Prophylactic Effect of Omega-3 Polyunsaturated Fatty Acids Monotherapy to Prevent Recurrent Major Depressive Disorder: A Randomized Controlled Trial

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Abstract

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have demonstrated efficacy as adjunctive treatment for MDD. However, fewer studies assessed the prophylactic properties of n-3 PUFAs as monotherapy on the recurrence of MDD. This 6-month randomized controlled trial (RCT) aimed to assess the prophylactic effect of n-3 PUFAs monotherapy to prevent recurrent MDD. Sixty remitted MDD patients were recruited and assigned to n-3 group (*n*=30) and placebo group (*n*=30). The difference in depression severity and MDD recurrence were evaluated using the 21-item Hamilton Rating Scale for Depression (HRSD) at month 1, 2, 3, 4, and 6 between groups. Furthermore, biochemical parameters in plasma were assessed as the secondary outcomes. Our study results indicated that there was no significant difference in the HRSD score between the n-3 group and placebo at each month. MDD patients in the n-3 group had a lower recurrence rate compared to the placebo group at month 6. Comparatively, at month 6, the eicosapentaenoic acid (EPA) plasma level of the n-3 group was significantly higher than the placebo, while there was no significant difference in docosahexaenoic acid (DHA). In conclusion, n-3 PUFAs monotherapy demonstrated a prophylactic effect on prevention of the recurrence of MDD.

Keywords: eicosapentaenoic acid, docosahexaenoic acid, prevention, recurrence, remitted

Introduction

- Major depressive disorder (MDD) is one of the major leading causes of disability worldwide compared to other mental disorders (2022).
- Persons with a history of MDD are at risk of experiencing a higher level of recurrence (Malhi and Mann, 2018).
- Moreover, MDD is challenging as the standard treatments are often end up with treatment-resistant depression followed by mild to severe adverse effects (Howes, Thase and Pillinger, 2022).
- Clinical-based evidence revealed a correlation between lower plasma n-3 PUFAs levels and an increased risk of depression (Thesing et al., 2020).
- As an essential nutrient, n-3 PUFAs could not be synthesized within the human body. Therefore, it is crucial to emphasize the importance of n-3 PUFAs enriched diet and supplementation (Zhou et al., 2022).
- Majority of studies explored the adjuvant use of n-3 PUFAs in combination with antidepressants that contributed to lower mood scores.
- On the contrary, there are only few studies considered n-3 PUFAs as monotherapy to treat MDD.
- This multi-site randomized controlled trial (RCT) aimed to fill this research gap by examining the potential of n-3 PUFAs monotherapy in preventing the recurrence of MDD, independent of antidepressant medications in remitted MDD patients.

Methods

- 6-month **multi-site** randomized controlled trial (RCT).
- We assessed the eligibility of participants from two outpatient psychiatry departments (**China Medical University Hospital** and **Taipei Cathay Hospital**).
- Participants aged 18-65 years old who have met the DSM-IV diagnosis of major depressive disorder in the past year and are currently in full remission, with less than or equal to two depressive symptoms in the last eight weeks, and a 21-item Hamilton Rating Scale for Depression (HRSD) score of less than 7 (non-depressive symptom) at the baseline.
- Sixty eligible patients were included and randomly assigned to n-3 group and placebo, in a 1:1 ratio using computer-generated randomization with block randomization.
- All participants in this study did not receive any antidepressant or psychosocial therapy during their participation.
- Participants who were diagnosed with schizophrenia, bipolar disorder, psychotic disorder, organic mental disorder, substance use disorder, and acute psychotic state or strong suicidal intention were excluded from the study.
- **Intervention** was given to n-3 group with a fish oil capsule with 2:1 ratio of EPA and DHA (420mg EPA, 220mg DHA, 0.2 mg of tertiary-butylhydroquinone, and 2.0mg of vitamin E), while **placebo group** were provided with a soybean oil capsule. Each subject in both groups consumed 4 capsules per day.
- The clinical team conducted interviews with participants using a semi-structured questionnaire and calculated the total score of the **21-item HRSD questionnaire** to assess the level of depression in all participants at month 1, 2, 3, 4, 5, and 6.
- The patients' fatty acid compositions were analyzed using gas chromatography with fatty acid methyl esters (FAME).

Results

Table 1. Characteristics of participants at baseline

Characteristics	n-3 Group (n= 30)	Placebo (n= 30)	p-value[1]
Age, years	38.3 ± 12.9	39.3 ± 14.1	0.768
Male (n, %)[2]	(25, 83.3)	(25, 83.3)	0.994
Depression Severity			
HRSD	6.0 ±1.9	6.0 ±2.0	0.947
BDI	13.7 ± 11.5	15.2 ± 11.2	0.618

Mean ± SD (all such values), [1]Mann-Whitney U Test unless stated otherwise, [2]Chi-square test, n-3: Omega-3, HRSD: Hamilton Rating Scale for Depression, BDI: Beck Depression Inventory.

Table 2. The incidence of MDD recurrence between the two groups at each time point

Assessment (Month)	0	1	2	3	4	5	6
n-3 Group	0/30	0/30	2/30	4/30	6/30	7/30	8/30
Placebo	0/30	0/30	3/30	5/30	9/30	12/30	16/30
p-value[1]	--	--	0.640	0.718	0.371	0.165	0.035*

Data presented as incidence of recurrence/number of participants of each group, [1]Chi-square Test, **p*-value < 0.05, n-3: Omega-3.

Table 3. Comparison of HRSD scores between two groups at each time point

Assessment (Month)	HRSD Scores		p-value[1]
	n-3 Group	Placebo	
0	6.0±1.9, 30	6.0±2.0, 30	0.947
1	6.0±3.3, 30	7.8±4.9, 30	0.109
2	6.6±3.4, 28	7.0±4.6, 27	0.653
3	7.3±4.0, 26	8.2±6.3, 25	0.567
4	7.1±4.9, 24	8.7±6.3, 21	0.324
5	7.0±5.5, 23	8.9±7.0, 18	0.294
6	7.1±5.7, 22	8.9±6.8, 14	0.324

Figure 1. Survival rate comparison of recurrent MDD between the n-3 group and the placebo group

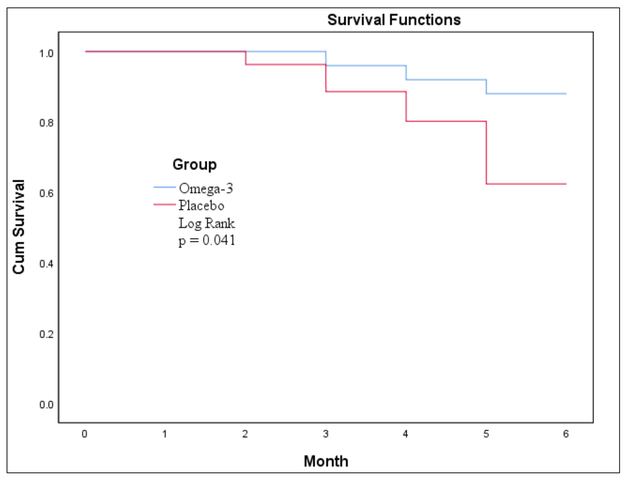

Table 4. Comparison of erythrocyte PUFAs and biochemical parameters levels between two groups at baseline and month 6 (endpoint)

Parameters	Baseline			Month 6		
	n-3 Group (n= 30)	Placebo (n= 30)	p-value[1]	n-3 Group (n= 22)	Placebo (n= 14)	p-value[1]
AST(GOT)	20.39±6.774	21.04±4.514	0.696	21.50±6.587	23.90±5.665	0.379
ALT(GPT)	19.00±17.015	18.65±7.504	0.926	18.12±6.833	16.50±3.171	0.512
BUN	13.12±3.140	13.85±3.416	0.426	14.00±4.648	12.50±2.747	0.352
Creatinine	0.90±0.182	0.99±0.659	0.528	0.90±0.130	0.89±0.202	0.810
Albumin	4.32±0.291	4.35±0.391	0.762	4.32±0.324	4.33±0.284	0.879
Cholesterol	172.00±13.223	175.13±17.254	0.578	164.86±14.253	156.83±57.464	0.726
Triglycerides	78.78±39.788	91.29±39.154	0.330	72.30±40.000	95.90±40.397	0.206
HDL	55.01±13.819	58.50±16.168	0.422	51.09±13.794	57.60±11.520	0.233
LDL	106.39±14.826	103.89±18.000	0.692	93.15±11.728	120.51±26.098	0.119
PT (secs)	11.50±0.665	11.54±0.565	0.836	11.54±0.415	11.62±0.545	0.529
APTT (secs)	30.38±2.196	30.10±2.767	0.717	31.54±2.408	30.37±2.157	0.720
Glucose	92.78±5.954	91.89±7.711	0.654	92.33±5.990	95.91±7.217	0.209
Prolactin	9.98±8.518	10.46±4.966	0.847	10.60±4.916	12.36±6.991	0.579
AA	5.38 ± 0.35	5.38 ± 0.22	0.989	5.83±0.335	5.38±0.284	0.141
EPA	0.80 ± 0.01	0.79 ± 0.02	0.945	0.85±0.041	0.79±0.025	0.023*
DHA	3.23 ± 0.05	3.27 ± 0.05	0.184	3.81±0.660	3.30±0.073	0.119

Mean ± SD (all such values), [1]Mann-Whitney U Test, **p*-value <0.05, n-3: omega-3, GOT: Glutamate Oxaloacetate transaminase, GPT: Glutamate Pyruvate transaminase, BUN: Blood Urea Nitrogen, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, PT: Prothrombin time, APTT: Activated Partial Thromboplastin Time, AA: Arachidonic Acid, EPA: Eicosapentaenoic Acid, DHA: Docosahexaenoic Acid.

- ❖ This is the first study assessing the prophylactic effect of n-3 PUFAs monotherapy to **prevent the recurrence events** in remitted MDD patients.
- ❖ The results highlighted the potential of n-3 PUFAs monotherapy as a prophylactic treatment option for **individuals with a history of MDD.**
- ❖ The primary results of this study revealed a significant reduction in the recurrence of depressive episodes among participants receiving EPA-predominant n-3 PUFAs monotherapy with **better survival rate** at month 6 compared to the placebo.

Conclusion

We conclude that n-3 PUFAs monotherapy had a beneficial effect to prevent the recurrence of MDD and contributed to a better survival rate at month 6 of intervention.

References

2022. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry 9 (2), 137-150.

Malhi, G.S., Mann, J.J., 2018. Depression. Lancet 392 (10161), 2299-2312.

Howes, O.D., Thase, M.E., Pillinger, T., 2022. Treatment resistance in psychiatry: state of the art and new directions. Molecular Psychiatry 27 (1), 58-72.

Thesing, C.S., Bot, M., Milaneschi, Y., Giltay, E.J., Penninx, B., 2020. Bidirectional longitudinal associations of omega-3 polyunsaturated fatty acid plasma levels with depressive disorders. J Psychiatr Res 124, 1-8.

Zhou, L., Xiong, J.Y., Chai, Y.Q., Huang, L., Tang, Z.Y., Zhang, X.F., Liu, B., Zhang, J.T., 2022. Possible antidepressant mechanisms of omega-3 polyunsaturated fatty acids acting on the central nervous system. Front Psychiatry 13, 933704.