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Lauren Cabana

Philadelphia College of Osteopathic Medicine, LaurenCa@pcom.edu

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**Does Fish Oil Supplementation (omega-3 PUFA) Cause Mood Improvement
in Adults with Depression**

Lauren Cabana, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
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ABSTRACT

Objective: The objective of this systematic review is to determine whether or not “Does fish oil supplementation (omega-3 PUFA) cause mood improvement in adults with depression?”

Study Design: Review of all English language primary double blind randomized controlled trial studies from 1997-2010

Data Sources: Randomized, controlled, double-blind clinical trials comparing fish oil supplementation to placebo were found using OVID, PubMed, Medline and Cochrane databases

Outcomes Measured: Each of the three trials compared mood improvement in depressed patients using depression scales, such as the Hamilton Rating Scale for Depression and the Beck Depression Inventory, and subjective ratings, such as aches/pains, energy, fatigue, sleep and appetite. Study participants were evaluated at baseline and subsequently evaluated at 2-3 week increments for 8, 12 or 16 weeks.

Results: Three double-blind randomized controlled trials were included in this review. The study done by Kuan-Pin used 440mg EPA and 220mg DHA and indicated a significant reduction in HRSD score for the omega-3 PUFA group in comparison to the placebo group beginning at the fourth week of the trial. The remaining two studies, by Grenyer and Silvers, used 0.6g EPA and 2.2 and 2.4g DHA, respectively, and did not find any significant difference in mood improvement between participants taking omega-3 PUFA and participants in the placebo group. Participants in each of the three studies reported minor adverse effects however none encountered any major adverse effects caused by the therapy.

Conclusions: The results of the Kuan-Pin trial using 440mg EPA and 220mg DHA showed that omega-3 PUFA may be effective in improving mood in adults with depression based on the Hamilton Rating Scale for Depression. The Grenyer and Silvers study using 0.6gEPA and 2.2 and 2.4g DHA, respectively, did not show a significant improvement in mood for adult depression patients using the therapy.

Key Words: Fish oil, Omega-3 fatty acids, Depression

INTRODUCTION

Depression is defined as a depressed mood that is present daily and persists for at least a period of two weeks. Frequent episode characterizations of depression include anhedonia, apathy, sadness or irritability. It is one of the most common mental health problems experienced by individuals in the United States marked by a lifetime prevalence of 16.2%. Onset occurs anywhere from childhood to late life; however, the mean age of onset is the late 20s, with the incidence rate for adult women twice as great in comparison to men. The effect of depression on an individual not only causes emotional instability, but also physical signs and symptoms.

Patients affected by depression often do not seek medical care for the illness, which accounts for an extensive number of undiagnosed cases. While the exact number of annual healthcare visits for depression is unknown, data does show that depressed individuals most often present to primary care physicians and emergency rooms. The estimated cost of depression for the US economy is \$43 billion annually. These expenses are related to care, absenteeism, reduced productivity on the job, premature death and suicide. The total amount of US healthcare expenses for the treatment of depression amounts to \$12 billion per year.

The exact etiology of depression remains unknown; yet, there are a number of factors that are theorized to increase a person's risk for the disease: genetics, neurotransmitter alterations, neuroendocrine dysregulations, negative life events, and stressful environments. A patient presenting with depression admits to depressed mood and anhedonia daily for at least two weeks, as well as five or more of the following clinical features: sleep (insomnia or hypersomnia), decreased interest, guilt and worthlessness, fatigue, impaired concentration, decreased or increased appetite, psychomotor retardation or agitation, suicide, or somatic complaints (headache, backache, GI complaints, dizziness, lethargy). The mainstays of treatment for

depression include psychotherapy and pharmacotherapy, with best results stemming from the combination of the two. OTC remedies such as St. John's Wort are also used as adjuvant therapies for depressed patients. Persistent cases of depressions despite the use of pharmacological and behavioral therapies may benefit from surgical interventions such as electroconvulsive therapy or vagus nerve stimulation. The forementioned depression treatment options require extended periods of time before effective and are often associated with negative side effects. In lieu of this, fish oil supplementation may provide significant improvement in mood for depressed adults over other products and therapies, giving healthcare providers the option of introducing omega-3 PUFA supplements into the course treatment of individuals affected by major depressive disorder.

OBJECTIVE

The objective of this systematic review is to determine whether or not "Does fish oil supplementation (omega-3 PUFA) cause mood improvement in adults with depression?"

METHODS

All three studies selected for this review met the following criteria. The population included adults age 18 and older with a clinical diagnosis of depression. The intervention used in the studies was fish oil (omega-3 PUFA) supplementation in the following three doses: 440mg EPA and 220mg DHA (Kuan-Pin et al), 0.6g EPA and 2.2g DHA (Grenyer et al) and 0.6g EPA and 2.4g DHA (Silvers et al). Only those articles that compared the treatment groups receiving omega-3 PUFA supplementation compared to a placebo group were considered. Outcomes were based on mood improvement in depressed patients using depression scales and subjective ratings, which qualifies as patient oriented evidence that matters (POEM). Three double-blind, randomized, placebo-controlled clinical trials were identified and included in this review.

The key words fish oil, omega-3 fatty acids, and depression were used in combination to search literature for English articles, of which all resulting articles were published in peer-reviewed journals. A detailed literature search and selection of studies for this review was completed by the author using OVID, Medline, PubMed and Cochrane databases. Inclusion studies were those that were randomized, controlled, prospective and based on patients outcomes (POEMS) dated after 1996. Studies excluded from this review were articles that included patients less than 18 years of age. Statistics utilized in the studies include *p*-values, NNH, chi-square, t-test, and Intention to Treat (ITT).

Table 1: Demographics and characteristics included for analysis of fish oil supplementation in the treatment of depression

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Grenyer, 2007 (1)	Double-blind RCT	83	18-70	Pts with a primary diagnosis of major depression based on DSM-IV criteria and HDRS score >16	Pts with a serious medical condition, objection to venipuncture, co-morbid substance abuse, psychotic, bipolar or eating disorder, or OCD	23	Eight 1g soft gelatin capsule of pacific tuna oil (provided 3g of omega-3 PUFA) per day VS. Eight 1g soft gel capsules of olive oil per day for 16 weeks
Silvers, 2005 (2)	Double-blind RCT	77	18-65	Healthy males and females between the ages of 18-65 with a current diagnosis of depression ad current medication use >2 months	Pts with a co-existing psychiatric disorder, post-menopausal or irregular menstruation cycle (females), blood clotting disorder, use of anticoagulants, unstable medical condition, seafood allergies, objections to taking fish oil or olive oil-based products, or objections to venipuncture	18	8g soft gel capsule of DHA enriched tuna fish oil per day VS. 8g soft gel capsule of olive oil per day for 12 weeks
Kuan-Pin, 2003 (3)	Double-blind RCT	32	18-60	Healthy pts from 18-60yo with a major depressive diagnosis based upon DSM-IV criteria and >18 on Hamilton Rating Scale for Depression	Pts with co-morbid Axis I or II psychiatric disorder, change in medications or psychotherapy 4 weeks prior to enrollment, incompetent or unable to understand study rules, >20% decreased in HRSD score during placebo-lead-in phase	10	Five gelatin capsules containing omega-3 fatty acids BID VS. five gelatin capsules containing olive oil ethyl esters BID for 8 weeks

OUTCOME MEASURED

Each of the three studies measured participants' outcome of mood improvement based on depression scales and subjective ratings. Depression scales included the 21-item Hamilton Depression Rating Scale (Kuan-Pin et al, Silvers et al and Grenyer et al) and the Beck Depression Inventory (Silvers et al and Grenyer et al). HDRS is a 21-question survey performed by a healthcare professional that assesses a patient's severity of depression. Assessment questions include the following topics: depressed mood, feelings of guilt, suicide, insomnia, work and activities, psychomotor retardation, agitation, psychological agitation, anxiety, somatic symptoms, genital symptoms, hypochondriasis, weight loss, insight, diurnal variation, depersonalization, paranoid symptoms and obsessive and compulsive symptoms. Scores between 7 and 17 indicate mild depression, scores between 18 and 24 indicate moderate depression, and scores over 24 indicate severe depression. BDI is a 21-item self-report survey that also assesses depression severity. Each answer is scored on a scale from 0-3. Score breakdown is as follows: 0-13: minimal depression; 14-19: mild depression; 20-28: moderate depression; and 29-63: severe depression. As the same with HDRS, higher total scores for BDI indicates more severe depressive symptoms. Subjective ratings took into account participants' degree of aches/pains, energy, fatigue, sleep, and appetite.

The Global Assessment of Functioning (GAF) was used by Grenyer as a secondary means of measuring patient outcomes. GAF is a numeric scale (0-100) that is used by therapists and physicians to subjectively assess adult function in social, occupational and psychological aspects of life.

RESULTS

The three randomized controlled trials presented in this review are double-blind, prospective clinical trials that provided continuous data to assess the outcome of mood improvement in adults with a clinical diagnosis of depression. Treatment results were based on changes in HRDS scores (Kuan-Pin and Silvers) or BDI scores (Silvers and Grenyer) as shown in Table 2. Analysis of harm for all three studies was done by converting the continuous data to dichotomous data and presented as NNH (number needed to harm) analysis (Table 3).

The Kuan-Pin study, which originally enrolled 32 participants, completed the eight-week trial with a total of 22 participants ranging from 18-60 years old. At baseline, the omega-3 PUFA group had a mean HRSD score of 22.5, while the mean score for the placebo group was 22.1. The experimental group received a total of 4,400mg EPA and 2,200mg DHA per day. Participants were assessed at weeks 0, 2, 4, 6 and 8. At week 8, participants in the omega-3 PUFA group had a mean HRSD score of 8.9, while participants in the placebo group had a mean score of 15.7. According to the study, the percent reduction in HRSD scores for the omega-3 PUFA group was significantly greater than that of the placebo group ($p = 0.001$).

Silvers et al randomly assigned 40 participants to receive fish oil and 37 participants to receive placebo. At completion of the 12-week study, the trial participant composition included 24 fish oil participants and 21 placebo participants, all of which fell into the age group of 18-65. Each participant of the fish oil group received a total of 0.6g EPA and 2.4g DHA per day. Assessment of mood took place at baseline, and then at weeks 2, 4, 8 and 12 using the self-administered HDRS and Beck Depression Inventory (BDI). Mean baseline HDRS scores for the fish oil group and placebo group were 12.4 and 11.5, respectively. The fish oil group and placebo group mean BDI scores at baseline were 23.3 and 21.9, respectively. At week 12, the

placebo group and fish oil group had a mean change in HDRS score of 0.6 ($p = 0.6$) and 0.3 ($p = 0.8$), respectively. Mean changes in BDI scores were 1.5 ($p = 1.5$) and 0.3 ($p = 1.5$) for the placebo group and fish oil group, respectively. According to this data, there is no evidence that fish oil improved mood for enrolled participants.

Grenyer et al randomized 83 participants aged 18-70 to fish oil or placebo at the start of the study, with 60 participants completing the 16-week trial (28 placebo and 32 fish oil). Each participant of the fish oil group received 2.2g DHA and 0.6g EPA per day. Mood assessments were completed at week 0, 3, 6, 9, 12 and 16 using the HDRS and BDI. According to Grenyer, there was no significant interaction effect between time and group according to both the HDRS and BDI with p-values equaling .844 and .424, respectively. Mean BDI scores for the placebo group and fish oil group at baseline were 28 and 25, respectively. Upon completion of the trial, mean BDI scores for placebo and fish oil participants were 17.5 and 12, respectively. The overall Global Assessment of Functioning (GAF) scores did improve for both groups over time; baseline GAF scores averaged at 51 and improved to an average of 68 at week 16. Despite this, the scores were not found to be significant ($p = .399$). In terms of subjective ratings, Grenyer noted no differences in aches/pains, energy, fatigue, sleep or appetite between groups over the course of the 16 weeks.

Table 2: Efficacy of fish oil on mood improvement for depressed adults

Study	Baseline HDRS Fish oil Group	Post-tx HDRS Fish oil Group	Baseline HDRS Placebo Group	Post-tx HDRS Placebo Group	Baseline BDI Fish oil Group	Post-tx BDI Fish oil Group	Baseline BDI Placebo Group	Post-tx BDI Placebo Group
Kuan-Pin	22.5	8.9	22.1	15.7	X	X	X	X
Silvers	11.5	11.8	12.4	13.0	21.9	22.2	23.3	24.8
Grenyer	23.5	10.7	Unknown	Unknown	25	12	28	17.5

All three studies presented data in the form of continuous data. In order to analyze the harm for each trial, the data was converted into dichotomous data and analyzed as NNH. Participants that experienced no adverse effects to mild adverse symptoms were considered to have insignificant changes, while participants with marked adverse effects were considered significant changes. The CER (control event rate) was determined by the number of patients that experienced adverse symptoms as part of the placebo group. The EER (experimental event rate) was based upon the percentage of patients in the fish oil group that experienced significant negative effects. Using this data, RRI (relative risk increase) and ARI (absolute risk increase) was calculated. NNH (number needed to harm) is the number of patients that need to be treated with fish oil before a detrimental event occurs.

Table 3: Analysis of harm based on participants treated with fish oil vs. placebo for depression

Study	# participants	CER	EER	RRI	ARI	NNH
Kuan-Pin	32	10%	17%	70%	7%	14
Silvers	77	37%	35%	5%	-2%	50
Grenyer	83	0%	78	0	78	1

The most common side effects noted by Silvers et al were gastrointestinal disturbance and/or reflux, which were experienced by both the experimental and control groups. The only adverse effect experienced by participants of the Grenyer trial was a change in stools. This was experienced equally among the fish oil and placebo groups. Kuan-Pin et al noted that among the fish oil participants, one experienced mild excitement and another had mild diarrhea. One participant in the placebo group experienced insomnia for a two-week period during the course of study. Among all three studies presented, none of the participants experienced any major adverse effects related to the therapies provided throughout the trial.

Compliance issues were not a major factor for any of the three studies. Grenyer et al lost 23% of participants originally enrolled in the study due to violation of the trial protocol. Reasons included time/commitment, moving out of area, hospitalizations and time constraints. Grenyer noted that analyses of completers versus drop outs found no significant differences in measures at any point in time. According to Silvers et al, 63% of participants in the fish oil group and 63% of participants in the placebo group admitted to non-compliance with doses. Reasons included unable to take capsules as requested, capsules too large to swallow, GI disturbances, capsules showed no improvements, or stopped capsules because improvements were experienced. In lieu of this, there was no evidence that non-compliance was related to the assigned therapy ($p = 0.976$). Kuan-Pin et al lost six participants during the eight-week course of the study (2 fish oil and 4 placebo). Reasons were due to lost in follow-up or non-compliance.

DISCUSSION

Omega-3 fatty acids are a family of unsaturated fatty acids with a common carbon-carbon double bond located at the n-3 position. Two of the most common types are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both of which are polyunsaturated fatty acids. Since the body is unable to synthesize omega-3 fatty acids on its own, individuals must obtain sources from food or supplementation. It is widely known that omega-3 fatty acids are an essential component for normal growth and development, but recent studies have since increased our knowledge surrounding the associated health benefits. Most notably, omega-3 fatty acids are used to treat patients with hypertriglyceridemia, coronary artery disease, and hypertension. The American Heart Association recommends that patients with coronary artery disease consume 1g of fish oil per day, preferably by eating fish. Lovanza, a new drug on the market indicated for patients with severe hypertriglyceridemia, is composed of a combination of ethyl esters of

omega-3 fatty acids, principally EPA and DHA. For individuals that do not meet criteria for prescription omega-3 fatty acids, supplements are widely available OTC at pharmacies throughout the US. Other conditions known to benefit from fish oil ingestion include cancer (particularly breast, colon and prostate cancer), Alzheimer's and Parkinson's disease. While negative symptoms associated with fish oil supplementation is rare, one of the major adverse effects is prolonged bleeding times; doses of omega-3 fatty acids that exceed 3 grams per day may increase a patient's risk of bleeding and could put a person at risk for hemorrhagic stroke. Omega-3 fatty acids also have been shown to increase levels of LDLs, which should be used cautiously in patients with a history of hyperlipidemia.

The three studies presented in this review were all faced with certain limitations. 27% of participants in the Grenyer study, 23% of participants in the Silvers study, and 31% of participants in the Kuan-Pin study withdrew from the trial throughout the course of study. The potential outcomes associated with those participants were not analyzed as part of each study, but could have significantly impacted results if experimental participant HRDS or BDI scores were statistically significant in comparison to placebo. Silvers et al measured patient outcomes based on self-administered ratings only. In comparison, Kuan-Pin et al and Grenyer et al used self-administered ratings as well as healthcare professional survey scores to measure the outcomes of mood improvement for enrolled participants. Allowing individuals to assess their own mood improvement leaves room for dishonesty, resulting in unreliable data. In all three studies, participants often correctly guessed to which group they were randomized based upon the fishy aftertaste of the fish oil capsules. Future studies would benefit from concealing the fish oil taste by alternate means in order to devise a completely blinded trial.

CONCLUSIONS

The three studies reviewed for this paper provided each of their respective experimental fish oil groups with a certain dosage of EPA and DHA, both of which belong to the family of omega-3 PUFA. Two of the three studies determined that daily fish oil intake had no impact on mood improvement in adult patients with a clinical diagnosis of depression. The remaining study noted that while fish oil participants did in fact see an improvement in mood over the course of the trial, there is need for further studies in order to truly determine the effectiveness of omega-3 PUFA supplementation. Taking all results into consideration, it is decided that adult depression patients cannot use fish oil supplements as a means to improve mood. Future studies may wish to experiment with other types of omega-3 PUFA, instead of relying solely on EPA and DHA.

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