of Oral Biology
Oral Biology Department
Faculty of Oral and Dental Medicine
Cairo University**

**Prof. Dr. Gamal Eldein Zoalhammh
Al-Sharkawy**

**Professor of Oral Biology
Faculty of Oral and Dental Medicine
Oral Biology Department
Cairo University**

Acknowledgement

In the beginning, I would like to thank ALLAH firstly, lastly whose magnificent help is the main factor in every thing we can do in life.

*Words can never express my deepest thanks and appreciation to **Dr. Rabab Tawfik Moubarak** Associate Professor of Oral Biology, Faculty of Oral and Dental Medicine, Cairo University for her valuable guidance, unlimited assistance and great help to accomplish this work,*

*I am profoundly grateful to **Prof. Dr. Gamal Eldein Zoalhamh Al-Sharkawy**, Professor of Oral Biology, Faculty of Oral and Dental Medicine, Cairo University for his efforts and great help. My sincere thanks and respect to **Prof. Dr. Nahed Abdel Salam Khalil**, head of Oral Biology Department, Faculty of Oral and Dental Medicine, Cairo University, for her valuable advice and continuous support.*

I would like to extend my deep thanks to my Professors and all the staff members of the Oral Biology Department, Faculty of Oral and Dental Medicine, Cairo University.

Finally, I express my sincere gratitude, deep love endless appreciation to my mother and my small family for their continuous understanding help and support during the preparation of this work.

To

My Dear Mother

My Kind Husband

My Lovely Daughters

List Of Contents

	Page
Introduction	1
Review of Literature	
• What is depression?.....	4
• Depression complains.....	4
• Oral complains of depression.....	7
• Depression in children.....	9
• Treatment of depression.....	10
• Importance and uses of antidepressants.....	12
• Types of antidepressants.....	16
• Mode of action of antidepressants	18
• Oral side effects of antidepressants.....	21
• Pharmacology of amitriptyline.....	22
• Uses of amitriptyline.....	23
• Side effects of amitriptyline.....	26
• Mirtazapine.....	32
• Pharmacology of mirtazapine.....	33
• Uses of mirtazapine.....	34
• Advantages of mirtazapine.....	38
• Side effects of mirtazapine.....	41
• Nature of S-100.....	42
• Distribution of S-100.....	43
• Functions of S-100.....	43
• Distribution of S-100 in salivary glands.....	46
• S-100 expression in oral diseases.....	47
Aim of the study.....	48
Materials and Methods.....	49
Results	
• Results of light microscope	61
• Results of electron microscope.....	79
• Immunohistochemical results.....	122
Discussion	135
Summary and conclusions.....	153
References.....	161
Arabic Summary	

ABSTRACT

Amitriptyline is one of several tricyclic antidepressants used for treatment of depression. Mirtazapine is a tetracyclic piperazino azepine, which had a different structure from any other currently used antidepressants with fewer side effects. This study was designed to investigate the effects of amitriptyline and mirtazapine antidepressants on the submandibular salivary glands of the rats. A total of 100 male albino rats were used and divided into 5 groups (20 rats each). Group I was control group, group II was given a daily single therapeutic oral dose of amitriptyline for 8 weeks and group III was given a daily double oral dose of amitriptyline for the same period. Group IV was given a daily single oral therapeutic dose of mirtazapine for 8 weeks and group V was given a daily double oral dose of mirtazapine for the same period. Histological examination of submandibular salivary glands revealed degenerative changes and stagnation of secretion in the groups of both drugs. These degenerative changes increased from single to double dose of the drug. There was a highly significant difference of the mean value for optical density of S-100 protein between all groups.

Keywords: antidepressants; salivary glands; amitriptyline; histological structure; mirtazapine; depression, S-100 protein.

الملخص

الأميتريبتيلين هو واحد من عدة مضادات الاكتئاب الثلاثية الحلقات ويستخدم في علاج الاكتئاب. الميرتازابين وهو رباعي الحلقات وله بنية مختلفة عن مضادات الاكتئاب الأخرى المستخدمة حالياً ويتميز بقلة المضاعفات الجانبية. والهدف من هذه الدراسة هو تقصي أثر الأميتريبتيلين و الميرتازابين على الغدد اللعابية تحت الفك للفران. واستخدم ١٠٠ من فران التجارب البالغين الذكور وقسمت إلى ٥ مجموعات (٢٠ فأر لكل مجموعة). المجموعة الأولى واستخدمت كضوابط والثانية أعطيت جرعة يومية مكافئة للجرعة العلاجية من الأميتريبتيلين عن طريق الفم لمدة ٨ أسابيع. والمجموعة الثالثة أعطيت جرعة يومية مكافئة لمضاعفة الجرعة العلاجية من الأميتريبتيلين لنفس الفترة. أما المجموعة الرابعة فقد أعطيت جرعة يومية مكافئة للجرعة العلاجية للميرتازابين عن طريق الفم لمدة ٨ أسابيع. والمجموعة الخامسة وقد أعطيت جرعة يومية مكافئة لمضاعفة الجرعة العلاجية من الميرتازابين لنفس الفترة. وقد أظهر الفحص الهيستولوجي والالكتروني للغدد العلاجية تحت الفك تغيرات وتراكم الإفرازات في مجموعات العقارين. وهذه التغيرات ازدادت من جرعة واحدة إلى جرعة مضاعفة وكان هناك اختلاف كبير في متوسط الكثافة البصرية لبروتين اس ١٠٠ بين كل المجموعات.

LIST OF FIGURS2

Figures		Page
Figs.(1):	Photomicrographs of image analysis	60
Figs.(2-4):	Photomicrographs of rat submandibular salivary glands of control group (group I) (H & E).	63-64
Figs.(5-7):	Photomicrographs of rat submandibular salivary glands of group II (H & E).	66-67
Figs.(8-13):	Photomicrographs of rat submandibular salivary glands of group III (H & E).	70-72
Figs.(14-16):	Photomicrographs of rat submandibular salivary glands of group IV (H & E).	74-75
Figs.(17-20):	Photomicrographs of rat submandibular salivary glands of group V (H & E).	77-78
Figs.(21-26):	Electron micrographs of rat submandibular salivary glands of control group (group I).	81-86
Figs.(27-31):	Electron micrographs of rat submandibular salivary glands of group II.	89-93
Figs.(32-38):	Electron micrographs of rat submandibular salivary glands of group III.	96-102
Figs.(39-45):	Electron micrographs of rat submandibular salivary glands of group IV.	105-111
Figs.(46-53)	Electron micrographs of rat submandibular salivary glands of group V.	114-121

Fig.(54):	A photomicrograph of rat submandibular salivary glands of control group (group I) for immunohistochemical localization of S-100 protein.	124
Fig.(55):	A photomicrograph of rat submandibular salivary glands of group II for immunohistochemical localization of S-100 protein.	125
Fig.(56):	A photomicrograph of rat submandibular salivary glands of group III for immunohistochemical localization of S-100 protein.	126
Fig.(57):	A photomicrograph of rat submandibular salivary glands of group IV for immunohistochemical localization of S-100 protein.	127
Fig.(58):	A photomicrograph of rat submandibular salivary glands of group V for immunohistochemical localization of S-100 protein.	128
Fig.(59):	A histogram representing the difference in mean S-100 optical density between different groups.	134

List of tables

Tables	Title	Page
Table I	Difference in mean S-100 optical density between control and amitriptyline single oral dose (5mg/kg) groups using Paired Student's t-Test.	129
Table II	Difference in mean S-100 optical density between control and amitriptyline double oral dose (10mg/kg) groups using Paired Student's t-Test.	130
Table III	Difference in mean S-100 optical density between control and mirtazapine single oral dose (10mg/kg) groups using Paired Student's t-Test.	131
Table IV	Difference in mean S-100 optical density between control and mirtazapine double oral dose (20mg/kg) groups using Paired Student's t-Test.	132
Table V	Difference in mean S-100 optical density between different groups using ANOVA statistical test.	133

Introduction

INTRODUCTION

Depression is a major public health problem, which is predicted to be the second disease after cardiovascular problems that leading to disability all over the world by 2020. It affected the total health status and patients with depression generally experience worse outcomes. Depression is wide spread among women and in most countries; the prevalence is twice that among men of the same age (*Murray and Lopez, 1990*).

Depression is mental illness in which a person experience deep sadness and diminished interest in nearly all activities. Sever depression also called major depression which can dramatically impair a person's ability of function in social situation and at work. People with major depression often have feelings of hopelessness and worthlessness as well as thoughts of committing suicide. Anyone, regardless of age, gender, race, or socioeconomic status, can suffer from depression (*Harrington et al., 1990*).

In addition the specific complaints of headache, back pain, abdominal pain, joint pain and chest pain were frequently endorsed by depressed patient in primary care setting. The common occurrence of depression and pain symptoms was the main reason that depression was frequently unrecognized and therefore untreated in primary care. The somatic symptoms predominated and might distract attention from typical

depressive symptoms (***Kroenke et al., 1994***). The new emphasis on pain as the "fifth vital sign" by both Joint Commission on Accreditation of Health Care Organization and the Veterans Health Administration provided an opportunity for better reorganization and understanding the interaction between depression and pain. ***Katon and ciechanowski (2002)*** also reported that, depression was under recognition but poorly treated by primary care physicians and specialists. Numerous studies in developed countries reported that only half of the patients with depression in primary care or general hospital setting were identified and even fewer were adequately treated. ***Rugulies (2002) and Keefe et al., (2002)*** found that there was an association between arthritis, cardiovascular disease and depression. Also they found that, the high rates of poorly treated depression were the leading factor to high rates of suicide among medical subspecialty clinic depressed patients.

Stewart et al., (2004) stated that depression rates were slightly higher in the United States and slightly lower in Europe but followed the same sex based pattern. In addition to personal suffering, depression had a detrimental effect in general health, family well being, work productivity and health care costs. It might also lead to self injury and suicide.

It had been known for many years that treatment of depression was carried out using antidepressants. From these antidepressants, firstly discovered was tricyclic antidepressant.

. **Haller et al., (2007)** reported that tricyclic antidepressants (e.g. amitriptyline) were commonly employed orally to treat major depressive disorders. Tricyclic antidepressants had been shown to be of substantial benefit in various chronic pain condition associated with depression. In addition **Kim et al., (2008)** reported that mirtazapine was a newer and effective medication for treatment of depression. They also found that mirtazapine improved nausea, sleep disturbance, pain and quality of life.

Treatment of depression with antidepressant had many side effects as dizziness, insomnia, fatigue, xerostomia and constipation so that, attention had been directed towards studies of the side effects of the antidepressant drugs used and their potential hazards.