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Brief report

Eicosapentaenoic acid as an add-on to antidepressant medication for co-morbid major depression in patients with diabetes mellitus: A randomized, double-blind placebo-controlled study

M. Bot [a], F. Pouwer [a,b,*], J. Assies [c], E.H.J.M. Jansen [d], M. Diamant [e], F.J. Snoek [b], A.T.F. Beekman [f], P. de Jonge [a,g]

[a] CoRPS — Center of Research on Psychology in Somatic diseases, Department of Medical Psychology and Neuropsychology, Tilburg University, Tilburg, The Netherlands
[b] Department of Medical Psychology, EMGO Institute, VU University Medical Center, Amsterdam, The Netherlands
[c] Department of Psychiatry, Amsterdam Medical Center, Amsterdam, The Netherlands
[d] National Institute for Public Health and the Environment, Center for Prevention and Health Services Research, Bilthoven, The Netherlands
[e] Diabetes Center, Department of Internal Medicine, Amsterdam, The Netherlands
[f] Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands
[g] Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

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ABSTRACT

Background: Depression is common in individuals with diabetes. The present study is the first randomized controlled trial to test the efficacy of ω-3 ethyl-eicosapentaenoic acid (E-EPA) as adjuvant to antidepressant medication in the treatment of depression in adults with diabetes mellitus.

Methods: In the VU University Medical Center, we conducted a 12-week, placebo-controlled, double-blind, parallel-group intervention study of E-EPA (1 g/day) versus placebo in 25 diabetes patients meeting DSM-IV criteria for major depressive disorder, who were already using antidepressant medication. The primary outcome was severity of depressive symptoms, assessed by the Montgomery Åsberg Depression Rating Scale (MADRS) at baseline and 12-week follow-up at two-weekly intervals. Blood samples were collected at baseline and at 12-week follow-up to determine EPA levels in erythrocyte membranes. Data were analyzed with ANOVA for repeated measures.

Results: Thirteen participants were randomly assigned to E-EPA; 12 participants were given placebo. At 12-week follow-up, erythrocyte membranes from patients receiving E-EPA contained tripled levels of EPA, while no changes were noted in participants receiving placebo. In both groups, depressive symptoms significantly decreased over time ($F=21.14$, $p<0.001$), yet no significant differences were found between those treated with E-EPA versus placebo ($F=1.63$, $p=0.17$).

Limitations: Although having sufficient study power, this study had a relatively small sample size. Small effects could not be detected, and dose-dependent effects could not be studied.

Conclusions: No evidence was found for the efficacy of adding E-EPA to antidepressants in reducing depressive symptoms in diabetic patients with co-morbid depression.

1. Introduction

Depression is a common co-morbid disorder in both type 1 and type 2 diabetes mellitus, and is associated with impaired quality of life (Schram et al., 2009), poor glycemic control (Lustman et al., 2000), increased health care costs

* Corresponding author. CoRPS — Center of Research on Psychology in Somatic diseases, Department of Medical Psychology and Neuropsychology, Tilburg University, P.O. Box 90153, 5000 LE Tilburg, The Netherlands. Tel.: +31 13 466 3144; fax: +31 13 466 2067.
E-mail address: f.pouwer@uvt.nl (F. Pouwer).

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(Egede et al., 2002), and an increased all-cause mortality rate (Egede et al., 2005). Cognitive behavioral therapy, tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs) are effective treatments for major depression in diabetic patients (Lustman and Clouse, 2002). However, a considerable percentage of diabetic subjects receiving antidepressant drugs does not achieve full remission (TCAs: 43% and SSRIs: 52%) (Lustman and Clouse, 2002). This finding highlights the need for further research on ways how to improve treatment efficacy in depressed patients with diabetes. One candidate that could improve treatment success may be longer chain ω-3 polyunsaturated fatty acids (PUFAs) from fatty fish, including eicosapentaenoic acid (EPA; C20:5 ω-3) and docosahexaenoic acid (DHA; C22:6 ω-3) (Pouwer et al., 2005). Both depressed patients and diabetic patients are known to have relatively low levels of ω-3 PUFAs (Decsi et al., 2007; Sontrop and Campbell, 2006; Vessby, 2000). A recent meta-analysis showed that ω-3 PUFAs were efficacious as antidepressant therapy (Appleton et al., 2010) , although heterogeneity in study design was noted. However, a recent study did not observe an effect of ω-3 PUFAs on mood in depressed patients with a coronary heart disease (Carney et al., 2009). Furthermore, there is some evidence that EPA may be particularly effective as add-on treatment in patients with major depression using antidepressant medication (Pouwer et al., 2005; Sarris et al., 2009). The exact mechanisms of the relationship between depression and ω-3 PUFAs remain to be elucidated, but could include increased membrane fluidity, altered cellular signaling processes, altered neurotransmitter processing, and increased anti-inflammatory activity (Parker et al., 2006; Pouwer et al., 2005; Sarris et al., 2009).

The efficacy of ω-3 PUFAs on depressive symptoms in patients with diabetes mellitus is unknown. Therefore, we conducted a double-blind, randomized, placebo-controlled study to test the efficacy of add-on ω-3 ethyl-eicosapentaenoic acid (E-EPA) on depressive symptoms in depressed diabetic patients using antidepressant medication.

2. Methods

2.1. Study design and participants

Participants were recruited from the VUMC diabetes outpatient clinic and through advertisements on websites, in newspapers, and patient magazines. Patients were eligible if they were aged 18–75 years, diagnosed with diabetes (type 1 or type 2), and currently being on antidepressant medication for at least two months. Furthermore, participants had to meet the criteria for current Major Depressive Disorder (MDD), determined with the Composite International Diagnostic Interview (Andrews and Peters, 1998). Diabetes was verified with the medical status when the patient attended the VUMC. For those who were not patients of the VUMC, persons who used insulin or oral hypoglycemic agents were regarded as diabetes patients.

Exclusion criteria were: serious co-morbid disease, using fish oil supplementation, consuming more than three servings of fish per week, alcohol or drugs abuse, suicidal ideation, and/or allergy to fish, fish products or rapeseed oil.

Participants were recruited from April 2006 until May 2007 and the trial was performed between June 2006 and July 2007. The study protocol was approved by the ethical committee of the VU University Medical Center (VUMC). All participants gave informed consent.

2.2. Intervention

Patients were randomly allocated to 1 g/day E-EPA or to an equivalent dose of rapeseed oil + medium chain triglycerides (placebo) for 12 weeks. This dosage and duration are in line with other trials of ω-3 on depression (Appleton et al., 2010; Peet and Horrobin, 2002). Both intervention and placebo medication were provided in two soft gelatin capsules per day, stabilized with mixed tocopherols, and were produced by Minami Nutrition, Belgium. Patients were advised not to chew the capsules. Patients, research nurse and researchers were blinded toward treatment allocation until completion of the data collection.

2.3. Measurements

At baseline, demographic, anthropomorphic and health-related characteristics were assessed at the VUMC. Severity of depressive symptoms was assessed by the Dutch version of the 10-item Montgomery Åsberg Depression Rating Scale (MADRS) (Hartong and Goekoop, 1985), with a score range of 0–60. Higher scores reflect more severe depression.

The MADRS was administered at seven times during the study by the research nurse. At baseline and in week 12, the MADRS was administered in the VUMC. In week 1, 3, 5, 7, and 9 measurements of the MADRS were obtained per telephone. A validation study showed that the MADRS can be reliably administered by telephone instead of face-to-face (Hermens et al., 2006).

Furthermore, in weeks 1, 3, 5, 7, 9, and 12 the research nurse assessed whether the patient experienced one of the following side effects: abdominal pain, belching, diarrhea, and nausea. Other side effects were also noted. To study concealment, patients were asked whether they thought to be allocated in the E-EPA group or the placebo group in week 12.

2.4. Blood samples

Blood was collected by venipuncture at baseline and in week 12 and analyzed by the National Institute for Public Health and the Environment. EPA levels in erythrocyte phospholipids were measured with a gas chromatograph (GC-3900, Varian Assoc., Palo Alto, USA). The EPA content was expressed as percentage of the total fatty acids present in the chromatogram. Hemoglobin A_{1c} (HbA_{1c}) is an indicator for glycemic control (normal values: 4.3–6.1%) (Jeffcoate, 2004) and was measured by a turbidimetric immuno inhibition method using an auto analyzer (LX20-Pro, Beckman-Coulter, Fullerton, USA).

2.5. Statistical analyses

Sample size was calculated with G*Power 3.0.10 for the within–between interaction in Analysis of Variance (ANOVA). Because we obtained seven repeated measures of depression

symptom severity using the MADRS, 10 patients had to be included in each treatment arm to detect an effect size of 0.25 (power = 80%, two-sided $\alpha = 0.05$, correlation between repeated measures = 0.6 and non-sphericity correction $\varepsilon = 0.6$). Assuming a drop-out rate of 20% we had to include a total of 25 patients.

Intention to treat analyses were conducted. Because MANOVA for repeated measures has low power in small samples (Stevens, 2002), the course of depression symptoms was compared between both groups using ANOVA for repeated measures by testing the significance of the interaction term treatment*time, adjusted for the Greenhouse–Geisser epsilon. Sensitivity analyses were performed by excluding one person who discontinued E-EPA treatment and two participants in the placebo arm who discontinued using antidepressants during the study. The standardized effect size was calculated by dividing the difference of change in MADRS scores (from baseline to 12-week follow-up) between the E-EPA and placebo group by their pooled standard deviations. In all analyses, a 2-sided p value of <0.05 was used to determine statistical significance. Statistical analyses were performed with SPSS version 16.0 for Windows.

3. Results

3.1. Participant flow

Fig. 1 presents the participant flow during enrollment, randomization and follow-up. Seventy-five patients were willing to participate in the study. Thirty-five patients declined after they had received more detailed information about the study. Furthermore, twelve patients were excluded because they did not meet the inclusion criteria. The 25 eligible persons for the trial were randomly assigned to either the E-EPA group ($N = 13$) and the placebo group ($N = 12$). One patient receiving E-EPA was lost to follow-up. From all other randomized patients, all follow-up measurements were available. One participant discontinued treatment during the trial due to an allergic reaction to E-EPA (see below). Two participants (both from the placebo group) ceased using antidepressants during the trial. Table 1 provides the baseline characteristics of the participants assigned to E-EPA and placebo.

3.2. EPA levels in erythrocyte membrane

From baseline to 12-week follow-up, the mean level of EPA in the erythrocyte membrane tripled in the E-EPA group (from 0.53% (± 0.17) to (1.69%; ± 0.56)), whereas it remained stable in the placebo group (from 0.66% (± 0.20) to (0.61%; ± 0.19)) supporting the integrity of the intervention arms.

3.3. Course of depression symptom severity measured with the MADRS

At baseline, the mean MADRS score was 26.3 (± 8.2) in the E-EPA group and 26.4 (± 8.7) in the placebo group. At 12-week follow-up, the mean MADRS scores dropped to

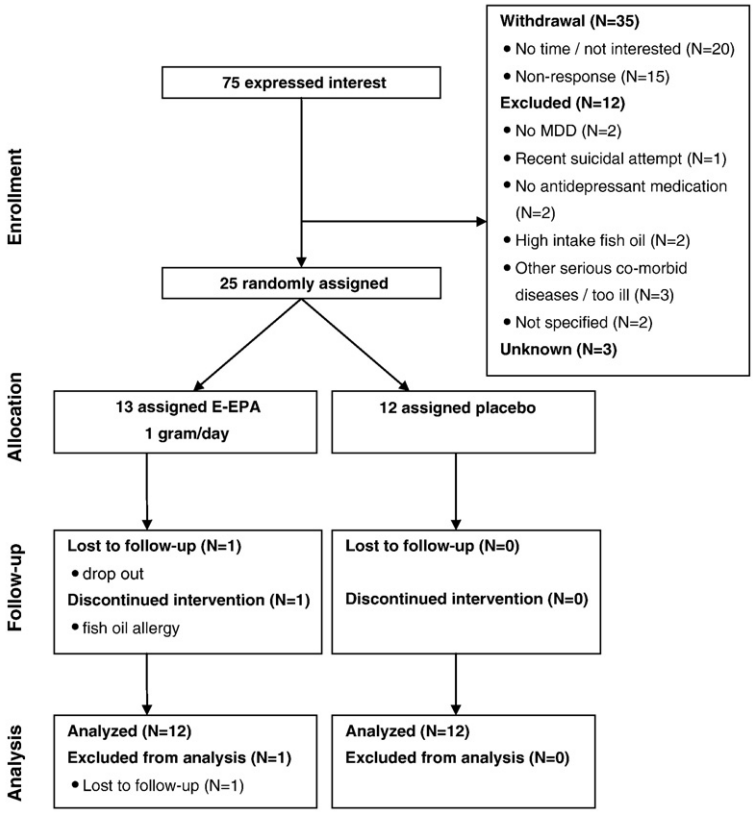

Fig. 1. Flow diagram of participants throughout the study.

Table 1
Baseline characteristics of the 25 diabetes patients with major depressive disorder.

	E-EPA ($N=13$)		Placebo ($N=12$)		p value
	Mean	SD	Mean	SD	
Age (years) [a]	53.1	13.8	55.0	8.6	0.85
Body Mass Index (kg/m²)	29.3	5.1	29.8	4.8	0.80
Waist circumference (cm) [a]	99	15	100	14	0.98
	N	%	N	%	
Women	8	62	5	42	0.32
Low educational level	3	23	5	42	0.41
Working full or part time	3	23	5	42	0.41
Living with a partner	7	54	9	75	0.41
Current smoker	0	0	3	25	0.10
Last month fish consumption ≥1 serving/week	3	23	4	33	0.67
Diabetes related	N	%	N	%	
Type 1 diabetes	5	38	5	42	1.00
Type 2 diabetes	8	62	7	58	1.00
One or more diabetes complications [b]	5	38	2	17	0.38
Treatment with diet	6	46	2	17	0.20
Treatment with oral blood glucose lowering drugs	7	54	5	42	0.54
	Mean	SD	Mean	SD	
Treatment with insulin	10	77	10	83	1.00
Duration of diabetes (years)	11.3	10.7	18.1	12.4	0.19
HbA_{1c} (%)	6.9	1.1	6.9	1.1	0.91
Depression related					
MADRS score	26.3	8.2	26.4	8.7	0.97
	N	%	N	%	
Depression severity [c]					
Mild	1	7.7	2	16.7	0.59
Moderate	11	84.6	7	58.3	0.20
Severe	1	7.7	3	25.0	0.32
Treatment [d]					
Tricyclic antidepressant	2	17	0	0	0.48
Selective serotonin reuptake inhibitor	9	75	10	91	0.64
Noradrenergic and specific serotonergic antidepressant	1	8	1	9	1.00

[a] Mann–Whitney u test.
[b] Having nephropathy, retinopathy, diabetic foot, macrovascular complications, or neuropathy.
[c] Depression severity according to MADRS score: 9–17 mild depression, 18–34 moderate depression, and ≥35 severe depression (Muller et al., 2000).
[d] At 12-week follow-up. Treatment was not specified for 1 person in the E-EPA arm (loss to follow-up) and for 1 person in the placebo arm.

14.0 (±6.9) in the E-EPA group and to 11.6 (±9.1) in the placebo group (standardized effect size favoring placebo $d=0.29$). Fig. 2 shows the development of the MADRS score for the E-EPA group and the placebo group over time. Repeated measures analysis revealed a statistically significant time effect: mean MADRS score decreased over time in both groups ($F=21.14$, $df=3.98$, $p<0.001$). However, no significant effect of E-EPA treatment versus placebo over time was found (treatment*time interaction ANOVA $F=1.63$, $df=3.98$, $p=0.17$). Excluding one participant who ceased using E-EPA during the study and two patients who discontinued using antidepressants marginally changed

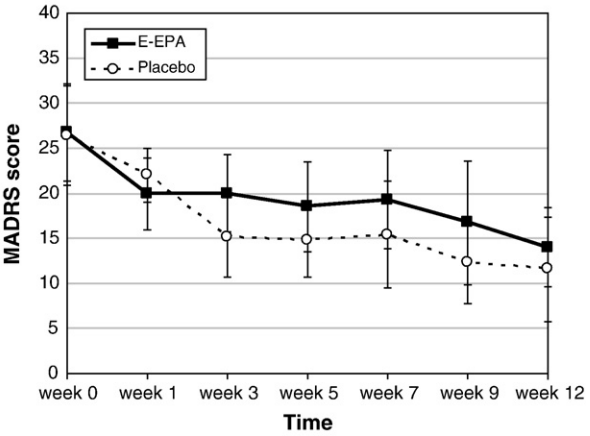

Fig. 2. Development of the MADRS score over time for the E-EPA ($N=12$) and placebo group ($N=12$). Error bars indicate 95% confidence interval. No significant treatment*time interaction ($F=1.63$, $df=3.98$, $p=0.17$).

the results of the ANOVA (treatment*time interaction $F=1.21$, $df=3.93$, $p=0.31$). Furthermore, in the E-EPA group, change in depression severity and change in E-EPA level from baseline to 12-week follow-up were uncorrelated (Pearson's $r=0.016$, $p=0.96$).

3.4. Side effects

Side effects were assessed at six occasions. Eight persons never had a side effect. Prevalent side effects were stomach ache ($N=10$), belching ($N=7$), nausea ($N=6$), and diarrhea ($N=5$). Number and type of side effects did not differ significantly between the E-EPA and the placebo group. One person assigned to the E-EPA group showed an allergic reaction during the trial which consisted of rashes and itching. No other serious side effects were reported.

3.5. Concealment

Concealment appeared to be successful. At 12-week follow-up, only 4 of the 12 participants (33%) correctly thought they received E-EPA, and 4 of the 12 (33%) participants correctly thought they received the placebo.

4. Discussion

In the present randomized, double-blind placebo-controlled study, we found no evidence of a therapeutic effect of 1 g/day E-EPA as an add-on to antidepressant medication compared to placebo in patients with diabetes and MDD during 12 weeks. This finding is not likely to be explained by a lack of contrast between the two groups, as we observed tripled levels of EPA in the erythrocyte membranes of participants in the intervention group and no change in the placebo group.

In a recent meta-analysis, Appleton et al. (2010) concluded that ω-3 PUFAs showed antidepressant efficacy in non-diabetic depressed patients, yet significant heterogeneity in study design was noted. Our results are in line with a recent randomized controlled trial in coronary heart disease patients with major depression that did not find evidence that ω-3

PUFAs augmentation of sertraline was superior to sertraline plus placebo for the treatment of depression (Carney et al., 2009). However, there are clear differences between our study and the other studies in sample characteristics (diabetes patients vs. other patient groups) and the ω-3 PUFAs provided. Although EPA showed more promising results on depression than DHA monotherapy (Pouwer et al., 2005), it might be that a specific ratio of DHA and EPA is more effective.

Strengths of our study included the small number of loss to follow-up, the large number of follow-up measurements, and its double-blind, placebo-controlled design. However, the study is also subject to some limitations. Information about fish consumption was only assessed at baseline. Yet, there was no indication that the placebo group increased fish consumption as the level of EPA did not increase. Also, we had a heterogeneous sample of patients with respect to type of diabetes and antidepressant use. In the case that E-EPA would be more effective in either type of diabetes or as add-on to a specific type of antidepressant, our study sample was too small to detect these effects. Furthermore, the dose of fish oil in our study (1 g/day) and duration might not have been adequate for patients with diabetes. Although we could not find studies about the effect of the placebo (rapeseed oil) on mood, we cannot fully exclude the possibility that rapeseed oil has some beneficial effect on mood. Finally, although we assessed the power of our study rigorously, we are aware that our sample size is smaller than most other randomized controlled trials. Therefore, the results may be more sensitive for chance fluctuations and warrant future replication studies.

Clinical trials registration

ISRCTN Register. ISRCTN 30877831.
http://www.controlled-trials.com/ISRCTN30877831/30877831

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Conflict of interest

M. Bot, J. Assies, E.H.J.M. Jansen, F.J. Snoek, M. Diamant, A.T.F. Beekman, and P. de Jonge report no financial or other relationship relevant to the subject of this article. F. Pouwer received financial support and verum and placebo supplements from Minami Nutrition, Edegem, Belgium. This study was performed without editorial direction or censorship from sponsors.

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