A Study to Evaluate the Efficacy of Eicosapentanoic Acid on Patients with Major Depression

Thesis

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List of Abbreviations

Abb.	Full term
5-HIAA	*5-Hydroxyindoleacetic Acid*
AA	*Arachidonic Acid*
ACTH	*Adrenocorticotropic Hormone*
APA	*American Psychiatric Association*
aPTT	*Activated partial Thromboplastin time.*
BAI	*Beck Anexity Inventory*
BDI	*Beck Depression Inventory*
CBT	*Cognitive Behavioral Therapy*
CCH	*Center for Community Health*
CES-D	*Center for Epidemiological Studies Depression Scale*
CGI	*Clinical Global Impression Scale*
CHD	*Coronary Heart Disease*
CIDI	*Composite International Diagnostic Interview*
CNS	*Central Nervous System*
CRH	*Corticotropin-Releasing Hormone*
CRP	*C-reactive protein*
CSF	*Cerebrospinal Fluid*
CVD	*Cardio Vascular Diseases*
CYP 2D6	*Cytochrome P 2D6 Enzyme*
CYP 3A4	*Cytochrome P 3A4 Enzyme*
D2	*Dopaminergic Receptors*
DALYs	*Disability Adjusted Life Years*
DBS	*Deep Brain Stimulation*
DEX	*Dexamethasone*
DEX-CRH	*dexamethasone/corticotrophin-releasing hormone*
DHA	*Docosahexaenoic acid*

List of Abbreviations cont...

Abb.	Full term
DSM-5	*Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition*
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition*
DST	*Dexamethasone Suppression Test*
ECG	*Electro Cardio Gram*
ECT	*Electro Convulsive Therapy*
ELISA	*Enzyme Linked Immunosurbant Assay*
EPA	*Eicosapentanoic acid*
EPDS	*Edinburgh Postnatal Depression Scale*
FDA	*Food and Drug Administration*
GABA	*γ-Amino butyric acid*
GBD	*Global Burden of Disease*
GIT	*Gastro Intestinal Tract*
GR	*Glucocorticoid receptor*
GRAS	*Generally Recognized As Safe*
HAM-D	*Hamilton Rating Scale for Depression*
HDRS-SF	*Hamilton Depression Rating Scale- Short Form*
HPA	*Hypothalamic–Pituitary Adrenal*
HS-CRP	*High-Sensitivity C-reactive protein*
IDO	*Indoleamine 2,3 Dioxygenase*
IFN-a	*Interferon-alpha*
IL-1	*Interleukin-1*
IL-6	*Interleukin-6*
INR	*International Normalized Ratio*
IPT	*Interpersonal Psychotherapy*
IPTH	*Intact Parathyroid Hormone*
IRF	*Interferon Regulatory Factor*
KYN	*kynurenine*

List of Abbreviations cont...

Abb.	Full term
LPS	*Lipo poly saccharides*
MADRS	*Montgomery-Åsberg Depression Rating Scale*
MAO	*Monoamine Oxidase*
MAOIs	*Monoamine Oxidase Inhibitors*
MAPK	*Mitogen-Activated Protein kinase*
MCP-1	*Macrophage Chemoattractant Protein-1*
MDD	*Major Depressive Disorder*
MDE	*Major Depressive Episode*
MDMA	*Methyl Endoxy Methamphetamine*
n-3	*Omega-3*
n-6	*Omega-6*
NF kB	*Nuclear Factor Kappa-light-chain-enhancer of activated B cells*
NMDA	*N-methyl-D-aspartate*
PGE2	*prostaglandin E2*
PHQ	*Patient Health Questionnaire*
PLA_2	*Phospholipase A_2*
PPARα	*Peroxisome Proliferator-Activated Receptor α*
PT	*Prothrombin time*
PUFA	*Polyunsaturated Fatty Acids*
SAMe	*S-Adenosyl Methionine*
SICAM-1	*Soluble Intracellular Adhesion Molecule- 1*
SNRIs	*Serotonin Norepinephrine Reuptake Inhibitors*
SNS	*Sympathetic Nervous System*
SPSS	*Statistical Package for Social Sciences*
SSRIs	*Selective Serotonin Reuptake Inhibitors*
*STAR*D*	*Sequenced Treatment Alternatives to Relieve Depression*

List of Abbreviations cont...

Abb.	Full term
STAT1a	*Signal Transducer and Activator of Transcription 1a*
t.i.d	*Ter In Die*
T3	*Triiodothyronine*
T4	*Thyroxine*
TMS	*Transcranial magnetic stimulation*
TNF-a	*Tumor Necrosis Factor-alpha*
TRAs	*Tricyclic antidepressants*
TRP	*Tryptophan*
WBC	*White Blood Cell*
WHO	*World Health Organization*
WMH	*World Mental Health*
YLDs	*Years of Life Lived with Disability*
QID	*Quick Inventory* of *Depressive Symptoms Clinician Rated*

Abstract

Background: Major depressive disorder (MDD) is a common brain disorder that affects approximately 10% of the world population and leads to significant disability. The current study aimed to evaluate the impact of Omega3 polyunsaturated fatty acids administration on the clinical outcome and inflammatory markers of patients with depression.

Patients and Methods: A prospective, randomized controlled study conducted at the outpatient clinics of Alzahraa University Hospital, Cairo, Egypt on patients diagnosed with depression according to a strict inclusion and exclusion criteria. Forty two patients were randomly assigned to either; Group1; (intervention n=21); received the prescribed antidepressant + omega3 (2100mg) which comprised of Eicosapentanoic acid 1350 mg, Decosahexanoic acid 600 mg and 150 mg other omega 3 fatty acids for 8 weeks, or Group 2; (control, n=21); received the prescribed antidepressant only for 8 weeks. Baseline evaluation and 8-week assessment included; patient demographic-data collection, history taking and clinical assessment of Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5) criteria and Hamilton Rating Scale for Depression (HAM-D) score. Laboratory assessment included; Complete Blood Count (CBC), Prothrombin Time (PT), Activated Partial Thromboplastin time (aPTT) and Tumor Necrosis Factor-alpha (TNF-α) levels (by ELISA technique). Patients were followed up regularly every week for 8 weeks for the occurrence of side effects due to antidepressants/ Omega 3 and compliance with medications.

Results: The 2 groups were comparable at baseline. The test group showed a significant improvement in the HAMD score & a reduction in TNF-a levels from baseline values and versus the control. There was no significant difference in the reported side effects between the 2 groups.

Conclusion: Omega -3 PUFAs administration at a dose of 2100 mg (EPA1350 mg/, DHA 600 mg/ 150 mg other omega 3 FA) for 8 weeks, improved depression symptoms and reduced inflammatory markers & was well tolerated.

Keywords: Omega-3 PUFAs, depression, TNF-a, EPA/DHA.

Introduction

Major depressive disorder (MDD) is a common brain disorder that affects approximately 10% of the world population ***(Song et al., 2016).***

Major depression is a commonly occurring, serious, recurrent disorder linked to diminished role functioning and quality of life, medical morbidity, and mortality. The World Health Organization (WHO) has ranked depression as the fourth leading cause of disability worldwide and projects that, by 2020, it will be the second leading cause ***(Kessler and Bromet, 2013).***

The lifetime prevalence of depression in urban and rural Egyptian populations found to be 11.4 and 19.7% ***(Beshai et al., 2016).***

New-generation antidepressants appear more effective than older drugs in treatment of major depression, with response rates of up to 50%, but they do not effectively treat all depressed patients. In addition, many drugs have side effects that can affect compliance and morbidity. So patients are increasingly using complementary and alternative medicine (CAM) therapies to treat depression ***(Qureshi and Al-Bedah, 2013)***. One such possibility is the use of n-3 omega polyunsaturated fatty acids (PUFAs) for the treatment of depression. A link between omega-3 fatty acids and mood

disorders has been suggested by some studies showing a lower incidence of depression among populations with a diet rich in omega-3 fatty acids ***(Gertsik et al., 2012).***

Omega-3 PUFA have been proposed, for treatment of major depressive disorder. The positive effects of omega-3 PUFA on depression may depend on their physiological abundant content in the human nervous system and their involvement in neurogenesis and neuroplasticity ***(Grosso et al., 2014).*** Moreover, their anti-inflammatory capacity may counteract inflammatory processes occurring in depression ***(Hennebelle et al., 2012).*** Also lower concentrations of omega 3 PUFA in plasma or red blood cells may contribute to depression. Administration of omega 3 PUFAs significantly improved depressive symptoms in patients with major depression ***(Lesperance et al., 2011).***

Several studies used omega-3 polyunsaturated fatty acids (PUFA) eicosapentaeoic acid (EPA) and docosahexaenoic acid (DHA) in similar doses with varying results. It has been previously documented that EPA at ratios > 60% can positively affect depression outcome. EPA and DHA are structurally similar and might be expected to compete in approximately a 1:1 ratio for binding sites. Thus the amount of EPA unopposed by DHA may be critical for effective PUFA supplementation in treatment of depressive episodes ***(Sublette et al., 2011).***

Hence the aim of the current study was to evaluate the impact of Omega-3 PUFAs administration (using an EPA in a dose more than twice the concentration of DHA), on the clinical outcome of patients with depression.

Part I:

Major Depression

1-Introduction

Major depressive disorder is also recognized as major depression, clinical depression, or unipolar depression. It is a medical disease that affects how you feel, think and perform causing persistent feelings of unhappiness and loss of interest in previously enjoyed activities. Major depressive disorder (MDD) is a common brain disorder that affects approximately 10% of the world population. According to the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5, 2013),MDD is characterized by the loss of interest in pleasure, low self-esteem, disturbed sleep or appetite, fatigue, and diminished ability to think or concentrate. These problems often become chronic and recurrent, and at the worst, can lead to suicide ***(Song et al., 2016).***

2- Epidemiology

Major depression is a severe, recurrent disorder linked to reduced role functioning and quality of life, medical morbidity, and mortality**.** The World Health Organization positions depression as the fourth leading cause of disability worldwide, and projects that by 2020, it will be the second leading cause of death ***(Kessler and Bromet, 2013)***. Moreover major depression is expected to be ranked first in disease burden in high-income countries by 2030 ***(Cuijpers et al., 2011).***