American Journal of Nursing Research, 2016, Vol. 4, No. 3, 69-73
Available online at http://pubs.sciepub.com/ajnr/4/3/3

DOI:10.12691/ajnr-4-3-3

Omega-3 Fatty Acids as Complementary and Alternative Medicine for Depression: Literature Review

Anas Husam Khalifeh*

Nursing Department, Prince Hamzah Hospital, Ministry of Health, Amman, Jordan
*Corresponding author: anaskhalifeh@yahoo.com

Abstract **Background:** Depression is a common mental and psychological disorder, rise globally. Depressed patients may resort to other sources to decrease the symptoms without side effects like complementary and alternative medicine (CAM), The most commonly used CAM treatments in the United States for people who have depression is Omega-3 Long-Chain Polyunsaturated Fatty Acids (LCPUFA). The purpose of this paper to highlight and explore more information about the effectiveness of omega 3 folic acid on patients who diagnosed with depression. **Methods:** Literature review of Randomized Control Trails (RCTs) studies, articles have been recovered for review of computer searches, from 2006 to 2016, databases that were used: PubMed, Medline, Wiley, PsychInfo, EBSCO host, Ovid database, Cinahl, and Google Scholar. Articles were selected based on a set of eligibility criteria. **Results:** The literature review content eight RCTs studies according to eligibility criteria, there are studies support the evidence of the effectiveness of omega-3 and dose of omega-3 with depression disorder as a monotherapy and combining with an antidepressant. However, there are studies that shown the inverse result. **Conclusions**: Although there are studies showed Influence effectively, the using and role of omega-3 for depression still under debate.

Keywords: *depression, depressive symptoms, omega-3, omega-3 long-chain polyunsaturated fatty acids, complementary and alternative medicine*

Cite This Article: Anas Husam Khalifeh, "Omega-3 Fatty Acids as Complementary and Alternative Medicine for Depression: Literature Review." *American Journal of Nursing Research*, vol. 4, no. 3 (2016): 69-73. doi: 10.12691/ajnr-4-3-3.

1. Introduction

Depression defined by the presence of persistent depressed mood (low mood), loss of interest or pleasure, feelings of grief and guilt or worthlessness, decreased energy, disturbed sleep or appetite, and poor concentration, and hopelessness [2,40]. According to reference [1], the criteria for diagnosed the depression represents a change in functioning (mood, pleasure, social, occupational, and Psychomotor) through 2 weeks [2]. It is a common mental and psychological disorder, rise globally and leading cause of disability which contributes to the global burden of disease, by 2020 depression will reach the second place in cause of disability [41], reference [33] stated in the United States depression is most common psychiatric illness, the prevalence as high as 18.9% in the primary care setting.

Moreover, National Institute of Mental Health (NIMH) estimated 6.9 % of all the U.S. adults that equal 16 million adults aged 18 or older had at least one episode of major depressive [25]. Four to eleven percent the prevalence of depressive illness in worldwide [32]. Furthermore, fifty percent of individuals who primary diagnosed with depression have committed suicide, according to WHO depression can lead to suicide [40]. Therefore; to decrease probability to incidence disability or suicide, so can treatable by non-pharmacological and pharmacological therapy to ensure recovery [1]. Although, pharmacotherapy for a depressed person considered the basic treatment [10].

However, side effects and high costs of pharmacotherapy that can be the main reasons for noncompliance [26], thirty percent of patients complain of problems with little or no response to the medication, and there are no significant clinical improvements with patients who currently treated with antidepressant drugs [20], so there is many depressed people did not seek formal care (pharmacotherapy) [14]. Complementary and Alternative Medicine (CAM) is other sources for depressed person use to decrease the symptoms without side effects, psychiatric patients and those diagnosed with anxiety and depression especially used CAM [27]. National Health Service (NHS) stated there are many definitions and disagree with the universal definition of CAM [18], so there is a different definition of CAM may cause a lack of clear definition [7].

However, the CAM uses as traditional medicine in some countries which differ in the term [32]. CAM are interventions and products consist of nutrient products (i.e. dietary and nutritional supplements such as vitamins and minerals), physical therapies (e.g. exercise, acupuncture, naturopathy), and herbal (i.e. plants and plant extracts) [34], considered an effective as conventional pharmacotherapy and have fewer side effects, more natural, economical, and available without need of prescription [27].

In the United States up to 40% of adults annually using at least one treatment of CAM and spent over of $33 billion dollars each year [5]. Forty-six percent of the populations in the UK use one or more CAM therapies in their lifetime [6]. Psychiatric patients already use CAM therapies which up to 63% of these patients who have psychiatric disorders [13], reference [39] reported the prevalence of use CAM in patients who have psychiatric disorders especially depression and anxiety which is 20 to 50% in depression and 20 to 40% in anxiety.

The most commonly used CAM treatments in the United States for people who have depression is omega-3 fatty acids [5]. Omega-3 polyunsaturated fatty acid (PUFA) as therapeutic indications such as treatment for certain forms of mental illness, including depressive disorders [12]. Omega-3 fatty acids are long-chain PUFA synthesized by dietary shorter-chained omega- 3 fatty acid alpha-linolenic acid (ALA) which form eicosapentaenoic acid (EPA) that composed of 20 carbon atoms and has five double bonds both of them starting from the methyl (omega) end of the chain, whereas docosahexaenoic acid (DHA) is composed of 22 carbon atoms and has six double bonds (Figure 1) [12,26].

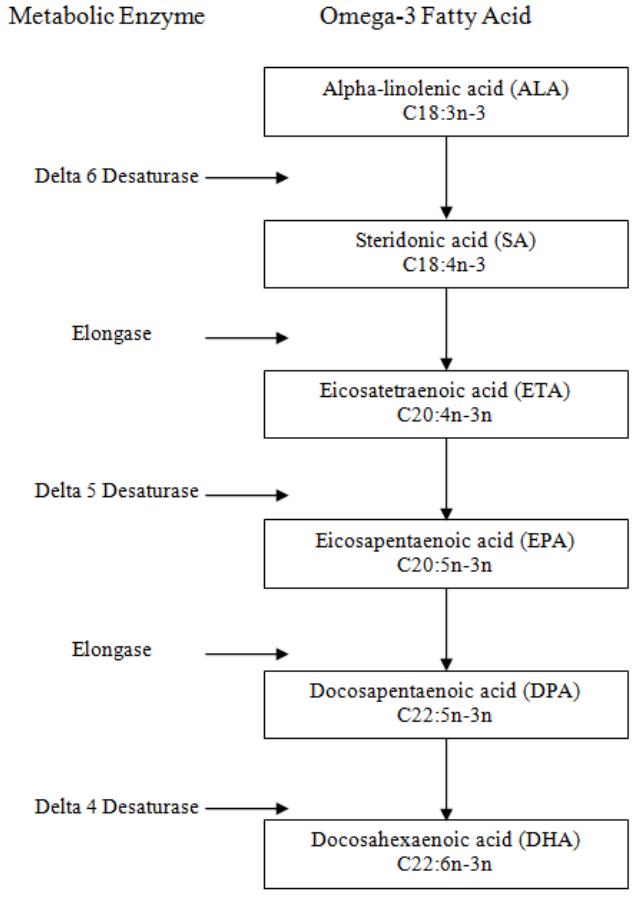

Figure 1. Biological Synthesis and Metabolic Pathway of Omega-3 Fatty Acid, Source: [12]

Glycerophospholipids in the brain contain a high rate of PUFA which is important for normal metabolism and may have therapeutic effects on depression, this role of omega-3 fatty acids with depression hypothesized depend on the physiological mechanisms which have probable interaction (metabolism, release, uptake, and receptor function) with both serotoninergic and dopaminergic transmission [12,35].

Moreover; EPA and DHA provides and play a crucial role in (a) membrane fluidity cells [8] (b) signal transduction [18], (c) regulation of membrane-bound enzymes (Na/K-dependent ATP'ase) [7], and (d) protein kinase C [38]. On the other hand; reference [16] stated that theoretically connection of fatty acids with the receptor and neurotransmitter showed when present changes in PUFA caused changes in number and function of serotonin (5-HT) and dopamine receptor (DR-2). Furthermore; cerebrospinal fluid in healthy adults has higher concentrations of plasma DHA predict an increase in serotonergic neurotransmission [14].

The sources of omega-3 PUFA that divide from oily fish as well as certain nuts, seeds, and some green vegetables [37]. Omega-3 Long-Chain Polyunsaturated Fatty Acids (LCPUFA), EPA, and DHA have been proven can be effective in cardiovascular disease (CVD) prevention due to their anti-inflammatory and cardioprotective effects [17], rheumatoid arthritis, infant development, important roles in the functioning of the brain, and the eye [23], and involved in multiple biological systems, including the nervous system [31]. Moreover, reference [3] reported omega 3 LCPUFA is beneficial in reducing depressive symptoms.

Therefore, the purpose of this paper to highlight and explore more information about the effectiveness of omega 3 folic acid on depressive symptoms with patients who diagnosed with depression.

2. Methods

2.1. Search Strategy

Articles have been recovered for review of computer searches, from 2006 to 2016 with the following combination of keywords: depression, depressive symptoms, omega-3, omega-3 long-chain polyunsaturated fatty acids, complementary and alternative medicine. Relevant search keywords identified within the databases that were used: PubMed, Medline, Wiley, PsychInfo, EBSCO host, Ovid database, Cinahl, and Google Scholar. Articles were selected based on a set of eligibility criteria.

2.2. Eligibility Criteria

Inclusion criteria included: all interventions of studies conducted on humans; RCTs studies; placebo and intervention group; use of omega-3 LCPUFA, DHA, and EPA supplement; participants diagnosed depression by DSM-IV or V. Exclusion criteria included: participants have medical illness (endocrine, neurologic, cardiovascular, hepatic, renal, respiratory, gastrointestinal, genitalia, or hematologic disease); active suicidal ideation or homicidal risk; history of seizure disorder; use of anticoagulants; diagnosed with psychiatric disorders (eating disorders, anxiety disorders, bipolar disorders, schizophrenia, delusional disorder, organic mental disorders, cognitive disorders, or substance use disorders); use maintenance antidepressant medication (duration of a minimum of 4 weeks previous study); history of electroconvulsive therapy (ECT) within 1 year preceding study entry; current or history drug or alcohol abuse or dependence; history of allergy to omega-3 fatty acids, finfish, or shellfish; current use of omega-3 supplements; pregnancy, use contraception or breastfeeding.

The eight RCTs analyzed and excluded 35 articles, 393 participants; the studies were undertaken in Italy, Iran, United States, Australia, and Canada. The average age of participants ranged from 18 to 95 years.

3. Literature Review

3.1. Findings

The benefit of omega-3 LCPUFA in individuals with diagnosed depressive disorder provided some support but no evidence of any benefit in individuals without a diagnosis of depressive disorder [4]. Studies RCTs, double-blind, have interventional and control groups. Studies evaluated depression level according to scales mentions in the review. The Table 1 in an appendix display studies in the review.

Thirty-five people participated and completed the study for 12 weeks, researchers distributed three double-blind dosing groups, group (A) received oral DHA 1 g per day; group (B) received 1 g per day for the first week and 2 g per day for the end of the study; and group (C) received 1 g per day for the first week, 2 g per day for the second week, and 4 g per day for the end of the study. group (A) showed high remission rate more than group (B) and (C), DHA effective in lower doses for Major Depressive Disorder (MDD) MDD as a monotherapy this result came out by 17-item Hamilton-Depression Scale (HAM-D-17) score decreased after 12 weeks, in group (A) had the largest decrease than group (B) and (C). Eight participants showed side effects: GI upset, headaches, anxiety, anorexia, dizziness, rash, dry mouth, warmth on hands, decreased libido [21].

Table 1

Author	Year	Inclusion criteria for depression	Age	Dose of n3 PUFA/day	Placebo	Intervention	Number of subjects (treatment/ placebo)	Dropouts	Duration (weeks)	Outcome measure	Setting
Grenyer et al. [11]	2007	DSM-IV and HAM-D-21 score >16	18–75 years	2.2 g DHA and 0.6 g EPA	Olive oil	DHA and EPA	83 (40,43)	23	16	HAM D-21 and BDI	Australia
Mischoulon et al. [21]	2008	DSM-IV, score >=18 of HAM-D-17, and score >=3 of CGI-S	18–80 years	1g,2g, and 4g DHA	Corn and soy oil	DHA	35 (14,11,10)	21	12	HAM-D-17	United States
Jazayeri et al. [15]	2008	DSM-IV criteria and score >=15 of HAM-D-17	20-59 years	1 g E-EPA	Rapeseed oil	E-EPA, E-EPA + fluoxetine, and fluoxetine	60 (20,20,20)	12	8	HAM-D-17	Iran
Mischoulon et al. [22]	2009	DSM-IV, score >=18 of HAM-D-17, and score >=3 of CGI-S	18-80 years	1g/day of EPA	Paraffin oil	EPA	35 (16,19)	3	8	HAM-D-17	United States
Rondanelli et al. [29]	2010	DSM-IV-TR, GDS score >10, and MMSE score > 24	65-95 years	1.67 g EPA and 0.83g DHA	Paraffin oil	EPA and DHA	46 (22/24)	0	8	GDS and SF-36	Italy
Rondanelli et al. [30]	2011	MMSE score > 24 and DSM-IV-TR criteria	66-95 years	1.67 g of EPA and 0.83 g of DHA	Paraffin oil	DHA and EPA	46 (22,24)	0	8	GDS and SF-36	Italy
Rizzo et al. [28]	2012	DSM-IV, GDS score >10, and MMSE score > 24	65-95 years	2.5 g of omega-3 PUFA with EPA/DHA 2:1	Paraffin oil	EPA and DHA	46 (22,24)	0	8	GDS	Italy.
Gertsik et al. [10]	2012	DSM-IV and HAM-D-21 score > 17	18-65 years	0.9 g EPA and 0.2 g DHA	Olive oil	EPA and DHA	42 (21,21)	2	8	HAM-D-21, BDI, MADRS, and CGI-S	United States

*DSM: Diagnostic and Statistical Manual of Mental Disorders; HAM-D: Hamilton Depression Scale; EPA: Eicosapentaenoic Acid; DHA: Docosahexaenoic Acid; MMSE: Mini-Mental State Examination; GDS: Geriatric Depression Scale; SF-36: Short-Form Health Survey; CGI-S: Clinical Global Impressions Scale; BDI: Beck Depression Inventory; MADRS: Montgomery-Asberg Depression Scale; PUFA: Polyunsaturated Fatty Acid.

Reference [22] conducted that potentially effective at doses of 1 g per day of EPA as monotherapy for MDD and well tolerated, but no significance different between EPA and placebo which by examined the efficacy and tolerability of ethyl-eicosapentaenoate (E-EPA) monotherapy for MDD for 8 weeks with 35 MDD adults (16 on EPA, 19 on placebo) which randomized received EPA or placebo. A score of HAM-D-17 decreased for the EPA group compared with placebo group but differences of response and change rate were not significance with the reason the small sample size. Though, this study reported mild side effects to seven subjects.

Moreover, there are three studies reported the same results on the same sample in elderly patients especially in depressed females. Forty-six depressed elderly females, aged 66-95 years recruited randomized placebo-controlled trial. Double-blind, 22 included in the omega-3 group which contained omega-3 LCPUFA and 24 included in the placebo group which contained paraffin oil for 8 weeks. The result was significantly decreased in the

Geriatric Depression Scale (GDS) and significantly increased in the Short-Form Health Survey (SF-36) with the omega-3 group, and the occurrence of depressive symptoms reduces with omega-3 LCPUFA [28,29,30]. About side effects, reference [29] reported there are no serious side effects but observed 11 cases complained some of these side effects in both groups; eructation, constipation, and especially bloating in the interventional group and mild headache in the placebo group. However, reference [30] did not observe any side effects in the interventional group.

There are other studies compared between omega-3 and some type of antidepressant medications. Reference [15] conducted by comparing therapeutic effects of EPA, fluoxetine and a combination of them in 60 outpatients with a diagnosis of MDD divided into three groups, E-EPA plus fluoxetine placebo, fluoxetine plus E-EPA placebo, and E-EPA plus fluoxetine for 8 weeks. The result was therapeutic effects in MDD by use E-EPA and fluoxetine had equal and use a combination of E-EPA and fluoxetine better effect than each either alone.

Furthermore, reference [10] explored efficacy of combination therapy with citalopram plus omega-3 fatty acids versus citalopram plus placebo (olive oil) in individuals with MDD as initial treatment the result was the signs and symptoms of MDD in combination therapy (citalopram with omega-3 fatty acids) decreased more than monotherapy during the 8 weeks of active treatment, but the speed of the initial antidepressant response to combination therapy did not enhance. The omega-3 and placebo group reported most of the side effects were gastrointestinal such as nausea, diarrhea, indigestion, and constipation; and other side effects were a headache, sedation, or sexual dysfunction.

On another hand, reference [11] administered long chain omega-3 PUFA or an olive oil placebo to 83 depressed outpatients as an adjunct to conventional treatment for 16 weeks. Despite patient compliance, there were no differences in HDRS or BDI scores between groups, nor were there any differences in personal, occupational or interpersonal functioning.

4. Summary and Conclusion

Depression is global mental disorder that affects to interest, pleasure, energy, sleep or appetite, and concentration, effect on activities. Psychotherapy and pharmacological therapy use to decrease and prevent depression disorder, so there are many forms of CAM to do this goal included omega-3 folic acid the most common use of depression disorder. There are many theoretical ways of connection between omega-3 folic acid and brain, the literature review content eight RCTs studies according to eligibility criteria, there are studies support the evidence of the effectiveness of omega-3 and dose of omega-3 with depression disorder as a monotherapy and combining with an antidepressant. However, there are studies that shown the inverse result.

Studies showed a low dose of omega-3 more effect on depression symptoms than a high dose. Omega-3 showed effective on elderly depressed female patients. So, the using and role of omega-3 PUFA for depression still under debate and which is more effective EPA or DHA, but EPA stay in blood more than DHA and synthesis in body without any external factors like DHA. Although, the studies included some limitations that effect on the study, small sample, inability to control all the many potential sources of heterogeneity, and short time of the study. On another hand, Omega-3 fatty acid not has negative side effects and may occur side effects consist of minor gastrointestinal symptoms, such as belching, indigestion, or diarrhea.

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