

Medical Studies Department

# Omega-<sup>#</sup> Fatty Acids versus Risperidone in Treatment of Children with Pervasive Developmental Disorders

Thesis

submitted for the fulfillment of Ph.D. Degree in Childhood Studies

(Child health and Nutrition)

Prepared By

#### Dr. Lamia Hamdy Aly Ibraheim

M.B., B. Ch., M.Sc. pediatrics

Ain-Shams University

### Supervised By

Dr. Olweya M. Abdel Baky	Dr.Azza Abdel Moneim Al Gamal
Prof. of Child	Consultant of Pediatrics
& Adolescent Psychiatry Dep.	Head of Pediatrics Department
of Medical Studies	Police Authority Hospital
Institute of Post-Graduate Childhoo	od
Studies Ain-Shams University	

#### ACKNOWLEDGMENT

I hope to express in words, through too inadequate, my gratitude, firstly to god and secondly to all those who have participated in one way or another in the planning execution and presentation of my study to give it its final form.

I am sincerely thankful to Dr. Olweya M. Abdel Baky, Prof. of Child & Adolescent Psychiatry, Medical Studies Department ,Institute of Post-Graduate Childhood, Ain Shams University, for her valuable advice, suggestions on the work and for her endless and patience constructive criticism throughout the study.

I would also like to express my utmost thanks and highest appreciation to Dr. Azza Abdel Moneim Al Gamal, Consultant of Pediatrics, Head of Pediatrics Department at Police Hospital, for her kind supervision, valuable observations and wise scientific advice during my work.

Lastly and not the last I like to express my deep heart feeling to my family especially my sweetheart ( Dareen and Nouran) and the invisible man behind every step to my success, my dear husband Eng. Tamer Ezz El-Din. This is an additional success he has pushed me to, but I am sure it will not be the last.

## **List Of Contents**

Introduction& Aim of the study	١
Definition of PDD	٤
Types of Pervasive Developmental Disorders	0
Epidemiology of Pervasive Developmental Disorders	۲.
Comorbid conditions to autism spectrum disorders	77
Differential diagnosis of autistic disorders	٣.
Causes of Autistic spectrum Disorders	٣٤
Mechanism of Autistic Disorders	٤٧
The Diagnosis of Autism Spectrum Disorders	0 2
Investigations used in Pervasive Developmental Disorders diagnosis	٦.
Autistic Disorders Therapies	٧٤
Antipsychotic in the treatment of autism	٩٢
Omega- <sup>r</sup> Fatty acids	١ • ٤
Subject and methods	١٣١
Results	1 £ £
Discussion	170
Summary and conclusion	١٨٨
Recommendations	١٩٨
References	١٩٩
Appendix(A)	211
Appendix(B)	۲٦٨
Appendix(C)	777
Arabic summary	۲۸.

Table	Subject	Page
('-')	Distinguishing Characteristics of Pervasive Development Disorders	۲.
(1-1)	Selected Level ) and Y ASD Screening Measures	٥٧
(1-1)	Key dietary fatty acids	١١٢
( <sup>1</sup> - <sup>r</sup> ) ( <sup>r</sup> - <sup>r</sup> )	Laboratory data of patients treated with Efalex Efamol Omega- <sup>\%</sup> Omega- <sup>\</sup>	157
(٣-٣)	Psychological tests of patients treated by Efalex Efamol Omega- <sup>۳</sup> & Omega- <sup>7</sup>	۱ ٤ V
(٣-٤)	EEG characteristics of patients treated with Efalex Efamol Omega- <sup>7</sup> & Omega- <sup>7</sup>	١٤٨
(٣-٧)	Laboratory data of patients treated with Risperdal	107
(٣-٨)	Psychological tests of patients treated by Risperdal	107
(۳-۹)	EEG characteristics of patients treated with Risperdal	102
(٣-١١)	Effect of Risperdal on ATEC score	101
(٣-١١) (٣-١٢)	Effect of Efalex Efamol Omega- <sup>r</sup> & Omega- <sup>1</sup> on ATEC score	101
(٣-١٣)	Comparison between Risperdal and Efalex Efamol Omega- <sup>*</sup> & Omega- <sup>*</sup>	109
(٣-١٤)	Percent of change in group of patients treated with Risperdal	١٦٠
(٣-١٥)	Percent of change in group of patients treated with Efalex Efamol Omega- <sup>\%</sup> Omega- <sup>\</sup>	١٦١

Figure	Subject	Page
(')	Diagram of the Pervasive Developmental Disorder categories	۲٩
(1-1)	Autism affects many parts of the brain	٤٨
(1-٣)	Classical omega- <sup>r</sup> and omega- <sup>1</sup> fatty acid synthesis pathways	1.7
(٣-١)	Sex percent in patients treated by Efalex	120
(٣-٢)	EEG abnormalities percent in patients treated by Efalex	1 2 9
(٣-٣)	EEG characteristic in patients treated by Efalex	1 2 9
(٣-٤)	Sex percent in patients treated by Risperidone	101
(٣-٥)	EEG abnormalities percent in patients treated by Risperidone	100
(۳-٦)	EEG characteristic in patients treated by Risperidone	100
(٣-٧)	Diagram showing improvement of patients after ttt by Risperidone by ATEC	١٦٢
(٣-٨)	Diagram showing improvement of patients after ttt by Efalex Efamol O- <sup>r</sup> & <sup>¬</sup> by ATEC	17٣
(٣-٩)	Diagram showing ATEC scores of patients treated by Omega- <sup>r</sup> & <sup>¬</sup> versus Risperidone	175

# List Of Figure

#### Abbreviations:.

AA: arachidonic acid.

AAC: augmentative and alternative communication

AAP: American Academy of Pediatrics.

ABA : Applied behavior analysis

ABC: Aberrant Behavior Checklist

ABC: Autism Behavior Checklist

ABLLS : Assessment of Basic Language and Learning Skills

Abn: abnormal.

ABR/BSER: Auditory brainstem response/brain stem evoked response

AD: autistic disorder.

ADD: attention deficit disorder

ADHD: attention- deficit /hyperactivity disorder.

ADI-R: Autism Diagnostic Interview-Revised

ADOS: Autism Diagnostic Observation Schedule

ALA: alpha- linoleinic acid.

ARI : Autism Research Institute

AS: Asperger syndrome.

ASD: Autism spectrum disorders or Autism disorders.

ASIEP-<sup>*\mathcal{\mathcal{P}}*</sup>: Autism Screening Instrument for Educational Planning( Third Edition)

ATEC: Autism Treatment Evaluation Checklist

BAP: broader autism phenotype.

BD: bipolar disorder.

Bl Pr: Blood pressure.

BPD: borderline personality disorder.

CAM : complementary and alternative medicine

CARS : Childhood Autism Rating Scale

Case no: case number.

CAST: childhood Asperger syndrome test.

CDC: Centers for disease control.

CDD: childhood disintegrative disorder.

CDKL°: cyclin- dependent kinase – like °.

CGAS : Children's Global Assessment Scale

CGI: Clinical Global Impression

CGI-I : Clinical Global Impression-Improvement scale

CHARGE study: childhood Autism Risk from Genetics and the environment study.

CHAT : checklist for autism in toddlers.

CNS: central nervous system.

CNVS: copy number variation.

CPRS : Children's Psychiatric Rating Scale

CRS-R: Conner's Rating Scales Revised

CSF: cerebro spinal fluid.

CT: computerized tomography.

CY-BOCS : Children's Yale-Brown Obsessive Compulsive Scale

DA : dopamine receptor antagonists

DAN: Defeat Autism Now

DAT: dolphin-assisted therapy

DCD: developmental coordination disorder.

DGLA: dihomo gammalinolenic acids .

DHA: docosahexaenoic acid.

DIR: Greenspan and Wieder's developmental, individual-difference,

relationship-based model

DMG: Dimethylglycine

DPT: diphtheria-tetanus-pertussis.

DSM: Diagnostic and statistical Manual of Mental Disorders.

DSM-III: Diagnostic and Statistical Manual third Edition.

DSM-IV: Diagnostic and Statistical Manual fourth Edition.

DT: diphtheria-tetanus.

DTT: discrete trial teaching

ECG: electro-cardiogram.

ECT: Electroconvulsive therapy

EEG: electroencephalography (electroencephalogram).

E-EPA: ethyle ester of EPA.

EFAS: essential fatty acids.

EPA: eicosapentaeoic acid.

EPS : extrapyramidal symptoms

FDA : US Food and Drug Administration

FDA: food and Drug Approval.

FISH: fluorescence in situ hybridization.

FSA: food standard agency.

GARS: Gilliam Autism Rating Scale

GDD: global developmental delay.

GI: gastrointestinal symptoms.

GI: gastrointestinaltract.

GLA: gamma linolenic acids.

HB: hemoglobin concentration.

HBOT: Hyperbaric oxygen therapy

HDL: high density lipoprotein.

HFA: high functioning autism.

HT-o: o-hydroxytryptamine

HUFAS: high unsaturated fatty acids.

IBD: inflammatory bowel disease.

IgA: immunoglobulin A

IgE: immunoglobulin E

IgG: immunoglobulin G

IgG: immunoglobulin G

IL- $\beta$ : interleukin  $\beta$ .

IQ: Intelligence Quotient

IVIG: intra-venous immunoglobulins

JA: joint attention.

LA: linoleinic acid.

LBW: low birth weight.

LCPUFAS: long chain polyunsaturated fatty acids.

LDL: low density lipoprotein.

LFA: low functioning autism.

LT<sup> $\xi$ </sup>: series <sup> $\xi$ </sup> leukotrienes.

LT°: series ° leukotrienes.

LTS: leukotrienes.

Max: maximum.

MCDD: Multiple complex developmental disorder.

M-CHAT: Modified checklist for Autism in toddlers.

MDD: major depressive disorder.

MDI: mental developmental index

MDI: Multi-Dimensionally Impaired disorder.

MECP<sup>7</sup>: methyl-CPG- binding protein-<sup>7</sup>.

MFA: medium functioning autism.

MI: myocardial infarction.

Min: minimum.

MMR: measles- mumps- rubella vaccine.

MNS: mirror neuron system.

MR: mental retardation.

MRI: magnetic resonant image.

MSAIDS: non steroidal anti-inflammatory drugs.

MSM: methylsulfonylmethane

MUFAS: monounsaturated fatty acids.

MZ: monozygotic twin.

NIMH: National Institute of mental Heath.

Nor: normal.

NVLD: non verbal learning disorder

OCD: Obsessive Compulsive disorder

OTs : occupational therapist

PANSS: positive and negative syndrome scale.

PCP: primary care pediatrician.

PCV: hematocrite value.

PDD: pervasive developmental disorder.

PDD-NOS: pervasive developmental disorders not otherwise specified.

PEBM: parent education and behavior management program

PECS: Picture Exchange Communication System

PG $\gamma$ : series  $\gamma$  prostaglandins.

PG<sup>*\mathcal{\mathcal</sup>* 

PGS: prostaglandins.

PLA<sup>*γ*</sup>: platelet activating.

PRT: Pivotal response therapy or treatment

PSC: Pediatric Symptom Checklist

PUFAS: polyunsaturated fatty acids.

RA: rheumatoid arthritis.

RBC : Rossago Behavioral Checklist

RBC: red blood cell count.

RCT: randomized controlled trial

R-F RLRS: Ritvo-Freeman Real Life Rating Scale R-F RLRS

RS: Rett syndrome.

S-B IV: Stanford-Binet Intelligence Test Fourth Edition

SD: standard deviation.

SI: Sensory integration

SIB : self-injurious behavior

SLP ; speech-language pathologist.

SPD: schizotypal personality disorder.

SPD: semantic- pragmatic disorder.

SPS: semantic- pragmatic syndrome.

SSRI : selective serotonin reuptake inhibitors

TCVs: thiomersal containing vaccines.

TD: tardive dyskinesia

TEACCH: Treatment and education of autistic and related

communication handicapped children

TG: triglycerides.

TLC: Test of Language Competence

TLC: total leucocytic count.

TMF- $\alpha$ : tumor necrosis factor.

TOLD-7: Test of Language Development--7 Intermediate

TOLD-<sup>7</sup>: Test of Language Development--<sup>7</sup> Primary

TX: thromboxane.

VLDL: very low density lipoprotein.

VLN-<sup>°</sup>FA: very long chain n-<sup>°</sup> fatty acids.

WAIS-R : Weschler Adult Intelligence Scale

WISC-III : Weschler Intelligence Scale for Children-Third Edition

WISC-R : Weschler Intelligence Scale for Children-Revised

WPPSI : Weschler Preschool and Primary Scale of Intelligence

ZU: zinc.

### Introduction

The pervasive developmental disorders (PDD) are a group of neuropsychiatric disorders that include autistic disorder, Asperger's disorder, childhood disintegrative disorder, Rett's disorder, and PDD not otherwise specified. (American Psychiatric Association, 1994) These disorders are characterized by atypical development in social, communicative, and behavior areas. Onset typically occurs within the first years of life.

Most recent reviews tend to estimate a prevalence of 1-7 per 1... for autism and close to 7 per 1... for ASD (Newschaffer, 7...) Although commonly associated with mental retardation, the developmental and behavioral features of PDD are distinct and do not simply reflect developmental level. (Volkmar et al, 7...)

PDD are characterized by severe and pervasive deficits in several areas of development. These include reciprocal social interaction skills; communication skills; or the presence of stereotyped behavior, interests, and activities. Children with PDD may present with difficult behaviors including hyperactivity, inattention, impulsivity, stereotypies, screaming, children with autism frequently have serious behavioral disturbances, such as self-injurious behavior, aggression, and tantrums in response to routine environmental demands. ( American Psychiatric Association, 1991)

Risperidone is an antagonist of both dopamine  $(D^{\gamma})$  and serotonin (°HT<sup>{</sup>A and others) receptors (**Janssen**, <sup> $\gamma$ </sup> · <sup> $\gamma$ </sup>). A number of open-label trials were undertaken to investigate the use of risperidone in children

۱