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Fish oil supplementation in the treatment of major depression: A randomised double-blind placebo-controlled trial

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Abstract

Dietary deficiencies in essential omega-3 polyunsaturated fatty acids derived from fish are associated with depression and some fish oils may have therapeutic benefits. We aimed to determine whether taking tuna fish oil confers any additional benefit to conventional outpatient treatment for major depression. A randomized double-blind placebo-controlled four-month trial comparing tuna fish oil versus placebo was conducted on 83 outpatients with major depression. Despite large reductions in depression there were no significant differences at any assessment time point between patients receiving fish oil compared to placebo. Red blood cell incorporation of fatty acids indicated good compliance with oil supplementation, although this sample was not initially deficient in omega-3s. This particular dose and type of fish oil conferred no additional benefit to conventional treatment of depression in this sample. Future studies could target participants with pre-existing omega-3 deficiency and appraise alternate enriched types and higher doses of omega-3 supplementation.

Keywords: Docosahexaenoic acid; Eicosapentaenoic acid; Major depression; Omega-3

1. Introduction

There is considerable putative evidence suggesting a relationship between omega-3 polyunsaturated fatty acid intake derived from fish and depression (Hibbeln, 1998; Tanskanen et al., 2001). Despite considerable interest in the possible treatment of depression with omega-3s, pilot studies predominate and are variously limited by small samples, unbalanced distribution of prognostic factors, insufficient sample specification or diagnosis, or an absence of biochemical compliance assessment. Two studies report a positive response (Nemets et al., 2002; Su et al., 2003), two no response (Marangell et al., 2003; Silvers et al., 2005), and one a mixed dose-dependent response (Peet and Horrobin, 2002). Most studies supplement antidepressants with fish oil, although one investigated a fish oil alone as a treatment (Marangell et al., 2003). Fish oil formulations have varied between studies, with some rich in Eicosapentaenoic Acid (EPA), others with Docosahexaenoic Acid (DHA), and some with a combination of both. DHA is the predominant omega-3 fatty acid obtained by eating fish and therefore may account for the negative correlation between fish consumption and depression (Hibbeln, 1998). Moreover, DHA is the major fatty acid component of brain phospholipids and is essential for normal brain development (Anderson et al., 1990). Although studies that have reported a positive effect on mood have tended to use highly concentrated EPA-rich doses, a natural fish oil containing both DHA and EPA could provide a non-pharmaceutical option to be used in depression treatment. The aim of this study was to assess the efficacy of administering moderate doses of a tuna fish oil supplement to patients with major depression receiving conventional treatment in a randomized double-blind placebo-controlled trial.

Abbreviations: EPA, Eicosapentaenoic Acid; DHA, Docosahexaenoic Acid; SCID DSM-IV, Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edn; HDRS, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; GAF, Global Assessment of Functioning scale; VLCn3, Very long chain omega-3 fatty acids; PUFA, Polyunsaturated Fatty Acid.

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2. Methods

Participants were outpatients of Northfields Clinic, University of Wollongong, serving the local community of 250,000 people south of Sydney. Inclusion criteria were: SCID DSM-IV primary diagnosis of major depression (First et al., 1997a,b), Hamilton Depression Rating Scale (HDRS) score > 16 to ensure clinical significance of depression severity (Elkin et al., 1989), age range 18–75, no serious medical condition (e.g. heart disease, cancer), consent for venipuncture, and no comorbid substance abuse, psychotic, bipolar, obsessive-compulsive or eating disorder. Urn randomization (Stout et al., 1994) balanced allocation to groups on four depression sensitive prognostic factors: sex, age, concurrent antidepressant therapy, and HDRS severity. Participants, clinicians and researchers were blind to allocation, with randomization and capsule packing performed externally. All participants gave written informed consent following Institutional Review Board approval.

Patients consumed eight odorless visually identical 1 g soft gelatin capsules per day of either placebo (olive oil) or south pacific tuna oil, supplied by Clover Corporation PLC, Australia. Eight capsules of fish oil provided 3 g of omega-3 polyunsaturated fatty acids (2.2 g DHA, 0.6 g EPA, stabilized with 80 mg vitamin E). The proportions of DHA and EPA are those naturally found in this tuna fish and were not changed during manufacture. Patients receiving maintenance antidepressant medication at intake (with a duration of a minimum of 3 weeks at the current therapeutic dose prior to acceptance) were required to maintain their dose during the trial. All patients received weekly 50-minute appointments with a clinical psychologist using a standard manualized treatment (Diguer et al., 1993) which helped to monitor suicidal ideation, manage mood and promote trial adherence. Compliance was assessed using fortnightly capsule counts and venipuncture at baseline, 6 weeks and 16 weeks to assess fatty acids in membrane red blood cells (Lepage and Roy, 1986), plasma total cholesterol, and alpha-tocopherol levels. Diet history and food records were also monitored at each assessment to ensure there were no changes in baseline consumption of omega-3 rich food sources.

Main outcome measures were HDRS and Beck Depression Inventory (BDI) (Elkin et al., 1989). Secondary measures investigated interpersonal, occupational and personal functioning (Global Assessment of Functioning (GAF)) (Diguer et al., 1993) and subjective Likert ratings of aches/pains, energy, fatigue, sleep and appetite. Side effects rated were change in stools, indigestion-stomach pain, indigestion-heart burn, flatulence, belching, and aftertaste in mouth and breath.

Aggregating previous studies (Nemets et al., 2002; Peet and Horrobin, 2002), a mean treatment-control difference of 6 HDRS points was estimated requiring a minimum cell size of 26 to achieve a power of 0.8 or more to detect a difference at the .05 level, 2-tailed. The study was analyzed as intention-to-treat, using a multilevel modeling approach (SPSS-12 Linear Mixed Models) with Time as a repeated measure ensuring all data were retained in the repeated-measures analyses (Gueorguieva and Krystal, 2004). Where applicable the covariance structure for the residuals was specified as ante-dependent. Secondary investigations were conventional chi-square, regression and *t*-tests with criteria for statistical significance at $P<.05$.

3. Results

183 patients were assessed, 83 met the study criteria and were randomized (40 fish oil, 43 olive oil; 51 females; mean age 45.27 y, range 18–70 y). Most ($N=61$, 74%) were currently taking therapeutic doses of antidepressants ($N=33$ SSRIs, $N=4$ tricylic, $N=22$ others predominantly venlafaxine). Overall, the sample was chronic or recurrent with long histories of depression (average 13 y), previous hospitalization (29%), co morbid anxiety (54%) and personality disorders (57%). Over half (57%) met the criteria for antidepressant treatment resistance, defined as a failure to respond to two adequate courses of antidepressant treatment. There were no significant differences between groups on any demographic or clinical characteristic and controlling for severity had no influence on group comparison outcomes. Twenty-three (28%) violated the trial protocol ($N=15$ placebo, $N=8$ fish), all violations occurred early between randomization and the 6th week. Reasons for violation were: time/commitment (work/family/personal) ($N=8$), moving out of area ($N=4$), being hospitalized ($N=3$), time constraints ($N=2$), and unknown/uncontactable ($N=6$). Analyses of completers versus drop outs found no differences on any measure at any time point.

Compliance with the trial protocol was excellent: the DHA, EPA and the total very long chain omega-3 (VLCn3) fatty acids increased significantly by 2.8, 0.7, and 3.4% respectively, and omega-6 fatty acids significantly decreased (total 3.2%) for the fish group compared to placebo. As expected plasma HDL-cholesterol and plasma alpha-tocopherol increased only for the fish oil group ($P<.05$). Capsule counts confirmed biomedical measures and diet history and food records supported that baseline diet did not change.

For the HDRS, no significant fixed interaction effect was found between Time and Group $F(2,55.83)=.17$, $P=.844$, or Group, $F(1,66.96)=.207$, $P=.651$, however there was a significant effect due to Time $F(2,55.83)=114.04$, $P=.000$, with a baseline to 4 month pre–post effect size across groups = 2.73 (mean intake score = 23.5, 4-month score = 10.7). Similarly, for the BDI there was no significant interaction between Time and Group $F(5,261.74)=.34$, $P=.424$, or Group $F(1,83.02)=1.19$, $P=.293$, however, there was a significant effect due to Time, $F(5,261.74)=34.12$, $P=.000$. There were no differences between groups at any of the six assessment points on raw scores or covariate analyses that controlled for initial baseline severity (Fig. 1). Given the high prevalence of comorbid personality disorder, anxiety disorders and antidepressant treatment resistance, the effect of these variables were modelled in relation to predicting change in HDRS. Neither comorbid personality disorder (beta = −.21, $t=-1.49$, $P=.17$), anxiety disorder (beta = −.065, $t=-$n.44, $P=.66$) nor antidepressant treatment resistance (beta = .11, $t=.73$, $P=.47$) showed any relation to clinical changes in depression.

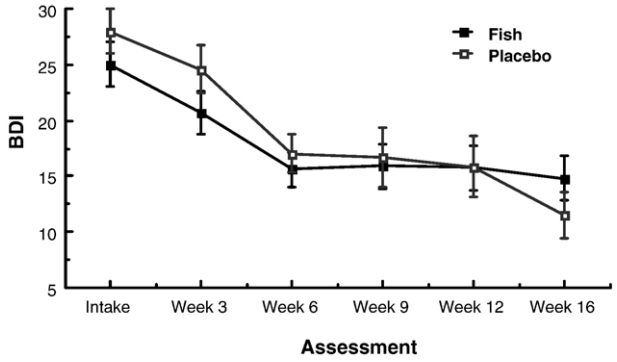

Fig. 1. Mean change in depression severity measured by the Beck Depression Inventory (BDI) at 3-week intervals over the 16-week trial for the fish oil and placebo interventions (bars represent ±standard error of the mean).

Similarly, entering these three factors as covariates did not alter the above reported lack of a difference between the groups on depression change (overall model $F=.65$, $P=.63$).

Secondary analyses investigated changes in GAF and subjective ratings. For the GAF rated at intake, 6 weeks and 16 weeks, there was no significant interaction between Time and Group $F(2,194)=.92$, $P=.399$, or Group $F(1,194)=.54$, $P=.464$, however, there was a significant effect due to Time, $F(2,194)=52.18$, $P=.000$. Overall, GAF ratings improved from an intake average score of 51, to a six-week 63 and 16-week 68 score. There were no reported differences on subjective ratings of aches and pains, energy, fatigue, sleep or appetite between groups, with most participants rating that there was 'no change' (score of 5) or a very slight improvement in these items over the course of the trial. With respect to side-effects, approximately one third of the sample noticed changes in their stools due to consuming the capsules, across both groups. The only significant differences between groups were at 6 weeks the fish oil group reported more belching and at 16 weeks a noticeable aftertaste in the mouth (44%) and breath (28%). At the end of the trial 90% fish and 64% placebo participants correctly guessed their assignment, which would not be expected by chance ($P<.05$). Some participants admitted to having broken open a soft gel capsule and others highlighted that they reported using the aftertaste as a clue.

4. Discussion

This study aimed to investigate the efficacy of providing very long chain omega-3 polyunsaturated fatty acid (VLCn3 PUFA) supplementation in the treatment of depression. Compliance with the protocol was excellent, with supplementation leading to significant increases in the red blood cell incorporation of the VLCn3 PUFA for those receiving fish capsules. The results of this study show no detectable benefit of fish oil compared to placebo when added to a standard outpatient treatment. Several factors should be noted in interpreting these findings.

First, the dose (3 g) falls between other published studies, which range between 1 g–9 g. There is considerable speculation regarding optimal doses, leading some to suggest that the balance of n-3 and n-6 fatty acids is more critical. We chose to evaluate a natural fish oil with both DHA and EPA, however others have shown benefits with predominantly EPA-rich oils (Frangou et al., 2006; Nemets et al., 2002, 2006; Peet and Horrobin, 2002). Whereas the brain contains far more DHA than EPA, their mechanism of action is different. DHA as a component of neuronal membrane phospholipids affects neurotransmission, whereas EPA may influence mood to a greater extent by acting through eicosanoid mechanisms to increase cerebral blood flow.

Second, erythrocyte VLCn3 PUFA levels found here (8.2% at baseline) were, on average, no lower than the normal healthy population (Siscovick et al., 2000), possibly therefore obviating any benefits from supplementation. However, it should be noted that some studies have found pharmacological effects for specific refined omega-3n (such as ethyl-EPA), which appear to confer effects independent of any nutritional deficiency (Frangou et al., 2006).

Third, although the trial was double blinded, when asked most participants could guess which supplements they were taking. This fact alone did not appear to influence the outcome, however future studies should use more effective blinding (e.g. citrus flavoring).

Some authors have suggested that the selection of olive oil as a placebo may be problematic, since oleic acid converts to oleamide, a fatty-acid amide, however the elevation from this dose is small and unlikely to be of clinical significance (Stoll et al., 2000). An additional concern might also be that the fish oil is stabilized with vitamin E, since earlier work has found a relationship between depression severity and low levels of alpha-tocopherol (Owen et al., 2005). However, we found no relationship between alpha-tocopherol and changes in depression severity.

The sample studied was predominantly chronic with high comorbidity. Controlling for chronicity or comorbidity did not change our results, however one previous pilot study on non-complex antidepressant-responsive patients reported fish oil benefits (Nemets et al., 2002). There are, however, reports of a good clinical response to treatment-resistant refractory depression (Murck et al., 2004; Puri et al., 2002).

This is the first study to supplement standard psychological and antidepressant treatment with fish oil. It may be argued that the potency of the combined treatment created a ceiling effect (effect size=2.73), such that there was no additional variance in which the fish oil condition may have showed superiority. However, several recent studies without a psychological intervention still failed to detect any superiority of fish oil over placebo (Marangell et al., 2003; Silvers et al., 2005). On the whole, these findings do not support the routine use of this particular tuna fish oil as an addition to conventional treatment for major depression. Future research needs to ascertain if there are particular advantages of fish oil treatment in patients deficient in omega-3s, and whether certain other types of omega-3 oils, such as those rich in EPA, might offer more benefit.

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randomization and blinding; Prof Linda Tapsell monitored dietary intakes; and clinicians were Drs J. Martin, T. Cartmill, C. Walton, M. Greene, L. Parker, D. StQuintin, K. Hynes, M. Tendys, S. Green and V. Bel. Peter Howe is now located at the School of Health Sciences, University of South Australia.

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