A 12-week Randomized Placebo-controlled Trial of Adjuvant Omega-3 Polyunsaturated Fatty Acids in Bipolar Depression.

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Abstract

Background: Bipolar depression remains an unresolved challenge in the management of bipolar disorder. The efficacy of omega-3 polyunsaturated fatty acids (n-3 PUFAs) in managing bipolar depression is still inconclusive. This study aims to assess the efficacy of n-3 PUFAs in managing bipolar depression.

Methods: Thirty patients (n = 30) with bipolar depression were randomized to receive either n-3 PUFAs or identical placebo capsules for 12 weeks. The main outcome was differences in depression severity based on 21-item Hamilton Rating Scale for Depression (HRSD-21) across time points. Other outcomes were differences in mania based on the Young Mania Rating Scale (YMRS), erythrocyte n-3 PUFAs, and routine biochemical parameters.

Results: Patients supplemented with n-3 PUFAs had lower depression severity at week 12 (p=0.022) compared with those in the placebo group. n-3 PUFAs were not superior to placebo on mania across all the study time points. Moreover, supplementation with n-3 PUFAs has significantly increased erythrocyte docosahexaenoic acid (p=0.043) and eicosapentaenoic acid (p=0.011) at the study exit. No significant change in biochemical parameters was associated with n-3 PUFAs.

Conclusion: Adjunctive n-3 PUFAs supplementation for 12 weeks has improved depression severity in patients with bipolar depression and was well tolerated.

Introduction

- Bipolar depression is a major unresolved challenge in managing bipolar disorder.
  - Suboptimal efficacy of standard antidepressants and their potential to induce mania.
- Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have antidepressant effects (Chang et al., 2020; Su et al., 2014) and may be effective in managing bipolar depression.
- Previous trials of n-3 PUFAs in bipolar depression reported incoherent findings.
  - N-3 PUFAs showed a significant effect on bipolar depression (Chiu et al., 2004; Eslahi et al., 2023; Frangou et al., 2006; Stoll et al., 1999; Wozniak et al., 2022).
  - Others did not find any significant effect of n-3 PUFAs on bipolar depression (Frangou et al., 2007; Gracious et al., 2010; Keck et al., 2006; Marangell et al., 2006; Murphy et al., 2012).
- Previous trials were limited by a relatively short follow-up period, the use of DHA-predominant formulations, lower doses of the n-3 PUFAs or possible placebo response.
- We aimed to assess the efficacy of high-dose n-3 PUFAs (EPA-predominant) in managing bipolar depression through a 12-week double-blind placebo-controlled trial.

Method

- Thirty patients were randomized to receive either 3g/day of n-3 PUFAs (2:1 EPA: DHA) or placebo.
- All eligible patients were enrolled on a single-blind, 1-week placebo lead-in before the randomization, and those patients with a placebo response were excluded.
- The patients were interviewed and rated with the Hamilton Rating Scale for Depression (HRSD) and Young Mania Rating Scale (YMRS) at baseline and weeks 1, 2, 4, 6, 8, and 12.
- Erythrocyte EPA and DHA and biochemical parameters levels were measured at baseline and week 12

Results

Table 1. Baseline characteristics of the patients

Parameters	n-3 PUFAs (n = 15)	Placebo (n = 15)	*p-value
Age	38.11 ± 11.03	39.01 ± 12.12	0.829
Sex ratio (male: female)	4:11	3:12	0.680
HRSD	20.07 ± 2.52	19.9 ± 2.09	0.875
YMRS	0.87 ± 1.1	1.79 ± 2.1	0.276

Data presented as a ratio or mean ± SD. *Mann-Whitney U test unless stated otherwise. The difference in sex ratio was assessed using Chi-square. HRSD: Hamilton rating scale for depression, n-3 PUFAs: omega-3 polyunsaturated fatty acids, YMRS: Young mania rating scale.

Table 2: Erythrocyte n-3 PUFAs levels and biochemical parameters of the patients at the study entry and exit.

Parameters	Study entry			Study exit		
	n-3 PUFAs (n = 15)	Placebo (n = 15)	p- value	n-3 PUFAs (n = 15	Placebo (n = 15)	*p-value
GOT	17.75±3.20	16.00±4.76	0.680	22.27 ± 15.87	20.23 ± 9.50	0.462
GPT	17.88±9.61	14.00±6.22	0.575	19.73 ± 20.15	16.15 ± 11.18	0.485
BUN	12.25±4.03	10.00±2.94	0.103	11.47 ± 4.12	14.25 ± 4.39	0.348
Creatinine	1.01±0.23	3.23±4.52	0.566	0.97±0.25	1.03±0.34	0.177
Albumin	4.66±0.40	4.43±0.25	0.256	4.48±0.42	4.28±0.47	0.330
Cholesterol	190.88±26.05	184.00±22.06	0.840	191.80±36.00	188.62±46.65	0.662
Triglycerides	95.14±27.69	134.50±69.65	0.154	158.50±108.92	108.00±61.18	0.207
HDL	49.56±14.27	52.90±6.04	0.527	55.45±14.84	52.09±10.38	0.669
LDL	116.11±21.25	118.63±33.03	0.623	116.30±30.22	123.86±46.48	0.880
PT (secs)	13.71±1.40	11.07±0.83	0.259	11.58±0.58	11.29±0.56	0.565
APTT (secs)	32.63±4.52	29.63±2.28	0.057	31.68±3.53	28.79±3.06	0.312
Prolactin	11.35±1.03	9.90±1.45	0.322	17.83±12.67	11.73±8.41	0.170
**Lithium	0.68±0.62	0.85±0.35	0.780	0.46±0.31	0.52±0.34	0.738
**Valproate	73.96±5.56	72.90±3.68	0.997	62.53±38.95	62.65±36.56	0.832
DHA	3.20±0.02	3.24±0.04	0.519	4.14±0.70	3.19±0.03	**0.043**
EPA	0.76±0.03	0.78±0.03	0.623	0.98±0.03	0.70±0.03	**0.011**

Data presented as mean ± SD. *Mann-Whitney U test. **BD medications. BD: Bipolar disorder, N-3 PUFAs: omega-3 polyunsaturated fatty acids 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; EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid.

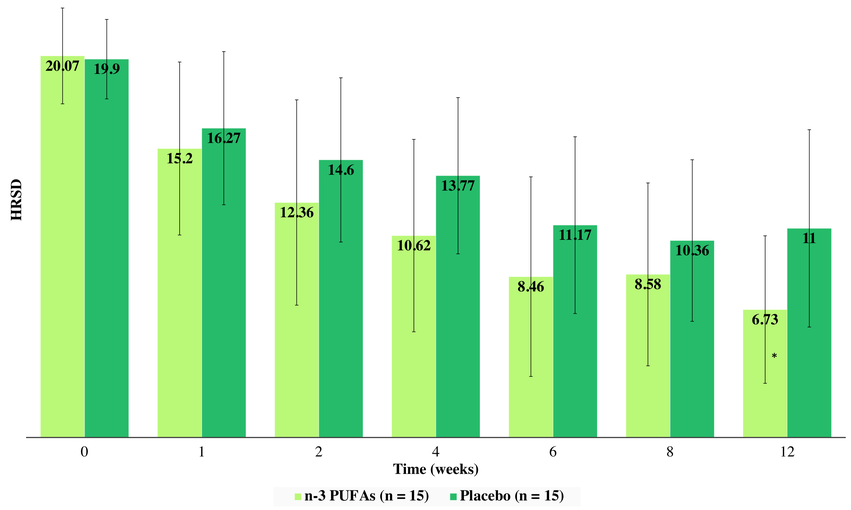

Figure 1: Depression severity of the patients across time points. Data presented as Mean ± SD of HRSD scores across time points *p < 0.05 based on the Mann-Whitney U-test. HRSD: Hamilton rating scale for depression, n-3 PUFAs: omega-3 polyunsaturated fatty acids.

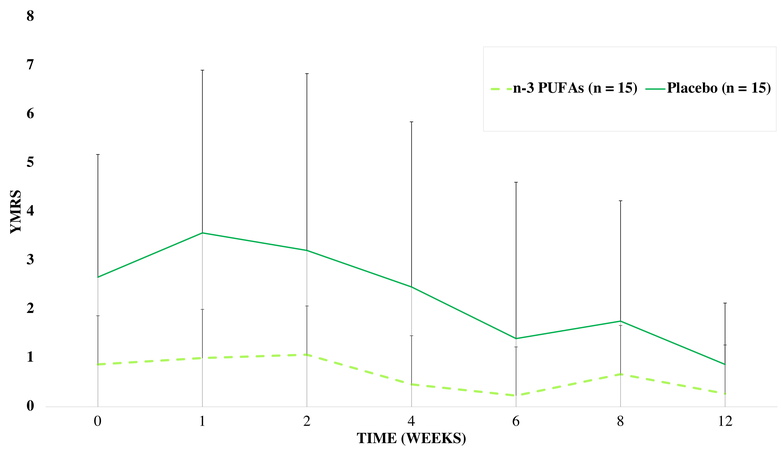

Figure 2: YMRS of the patients across time points. Data presented as Mean ± SD of HRSD scores across time points and intergroup differences in YMRS was assessed using the Mann-Whitney U-test. n-3 PUFAs: omega-3 polyunsaturated fatty acids, YMRS: Young Mania Rating Scale.

Conclusion

- Adjunctive n-3 PUFAs supplementation for 12 weeks has demonstrated significant efficacy on bipolar depression and did not induce mania.
- N-3 PUFAs supplementation was highly tolerated and did not pose any significant safety concerns.
- N-3 PUFAs may be promising alternatives to standard antidepressants in the treatment of bipolar depression owing to their safety and low potential to induce mania.