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Does the use of docosahexaenoic acid (DHA) supplementation decrease the rate of cognitive decline, as measured by the ADAS-Cog scale, for patients with Alzheimer's Disease?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not "Does the use of docosahexaenoic acid (DHA) supplementation decrease the rate of cognitive decline, as measured by the ADAS-Cog scale, for patients with Alzheimer's Disease?"

Study Design: A systematic review of three randomized controlled trials (RCTs) published between 2010 and 2018.

Data Sources: All three RCTs were published in English into peer reviewed journals and discovered via PubMed. The studies were selected based on relevance and ability to answer the clinical question.

Outcome Measured: Cognitive function is the outcome measured using the Alzheimer Disease Assessment Scale- Cognition (ADAS-cog) score.

Results: The Shinto et al. study found that after 12 months of daily treatment, the mean change from baseline in ADAS-Cog scores was 4.4 in the DHA treatment group and 3.2 in the placebo group, with no statistically significant difference ($p=0.86$) between the two mean changes. Eriksdotter et al. found a statistically significant ($p=0.016$) association between increasing plasma levels of omega-3 fatty acids with decreasing rates of cognitive decline as measured by ADAS-Cog scores. The association was measured by an unstandardized coefficient as $B=-0.834$. Quinn et al. found that after 18 months of treatment, the mean change from baseline in ADAS-Cog scores was 7.98 in the DHA group and 8.27 in the placebo group. The treatment effect was found to not be statistically significant with $p=0.41$.

Conclusion: One study in this review found a statistically significant association in increased levels of DHA with decreased rates of cognitive decline. However, two studies did not find data of DHA having a statistically significant effect on changes in ADAS-Cog scores. Therefore, this review does not show that DHA supplementation can decrease the rate of cognitive decline as measured by the ADAS-Cog scale in patients with Alzheimer's Disease.

Key Words: Alzheimer's, omega-3

INTRODUCTION

Dementia is the general term for a cognitive decline that eventually alters an individual's ability to carry out their usual activities of daily living. Alzheimer's Disease is the most common form of dementia and is characterized by the presence of amyloid plaques and neurofibrillary tangles within the brain. Alzheimer's Disease is progressive and can include symptoms that impact an individual's episodic memory, behavior, physical mobility, and can cause sensory hallucinations.[1] As of 2020, an estimated 5.8 million people over the age of 65 are living with Alzheimer's Disease in the United States.[2] This prevalence is expected to double by 2050 due to the aging baby boomer population.[2]

As health conditions, Alzheimer's Disease and dementia place a large burden on society and patients themselves. In 2020, an estimated $305 billion was spent on patients with Alzheimer's Disease in the United States.[2] When comparing costs, patients with dementia have total healthcare expenses over three times that of patients in the same age group without dementia.[2] As for use of healthcare services, patients with dementia experience nearly double the amount of hospital admissions compared to patients without dementia.[2] In the United States, there are 1,548 emergency room visits per 1,000 Medicare beneficiaries with Alzheimer's or other dementias each year.[2]

Given the insidious and complex nature of Alzheimer's Disease, ongoing research efforts are still being conducted to improve diagnostic and treatment options for patients. It is well known that amyloid plaque formation and neurofibrillary tangles play key roles in the pathogenesis of Alzheimer's Disease, but it is not yet clear as to how the two processes are related to one another.[1] This unclear picture of pathophysiology makes definitive diagnostic techniques outside of postmortem autopsies difficult.[3] Currently, two methods that aid in

diagnosis are specialized PET scans with radiolabeled tracer agents and evaluation of cerebrospinal fluid for peptides consistent with Alzheimer's Disease.[3] In regards to treatment, disease modifying treatment modalities that are able to effectively decrease the rate of cognitive decline have yet to be discovered.[3] Current treatment methods include symptomatic and preventative measures.[3]

Pharmacologic treatment options for the symptoms of Alzheimer's Disease currently include acetyl-cholinesterase inhibitors (AChEIs) and glutamate receptor antagonists. AChEIs, such as donepezil, rivastigmine, and galantamine, are recommended for patients with any stage of Alzheimer's Disease.[3] Glutamate receptor antagonists, such as memantine, are for patients with moderate to severe Alzheimer's Disease.[3] Both classes of medication have been shown to have small to modest benefit in cognition for patients.[1]

DHA is an essential fatty acid used in building neuronal cell membranes and therefore, is an important factor in the functional development and maintenance of healthy brain tissue. Supplementation and proper intake of DHA has been shown by some studies to be beneficial in reducing neuroinflammation and having an effect in slowing the pathogenesis of Alzheimer's Disease.[4] DHA may be used as an add-on pharmacological supplement to decrease the rate of cognitive decline in patients with Alzheimer's Disease. This paper evaluates three randomized controlled trials that assess the efficacy of DHA supplementation in decreasing the rate of cognitive decline in patients with Alzheimer's Disease.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Does the use of docosahexaenoic acid (DHA) supplementation decrease the rate of cognitive decline, as measured by the ADAS-cog scale, for patients with Alzheimer's Disease?"

METHODS

Three randomized controlled trials were chosen by this author to use as data sources. Articles were chosen based on relevance to the clinical question, how data was measured, and if the article addressed patient-oriented outcomes. Each study was published in peer-reviewed journals in the English language between 2010-2021. Articles were discovered using PubMed as the data source with the key search words "Alzheimer's" and "omega-3." Inclusion criteria for selecting articles were publication between 2010-2021, in English language, and being a randomized control trial. Exclusion criteria for article selection included studies that used secondary analysis, were for Alzheimer's prevention, or were for dementia. Statistical analysis used in these articles included p-value, mean change from baseline, and B-coefficient.

As detailed in Table 1, the population of patients in the selected studies is adults with Alzheimer's Disease. The intervention of focus is use of daily DHA acid supplementation with comparison to use of daily placebo supplementation. The outcome measured for all patients is cognitive function.

OUTCOMES MEASURED

All three studies used the Alzheimer Disease Assessment Scale- Cognition (ADAS-cog) scale to measure cognitive function of study participants. The ADAS-cog scale ranges from 0-70, with higher scores meaning greater cognitive impairment. Within each study, a test administrator would assess study participants throughout the ADAS-cog examination and determine a score for that point in time. Each study would administer the ADAS-cog test at certain intervals throughout the study duration. Although the ADAS-cog score is a quantitative measure of data, it reflects the overall cognitive ability of patients and aids in determining if a patient's cognitive impairment is worsening.

Table 1. Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Shinto et al. 2018	Parallel group RCT	39	Adults ≥55 years old	≥55 years old, diagnosis of probable Alzheimer's Disease, MMSE score of 15-26, Clinical Dementia Rating Scale 0.5-1.0, not depressed, in good general health, caregiver or informant available	Non-Alzheimer's dementia, residence in long-term care facility, history of stroke, cancer, liver disease, arrhythmia, CNS or psychiatric disorder; current use of lipid lowering agent, corticosteroids, neuroleptics, antiparkinsonian agents, or narcotics; use of fish oil, cod liver oil or lipoic acid supplements	5	Daily dose of fish oil concentrate (675 mg DHA) for 12 months vs daily placebo for 12 months
Eriksdotter et al. 2015	Double blind RCT	204	Adults age 64-82 years old	Diagnosis of Alzheimer's disease, MMSE score of 15-30, living in their own homes, treated with stable dose of AChEIs for at least 3 months	Treatment with NSAIDs or anti-coagulation agents, use of omega-3 preparations, alcohol abuse, suffered from serious co-morbidity, did not have a caregiver	39	Daily dose of fish oil capsules (430mg DHA) for 12 months vs daily placebo for 6 months and fish oil capsule for 6 months
Quinn et al. 2010	RCT	402	Mean age of 76 years old	Diagnosis of probable Alzheimer's disease, MMSE score of 14-26, medically stable, consumes <200mg/d of DHA, not taking DHA or omega-3 supplements	Treatment with drugs with anticholinergic effects or sedatives, receiving any investigational treatment for Alzheimer's disease	107	Daily dose of algal DHA capsules (900mg-1.1g DHA) for 18 months vs placebo capsules for 18 months

RESULTS

Shinto et al. conducted a double blind, parallel group, randomized controlled trial with 39 participants who were all adults aged 55 years or older with probable Alzheimer's Disease. The inclusion and exclusion criteria for participants is summarized in Table 1. Over a 12-month period, the study compared daily use of a fish oil concentrate containing 675 mg of DHA to daily use of placebo supplementation.[5] This review will not discuss the third comparison intervention measured in this study. Randomization was achieved by using a computer-generated system and compliance was assessed via pill counting at the 6-month and 12-month points in treatment duration.[5] Blinding was assessed at the 12-month point and it was concluded that neither participants nor study workers were aware of treatment assignments.[5] Five participants were lost to follow up, with losses being equal across the included study groups.[5] Worst-case analysis was not performed on participants lost to follow up. The primary outcome analyzed was the change in ADAS-Cog scores from baseline.[5] After 12 months of daily treatment interventions, ADAS-Cog scores were reevaluated for each participant still present.[5] Table 2 displays the mean change from baseline for the two treatment groups at the end of the study duration. For those in the fish oil concentrate group, there was a mean change in ADAS-Cog scores of 4.4 points after 12 months.[5] In the placebo group, there was a mean change of 3.2 points in ADAS-Cog scores after 12 months.[5] After adjusting for education and age related factors, it was found that there was no statistically significant difference (p=0.86) between the mean changes in ADAS-Cog scores between the two treatment groups.[5]

Table 2. Comparison of Mean Change from Baseline of ADAS-Cog Scores after 12 Months[5]

Intervention	ADAS-Cog Mean (SEM) at baseline	Mean change in ADAS-Cog over 12 months	P-value
Fish oil concentrate	31.8 (9.4)	4.4 points (±2.2)	P=0.86
Placebo	32.2 (9.5)	3.2 points (±2.1)	

Eriksdotter et al. conducted a double-blind, randomized controlled trial that investigated the effects of treatment with DHA for 6- and 12-month periods. The study included 204 participants who were adults between 64-82 years of age with a diagnosis of Alzheimer's Disease and were treated with acetylcholinesterase inhibitors for at least 3 months prior to the start of the study.[6] Inclusion and exclusion criteria for participants are summarized in Table 1. Participants were randomized into two treatment groups via a computerized system.[6] One group received treatment with daily dose of fish oil concentrate with 430 mg of DHA for 12 months and the other group received treatment with placebo capsules for 6 months followed by treatment with fish oil concentrate with 430 mg of DHA for 6 months.[6] Therefore, all participants received treatment with daily DHA for at least 6 months. The outcome analyzed was changes in ADAS-Cog scores from baseline to the end of the 12-month treatment period in relation to changes in the plasma levels of omega-3 fatty acids.[6] Of the 204 enrolled participants, 165 were able to provide plasma samples at baseline and at the end of the study duration.[6] Worst-case analysis was not performed on participants who did not complete the study or were not able to provide plasma samples. The data collected from both treatment groups were analyzed collectively for a total of a 6-month treatment duration.[6] The association between changes in ADAS-Cog scores and plasma levels of omega-3 fatty acid was represented by an unstandardized coefficient, B.[6] It was found that B=-0.834 meaning that increasing plasma levels of omega-3 were positively associated with slowing the increase in ADAS-Cog scores, or slowing the rate of cognitive decline.[6] This positive association was found to be statistically significant with a p-value of 0.016 ($p<0.05$).[6]

Quinn et al. conducted a double-blind, randomized, placebo-controlled trial that took place in 51 different clinical research sites across the United States. Specific inclusion and

exclusion criteria for participants are summarized in Table 1. A total of 402 participants were randomized into two treatment groups: one group received daily treatment with algal-derived DHA containing 900 mg-1.1 g of DHA and the other group received treatment with daily placebo.[7] The participants were randomized in a 3:2 ratio, with 238 participants in DHA group and 164 participants in placebo group, to maximize participant recruitment.[7] Randomization was achieved using an interactive voice response system and adherence to treatment was assessed every 3 months via pill counting.[7] During the 18-month treatment duration, 107 participants (67 participants in DHA group, 40 participants in placebo group) withdrew from the study.[7] With greater than 20% participant loss, the study primarily used an intention-to-treat analysis and worst-case analysis was not used in this study.[7] The primary outcome measured was mean changes in ADAS-Cog scores for both treatment groups.[7] As summarized in Table 3, at the conclusion of the 18-month treatment period, the placebo group had a mean change in ADAS-Cog scores of 8.27 from baseline and the DHA group had a mean change of 7.98 from baseline.[7] These treatment effects were found to not be statistically significant with $p=0.41$ ($p>0.05$).[7]

Table 3. Comparison of Mean Change from Baseline in ADAS-Cog Scores after 18-months[7]

Intervention	Mean change from baseline in ADAS-Cog scores after 18 months of treatment
DHA treatment	7.98
Placebo	8.27

DISCUSSION

Alzheimer's Disease is a debilitating and life-altering condition for many people and their family members. Without a permanent cure, it is increasingly important to have a variety of symptomatic treatment options for patients to try. This systematic review evaluated the efficacy of DHA supplementation to decrease the rate of cognitive decline, as measure by the ADAS-Cog scale, in patients with Alzheimer's Disease. Amongst the studies that were analyzed, one article

found a statistically significant correlation between DHA use and slowing the changes in ADAS-Cog scores, while two studies did not find statistically significant treatment effects. Eriksdotter et al. found that there was a statistically significant ($p=0.016$) positive association between increased plasma levels of omega-3 fatty acids from DHA treatment and a decreased rate of change in ADAS-Cog scores. However, Shinto et al. and Quin et al. did not find statistically significant differences in mean changes from baseline in ADAS-Cog scores when comparing DHA treatment groups to placebo treatment groups. Shinto et al. found that after 12 months, the DHA treated group had a mean change from baseline of 4.4 points and the placebo treated group had a mean change of 3.2 in ADAS-Cog scores with a p-vale of 0.86. Quinn et al. found that after 18 months, the DHA group had a mean change of 7.98 and the placebo group had a mean change of 8.27 in ADAS-Cog scores with a p-value of 0.41.

The limitations within this review included research methods. This review used PubMed as its only search engine and restricted itself to articles only available via one source. If other search engines had been utilized, it is possible that different studies could have been analyzed. Limitations also existed for each study analyzed in this review. In all three studies, worst-case analysis was not performed for participants who withdrew from the studies.[5-7] For Shinto et al. and Eriksdotter et al., participants were still allowed to continue taking additional medications that symptomatically treated Alzheimer's Disease, such as AChEIs, which could have also contributed to the changes in cognition levels of participants.[5-6] The sample size in Shinto et al. was also very small and this could have had an effect on the validity of the results. In Eriksdotter et al., participants were either treated with DHA for 6 or 12 months but despite these differing treatment durations, the data from both groups were analyzed collectively for a total of a 6-month treatment duration.[6] Participants were not analyzed with intention-to-treat analysis and

this affects the reliability for the study.[6] In Quinn et al., the treatment groups were purposefully disproportionate at a 3:2 ratio to enhance recruitment which introduces bias within the study.[7] Participants were also allowed to continue other medications, such as Warfarin, and this could have also had an effect on the data collected.[7]

CONCLUSION

This systematic review demonstrates that daily supplementation with DHA does not decrease the rate of cognitive decline in patients with Alzheimer's Disease. Although one study found a statistically significant association, two of the analyzed studies did not find statistically significant data of DHA decreasing the rate of cognitive decline, as measured by the ADAS-Cog scale, in those with Alzheimer's Disease.

Future research on this topic could include a less varied patient population with stricter inclusion and exclusion criteria. For example, analyzing studies that required all participants to be on a stable dose of AChEIs for a standard period prior to the start of the study to determine if DHA acts as an effect adjunctive medication for those with Alzheimer's Disease. Other areas of research could include analyzing DHA effects at earlier stages of an Alzheimer's diagnosis. Due to the progressive nature of the disease, it may be beneficial to analyze the effect DHA could have in patients that are in the earlier stages of diagnosis.

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