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Original Research Article

A prospective, randomized, open-label study to compare the different dosage forms of omega 3 fatty acids as an adjuvant in the bipolar depression

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ABSTRACT

Background: Bipolar affective disorder is a chronic disorder in which bipolar depression (BD) has poor prognosis than mania. There is a lack of universal pharmacotherapy for BD, with standard drug therapy having multiple long term adverse effects. Omega-3 fatty acids (O3FAs) act on key BD pathology and found to have reduction on symptom severity in BD. Thus, this study aims to compare efficacy and safety of 2 different doses, 1.2 g/day and 2.4 g/day of O3FAs with control group in BD patients.
Methods: This is an interventional, randomized, open-label, prospective and parallel study of 12 weeks with patients (n=90) randomly divided into three groups. This study compared the control group (Group A, n=30) on standard drugs only, with 1.2 g/day OD of O3FAs (Group B, n=30) and 2.4 g/day BD of O3FAs (Group C, n=30). Evaluation of efficacy was done on basis of Hamilton Depression Rating Score (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impression (CGI) scales every 15 days for 3 months. Adverse effects were reported every 15 days for 3 months.
Results: After 3 months of treatment, Group C had statistically significant improvement in HAM-D ($p<0.01$), MADRS ($p<0.01$) and CGI ($p<0.01$) scores as compared to group A and B. Group A (37) had adverse effects than Group B (21) and C (17) at 3 months.
Conclusions: Group C seems to had better efficacy and safety as compared to Group B and baseline drugs alone. Further extensive research with large sample size and studies with longer duration are required to validate the role of O3FAs in BD.

Keywords: CGI, Docosahexaenoic acid, Eicosapentaenoic acid, HAM-D, MADRSs

INTRODUCTION

Among mood disorders, bipolar affective disorder (BAD) is the common cause for disability. In BAD, patients may have recurrent episodes in which there could be an elevation of mood with increased energy and activity known as Mania and hypomania or a lowering of mood with decreased energy and activity called depression. There is a complete absence of symptoms in between such episodes. Manic episodes usually begin abruptly and last for 2 weeks to 4-5 months. Patients having bipolar depression (BD), have longer episodes and has a relatively poorer prognosis than mania.

Prevalence of BAD globally is around 0.3-1.2%. The prevalence of BAD in India is around 0.6% in both sexes and around 5% in Punjab.[1-4] BD patients have the feeling of sadness and hopelessness, feels tearful, guilt and agitation, have thoughts of self-harm and suicidal ideation, sleep disturbance, alterations in eating habits, lack of

energy and interest in previously enjoyable tasks, difficulty in making decisions for any problem and difficulty in remembering. Depressive symptoms are assessed by various scales like Hamilton depression rating scale (HDRS/HAM-D), Montgomery-Asberg depression rating scale (MADRS) and Clinical global impression (CGI) scale.[5-7]

Pharmacological treatment mostly includes a combination of two or more drugs from antipsychotics, anticonvulsants, antidepressants, lithium and benzodiazepines. Psychotropic drugs for treating BD may be effective but can cause significant acute and long-term adverse effects.[8-11] Polyunsaturated fatty acids (PUFAs) are two types, omega-6 fatty acids (O6FAs) and Omega-3 fatty acids (O3FAs). O3FAs consist of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

EPA helps in regulation of inflammation, immune responses & cell communication and DHA improves membrane fluidity & receptor nesting sites. It affects intercellular and intracellular signalling pathways in neurons and other cell types. A novel susceptibility locus in BAD at 11q12.2 contain regulatory genes encoding Fatty acid desaturase (FADS1/2/3) enzymes.

The balance between O6FAs and O3FAs is mandatory as they compete for FADS enzymes. FADS genotype leads to development of BD via increasing O6FAs which leads to increased TNFα level and increased inflammation and decreased O3FAs. Altered PUFAs also have role in neuronal cell functioning and lowers brain-derived neurotrophic factor (BDNF) levels in depression. These phenomena form the vital features of the pathogenesis of BD.[12-14]

O3FAs levels are is found to be less in the erythrocyte membrane of BAD patients as compared to healthy individuals.[15,16] Low O3FAs intake was associated with low EPA and DHA levels and supplementation with O3FA's may help in mood improvement. Various health organizations like American psychiatric association, the international college of neuropsychopharmacology and the royal Australian & New Zealand college of psychiatrists have suggested O3FAs as a supplement in the vast dose range of 1-9 g/day for mood disorders.[17-19]

The recommended daily allowance (RDA) for Indians according to Indian council of medical research, India for O3FA's is 200 mg/day and Indians have been found to consume only 20-50 mg/day.[20,21] Considering this data, it is proposed to assess the use of O3FA's in BD patients in Indian population.

Vital aspects of O3FAs like therapeutic dose, duration of treatment needed and the onset of improvement in BD are still unknown. Studies and data are scarcely available on all aspects of O3FAs in BD.[22-27] Therefore, in present study, we compared the efficacy and safety of two different doses 1.2 g/day OD and 2.4 g/day BD of O3FAs with a control group in BD over 3 months.

Aims and objectives

Primary objective

To compare and evaluate the efficacy of 2 different doses, 1.2 g/day OD and 2.4 g/day BD of O3FAs with control group in BD patients.

Secondary objective

To compare the adverse effects of all the drugs.

METHODS

Study design

This was a randomized, open-label and prospective study.

Study place

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Study population

Diagnosed cases of BD defined according to the International classification of diseases 10th revision (ICD-10) of either sex, between the age group of 15-65 years.

Study duration

The study duration was of 90 days.

Sample size

The sample size, N=90 (30 in each group).

Inclusion criteria

Patient diagnosed with BD according to ICD 10, of either sex aged from 15 to 65 years, visiting psychiatry OPD were recruited.

Exclusion criteria

Patients refusing to give written informed consent. Patients of known hypersensitivity to O3FAs were excluded. Patients with any organic/secondary cause of depression or having any major comorbidities like cardiovascular, renal and hepatic diseases or psychiatric comorbidities like schizophrenia or psychosis and pregnant women were not included. Patients on anticoagulant drugs or having bleeding disorders were also not included. Before starting the study, approval of Institutional Ethics Committee (No. 3356/D-26/2020) and thesis committee was taken. Patient recruitment was started on November 2021 and ended on

July 2022. 97 diagnosed cases of BD, defined according to ICD-10, of either sex, between the age group of 15-65 years who met the inclusion criteria, were recruited in the study. A written informed consent was taken from all the patients prior to enrolment and after explaining the study particulars in easily understandable vernacular language. A complete history was obtained from all the patients included in the study and a general physical examination was done. A detailed history of prior consumption of omega-3 fatty acids was taken from the patient. Patients were randomly divided into 3 groups- A, B and C consisting of 30 patients each. GraphPad software (2020 version) was used for generating random numbers. Mood disorder questionnaire (MDQ) was used for screening the patients for BD. Detailed history of prior consumption of O3FAs was taken from patients. Patients were advised to take O3FAs capsules in morning and evening depending on dose. Group A patients were given ongoing therapy only. Group B patients were given 1.2 g/day OD of O3FAs+ongoing therapy. Group C patients were given 2.4 g/day BD of O3FAs+ongoing therapy.

Investigations

A complete history was obtained from all the patients included in the study and a general physical examination was done. A detailed history of prior consumption of omega-3 fatty acids was taken from the patient.

Depression severity

At baseline, Hamilton depression rating score (HAM-D), Montgomery-Asberg depression rating scale (MADRS) and Clinical global impression (CGI)-Severity scale (to asses severity of symptoms) were assessed. From first follow-up (15 days), CGI (improvement scale score (to assess response of treatment) and adverse effects (of ongoing drugs also) were studied. Follow up was done every 15 days for 90 days.

Statistical analysis

The efficacy and safety data were recorded and analysis was done for patients who completed 90 days of the study phase. Data generated from the study was tabulated with respect to all parameters at specific intervals and results were expressed as Mean±SD of each variable. The study used Chi-square test for categorical data and 't' test and ANOVA tests for continuous data by using IBM SPSS software V21. Post hoc Tukey-Kramer 't' test was used for pairwise comparison of adverse effects. A p value of <0.05 was taken as statistically significant and that of <0.001, as highly significant.

RESULTS

The mean age (years) of patients was 44.73±15.74 in group A, 43.00±11.67 in group B and 35.43±11.54 in group C, were comparable (Table 1). Baseline population and their demographic parameters were comparable in all the groups (Table 2). Total 90 patients were analysed in this study after excluding dropouts. There were 3 dropouts (1–no relief in symptoms, 1-need for dose adjustment, 1–started alternate treatment) in group A. In group B, 2 dropouts (1-needed dose adjustment and 1–felt no improvement) and in Group C 2 dropouts (1- needed dose adjustment and 1 – felt no improvement).

Hamilton depression rating score

The mean HAM-D score started to decrease at 15 days, compared to baseline, in group C than group A and group B but significant reduction was seen from 60 days and 90 days in group C (5.23±4.36 in group A, 7.95±5.77 in group B and 13.33±9.80 in group C) ($p<0.001$) (Figure 2). On comparison, group C (60.15±31.5) showed a highly significant decrease in percentage change in mean HAM-D score ($p<0.001$) over 90 days of treatment than groups A (26.50±9.7) and groups B (41.08±15.5) (Table 3, Figure 1).

Montgomery-Asberg depression rating score

In group C, improvement in severity of depression symptoms by reduced mean MADRS score became statistically highly significant ($p<0.001$) at 15 days whereas in group A and group B significant reduction was seen from 60 days and 90 days (5.73±3.76 in group A, 9.23±7.99 in group B and 14.03±9.59 in group C) (Figure 3). The percentage change in mean MADRS score over 90 days was highly significant in groups C (58.87±29.52) than groups A (27.64±10.7) and groups B (43.01±16.6) ($p<0.001$) (Table 3, Figure 1).

Clinical global impression severity scale score

The mean Clinical global impression severity scale (CGI–S) score was declined at 15 days showing drop in depression symptoms compared to baseline in group A, group B and group C but significant reduction was seen from 60 days and 90 days in group C (1.31±0.74 in group A, 1.70±0.83 in group B and 3.14±0.89 in group C) ($p<0.001$) (Figure 4). Group C (64.47±33.40) had a highly significant ($p<0.001$) decrease in percentage change in mean CGI–S score than groups A (26.47±9.02) and groups B (38.37±12.45) throughout the study period of 90 days (Table 3, Figure 1).

Clinical global impression improvement score

On comparison, Group C (3.01±0.86) showed a highly significant ($p<0.001$) decline in mean CGI-I (global improvement) score at 45 days indicating improvement with treatment as compared to baseline in group A and group B. Significant drop in mean CGI-I score was seen from 60 days and 90 days in group A and group B (1.16±0.76 in group A and 1.67±0.61 in group B) (Figure 5). The percentage change in mean CGI–I score over 90 days was highly significant in groups C (63.42±34.37) than groups A (25.43±10.23) and groups B (37.69±11.45) ($p<0.001$) (Table 3, Figure 1).

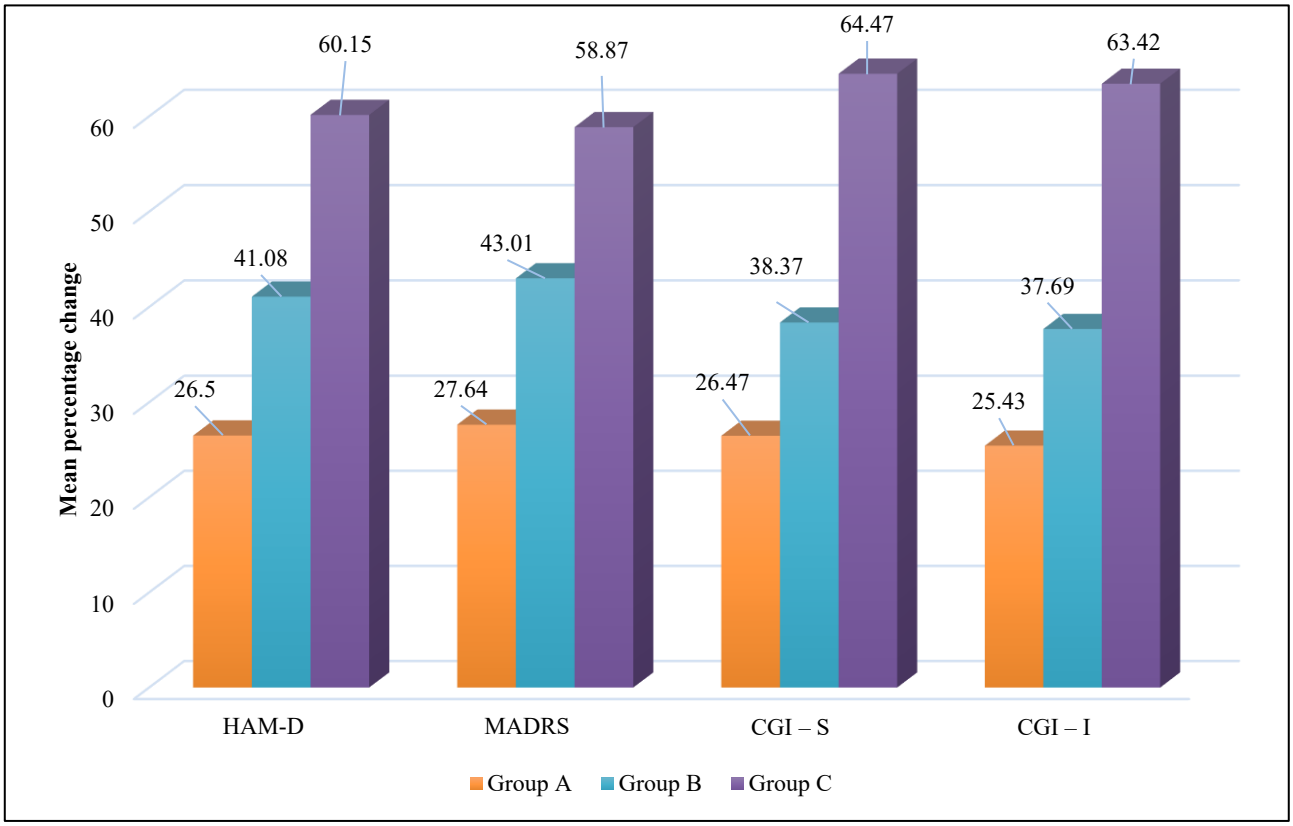

Figure 1: Intergroup comparison of depression parameters in Group 'A', 'B' & 'C' over '90' days of treatment.

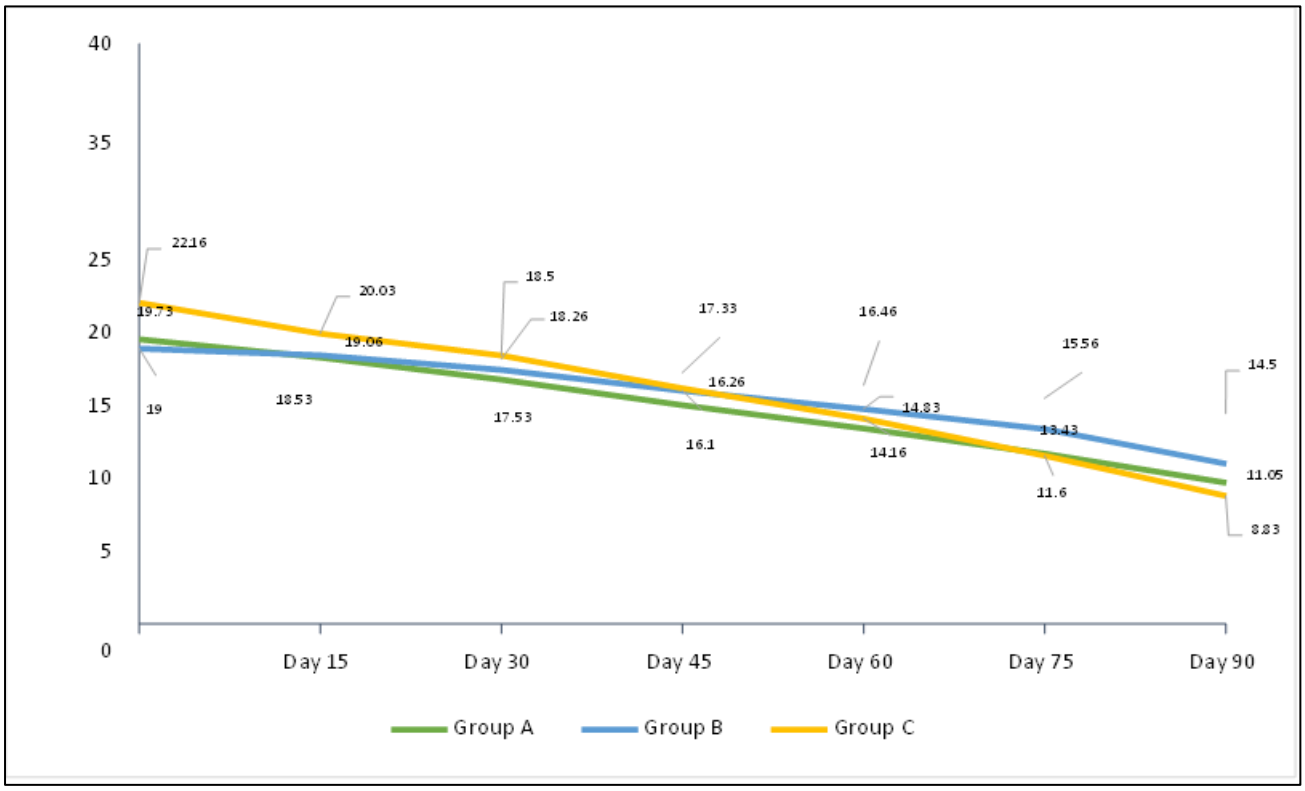

Figure 2: Intragroup comparison of mean HAM-D score in group 'a', 'b' & 'c' over '90' days of treatment.

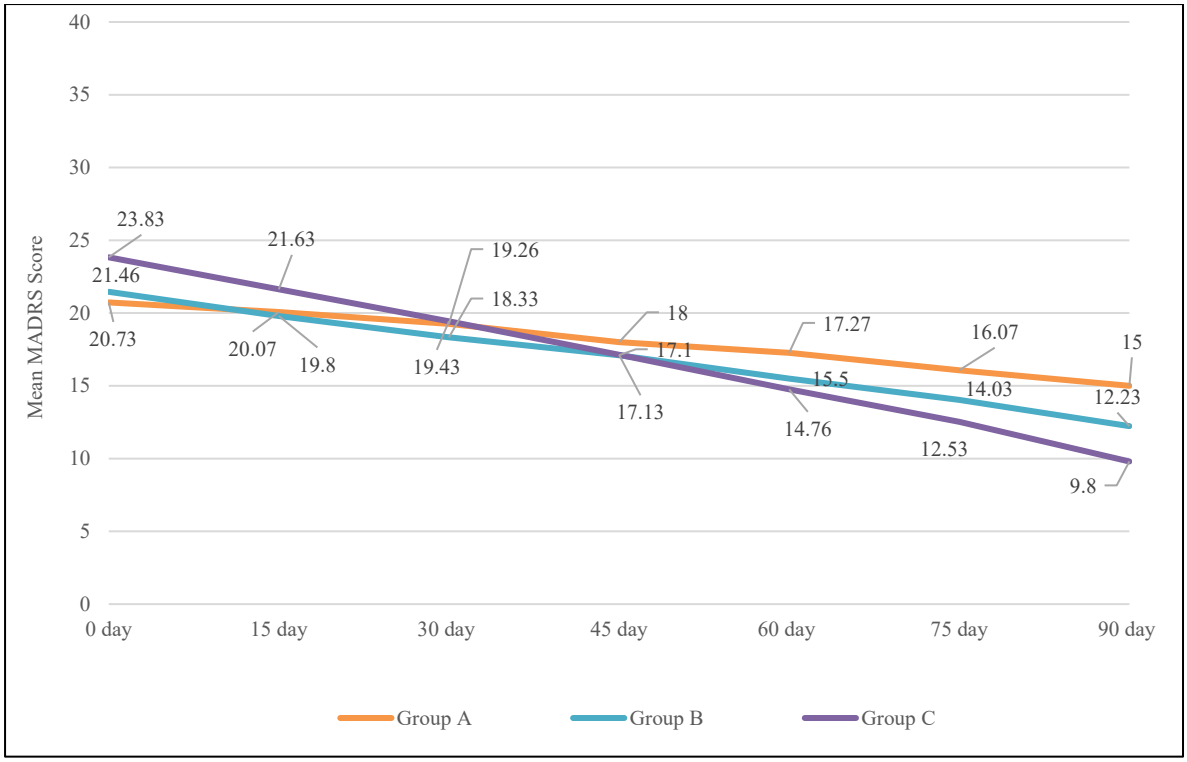

Figure 3: Intragroup comparison of mean MADRS score in group 'A', 'B' & 'C' over '90' days of treatment.

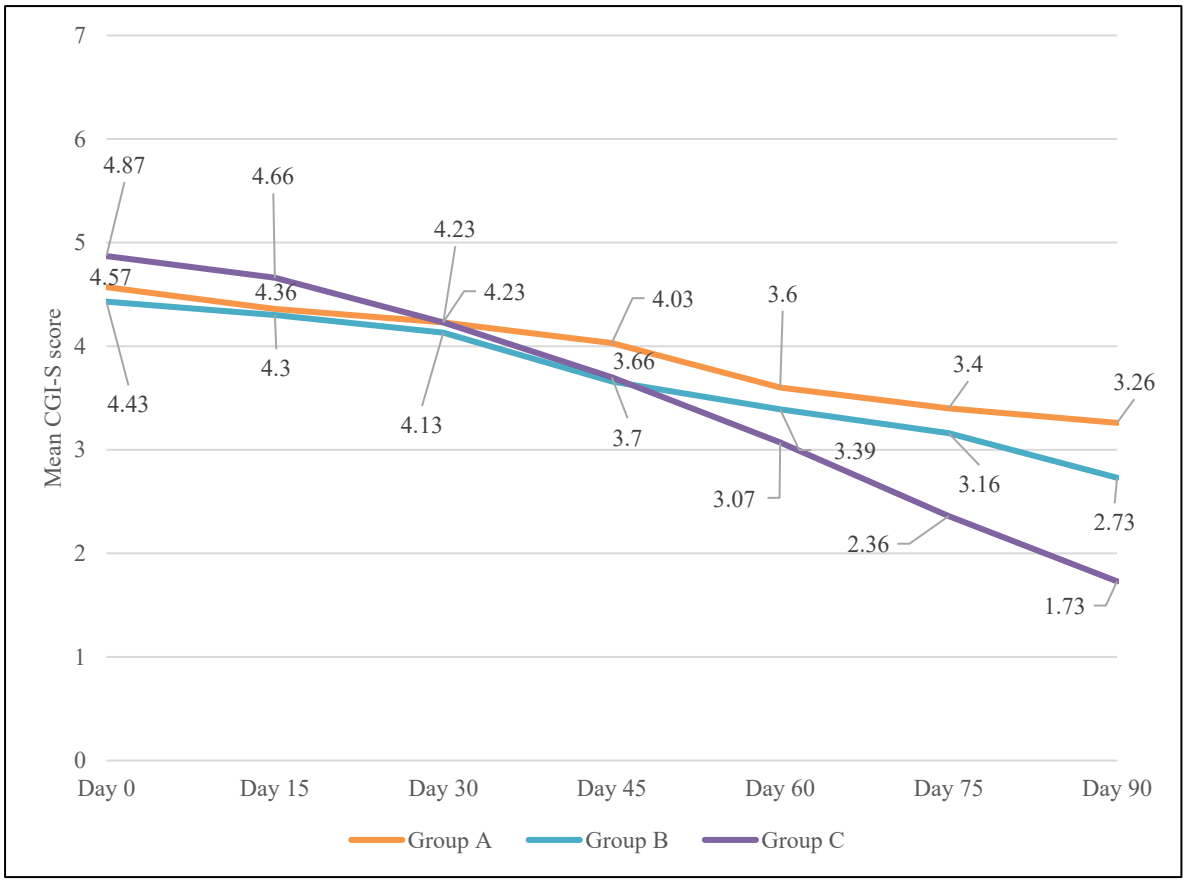

Figure 4: Intragroup comparison of mean CGI-S score in group 'A', 'B' & 'C' over '90' days of treatment.

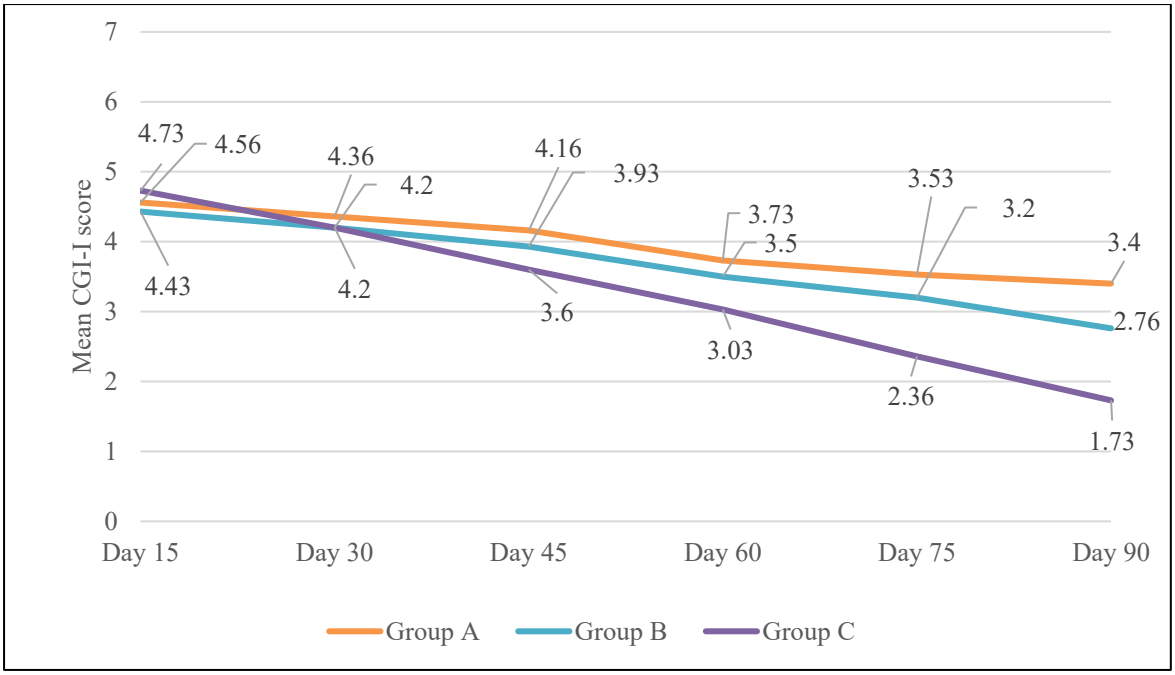

Figure 5: Intragroup comparison of mean CGI–I score in group 'A', 'B' & 'C' over '90' days of treatment.

Safety profile

In Group A, adverse effects observed (total no.37) were constipation (n=3), dyspepsia (n=4), diarrhoea (n=1), nausea (n=3), anxiety (n=1), dry mouth (n=1), fatigue (n=4), headache (n=3), lethargy (n=5), insomnia (n=5), weight gain (n=6) and hyperglycemia (n=1). Group B showed adverse effects (total no.21) of constipation (n=1), dyspepsia (n=3), diarrhoea (n=1), nausea (n=3), dry mouth (n=1), fatigue (n=2), headache (n=1), lethargy (n=1), insomnia (n=3), weight gain (n=3) and hyperglycemia (n=2). In group C adverse effects (total no.13) seen were constipation (n=1), dyspepsia (n=4), diarrhoea (n=1), nausea (n=2), headache (n=1), insomnia (n=2), weight gain (n=1) and hyperglycemia (n=1).

The prevalence of adverse effects in group A was statistically significant over group B and the difference in group B was statistically significant over group C ($p<0.05$) (Table 4). On further analysis, no statistically significant difference was found between group B and group C. The prevalence of adverse effects in group A was statistically significant among groups B and C. So, group C had better safety profile among all 3 groups. There were no serious/life-threatening side effects and there was no drop-out due to adverse effects. (Table 5).

Table 1: Gender distribution in the group 'A', 'B' & 'C'.

Demographic characteristics		Group A (n=30) N (%)	Group B (n=30) N (%)	Group C (n=30) N (%)	Total (n=90) N (%)	P value
Gender	Male	17 (56.6)	19 (63.3)	19 (63.3)	55 (61)	1.25
	Female	13 (43.3)	11(36.6)	11(36.6)	35 (39)	

p>0.05: Not significant *p<0.05: significant **p<0.001: highly significant (p-value: Chi-square test).

Table 2: Intergroup comparison of demographic parameters at day '0'.

Parameters		Group A (Mean±SD)	Group B (Mean±SD)	Group C (Mean±SD)	P value
Body mass index (kg/m^2)		23.89±1.80	23.37±2.57	22.93±1.87	0.211
Haemoglobin (mg/dl)		11.39±1.43	11.4±1.28	11.56±1.55	0.876
Total leucocyte count (cell/mm^3)		7173.39±1508.8	6643.3±1296.3	7296.7±1536.79	0.186
DLC (%)	Neutrophils	58.03±7.82	59.93±8.31	59.40±6.36	0.604
	Lymphocytes	30.43±5.53	29.70±5.45	27.70±5.66	0.148
	Monocytes	4.37±2.33	4.47±2.24	4.67±2.59	0.885
	Eosinophils	3.17±1.62	3.10±1.56	3.50±1.50	0.571
	Basophils	0±0	0±0	0±0	-
Fasting blood sugar (mg/dl)		86.97±9.72	90.13±16.77	82.33±6.16	0.058

Continued.

Parameters	Group A (Mean±SD)	Group B (Mean±SD)	Group C (Mean±SD)	P value
Aspartate aminotransferase (units/l)	24.93±6.57	24.60±6.55	24.57±6.41	0.086
Alanine Transaminase (units/l)	24.1±6.9	24.5±6.5	24.80±5.85	0.202
S. Creatinine (mg/dl)	0.84±0.20	0.84±0.17	0.90±0.16	0.32
Blood urea (mg/dl)	17.50±2.49	18.33±2.48	18.43±2.56	0.291
T3 (nmol/l)	1.89±0.37	1.98±0.32	1.90±0.42	0.600
T4 (nmol/l)	109.73±18.63	115.57±16.69	107.47±18.68	0.205
Thyroid-stimulating hormone (mIU/ml)	1.72±0.87	2.03±1.00	2.16±0.91	0.170
T. cholesterol (mg/dl)	136.53±32.42	145.80±37.19	147.77±33.07	0.185
Serum triglycerides (mg/dl)	135.25±17.69	144.61±27.86	146.24±24.63	0.079
High-density lipoproteins (mg/dl)	58.65±8.11	56.11±8.10	54.08±10.39	0.080
Low-density lipoproteins (mg/dl)	111.0±14.58	130.8±29.35	134.8±32.05	0.190
Prothrombin time (seconds)	12.20±0.72	11.91±0.69	12.16±0.67	0.236
Activated partial thromboplastin time (seconds)	28.84±1.76	29.68±2.11	29.12±2.59	0.321
International normalized ratio	0.92±0.15	0.90±0.14	0.93±0.12	0.258

p>0.05: Not significant *p<0.05: significant **p<0.001: highly significant (p-value: Unpaired T-test).

Table 3: Intragroup comparison of depression parameters in Group 'A', Group 'B' and Group 'C' over '90' days of treatment.

Parameters	Group A		Group B		Group C	P value
	% Change	P value	% Change	P value	% Change	
HAM-D Score	26.50±9.75	<0.001**	41.08±15.59	<0.001**	60.15±31.59	<0.001**
MADRS Score	27.64±10.76	<0.001**	43.01±16.60	<0.001**	58.87±29.52	<0.001**
CGI–S score	26.47±9.02	<0.001**	38.37±12.45	<0.001**	64.47±33.40	<0.001**
CGI–I score	25.43±10.2	<0.001**	37.69±11.45	<0.001**	63.42±34.37	<0.001**

p>0.05: Not significant *p<0.05:significant **p<0.001:highly significant (p-value: Unpaired T-test).

Table 4: Comparison of adverse effects in groups 'A', 'B' and 'C' over '90' days of treatment.

	Adverse effect	Group A (N)	Group B (N)	Group C (N)	P value
Gastrointestinal	Constipation	3	1	1	
	Dyspepsia	4	3	4	
	Diarrhoea	1	1	1	
	Nausea	3	3	2	
General	Anxiety	1	0	0	
	Dry mouth	1	1	0	
	Fatigue	4	2	0	p=0.003
	Headache	3	1	1	
	Lethargy	5	1	0	
	Insomnia	5	3	2	
Metabolic	Weight gain	6	3	1	
	Hyperglycemia	1	2	1	
Total number		37	21	13	

p>0.05: Not significant *p<0.05: significant **p<0.001: highly significant (p-value: ANOVA).

Table 5: Post hoc Tukey-Kramer analysis for comparison of adverse effects between groups A, B and C over 90 days of treatment.

Groups	Results
A vs B	Significant
B vs C	Not–significant
A vs C	Significant

The prevalence of adverse effects in Group A was statistically significant over group B and C. No significant differences in Group B over Group C were found.

DISCUSSION

Upon comprehensive literature search, there was a lack of studies investigating the dose range of O3FAs especially in Indian BD subjects. Moreover, no equivalent studies were found comparing the efficacy and safety of O3FAs in BD in Punjab, where the present study was conducted. Analysis of demographic profile in this study showed that the prevalence of BD was more in middle age group. The mean age (years) of patients was 44.73±15.74 in group A, 43.00±11.67 in group B and 35.43±11.54 in group C were comparable among the 3 groups.

The results in the present study were similar to a study conducted by Stoll et al, in the USA which also had patients with a mean age of 41.73±6.8 years in the O3FAs group and 44.6±10.4 years in the placebo group.[25] There was an overall male predominance (61%) as compared to females (39%) recruited in the present study (Table 1). Gender distribution in all the groups was comparable (p=1.25) (Table 1) which is in contrast to the Global Burden of Disease study 1990-2017, in which no differences in the prevalence of BAD between males and females was observed in India.[4]

Variable reports are there as far as gender preponderance is concerned. Also, a meta- analysis by Bernardo Dell'Osso et al, suggested that BAD affects women more frequently as compared to men, but it was not observed in the present study.[28] Presence of positive family history was found in 11 (12.22%) of BAD patients. These observations in the present study are as per the meta-analysis by Wilde et al, in which a systematic review of studies published between 1977 and July 2011 was conducted using the MEDLINE and EMBASE databases. From 22 studies, it was found that on comparing the first-degree relative (FDR) of one BAD proband to healthy control probands, estimates for BAD were Odds Ratio (OR)=7.92 (95% Confidence Interval (CI) 2.45–25.61) and OR=6.58 (95% CI 2.64–16.43) for FDRs of two BAD probands. Most patients with a positive family history of BAD had unipolar depression, so this familial similarity signifies a common genetic link between the two.[29]

Assessment of dietary patterns in the Punjabi population for O3FAs intake was carried out. In the present study, dietary pattern in group A, B and C was observed as vegetarian (66%, 73.33% and 70% respectively) and non-vegetarian (33%, 26.67% and 30% respectively) including occasional fish consumption (6.67%,6.67% and 3.33 respectively). These observations are similar to studies in which it has been found that O3FAs intake is very less in Indians diets. As seen in a prospective pregnancy cohort study by Dwarka Nath et al, in Bangalore, 829 pregnant women were assessed by food frequency questionnaire on their dietary portions and measurement of erythrocyte membrane phospholipid fatty acid concentration (from baseline and at end of study) on every follow-up. Low dietary intake of O3FAs was found by the end of pregnancy in all the participants.[21] According to data available on diet taken by Indians, intake of O3FAs is only about 20-50 mg per day, which is way less than given RDA.[20,21]

Hamilton depression rating score and clinical global impression score

Our results are in concordance with a pilot and parallel clinical trial with a 2×2 study design conducted by Arnold et al. Patients were randomized into 4 treatment arms. In the first treatment group, patients were given psychoeducational psychotherapy (PEP)+O3FAs (1.4 g of EPA, 0.2 g of DHA and 0.27 g of other O3FAs per day), the second group was given O3FAs, PEP monotherapy in the third group and fourth group was placebo group (mainly oleic and linoleic acid). BD patients (n=23) had child depression rating scale-revised (CDRS-R) (the pediatric equivalent of HAM-D) improvement (p=0.048 for O3FAs monotherapy, p=0.050 for combined treatment). Mean change observed in CDRS-R was from baseline 40.53±10.27 to end of study 29.11±8.83 (p<0.001).[22] In line with the present study, a pilot clinical trial to check the efficacy of O3FAs in juvenile bipolar disorder was done by Clayton et al, patients were randomized to receive a total of 360 mg/d EPA and 1560 mg/day DHA along with concomitant medications.[18] The observed significant reduction in mean HAM-D was from baseline 12.0±1.52 to the end of 6 weeks of study was 5.6±1.64 (p=0.002).[23]

Similarly, in a randomized clinical trial (RCT) by Frangou et al, BD patients were given EPA 1 g/day (n=24) and EPA 2 g/day (n=24) and placebo (n=26) as an adjunctive treatment along with psychotropic medications for 12 weeks. The mean change observed in HAM-D from baseline to end of the study was, in the placebo group 15.4±5.0 to 13.5±6.7, in EPA 1 g/day group 14.7±4.3 to 9.2±5.4 and EPA 2 g/day 14.8±5.6 to 9.9±6.6. The mean change observed in CGI score from baseline to end of the study was, in the placebo group (3.0±0.9 to 3.1±1.3), in EPA 1 g/day group (3.0±1.1 to 2.4±1.0) and EPA 2 g/day (2.9±1.1 to 2.3±1.1). The EPA group showed better results as compared with the placebo in the CGI (p=0.04) scores and in the HAM-D (p=0.04) scores. In this study by Frangou et al, no statistical significant difference (p=0.59) was seen among 1 g/day and 2 g/day EPA doses.[24]

O3FAs had shown a decrease in HAM-D and CGI scores on much higher doses also, as seen in an RCT by Stoll et al. The patients (n=30) with BD given 9.6 g/day of O3FAs (6.2 g/day of EPA+3.4 g/day of DHA) (n=14) or placebo (n=16) as an add-on therapy with psychotropic drugs. The duration of study was 16 weeks. The mean change observed in the O3FAs group in HAM-D was from baseline (9.5±5.7) to the end of the study (4.9±5.3). The mean change observed in the O3FAs group in CGI score was from baseline (3.4±1.3) to end of study (2.5±1.1). Statistically significant improvement was seen in the HAM-D (p=0.002) and CGI scale (p<0.01) at the end of the study duration.[25] Onset for significant reduction in mean HAM-D varies in different studies with different

doses of O3FAs. Early onset for significant improvement in present study with group C occurred at 15th day in HAM-D and CGI-S scores and on 45th day in CGI-I score, then in group A and B (in HAM-D at 45th days, CGI-S at 45th days and CGI-I at 60th days).

Montgomery-Asberg depression rating score

The result contrary to the present study was seen in a double-blind, RCT performed by Murphy et al. Study was conducted for 16 weeks. Patients with type I bipolar disorder were divided into 3 groups. Forty-five patients were given EPA 3 g/d and placebo, EPA 3 g/d and Cytidine 2 g/d or only placebo. There was no significant difference observed between all three groups in terms of reduction of depressive symptoms with MADRS score (p=0.83) at end of 16 weeks.[26]

In the present study, significant improvement was observed in MADRS score at 15th day in group C (higher dose) than in group A and B (at 30th day). Thus, group C might be better than groups A and B in efficacy with early onset of improvement in symptoms of depression.

Safety profile

Findings of the present study on O3FAs in the same dose range are supported by an RCT, carried out by McPhilemy et al. Study was done for 52 weeks in patients (n=80) diagnosed with BAD. Patients were randomized to either receive 1 g/day of EPA +1 g/day of DHA (n=40) or placebo (n=40) concomitantly along with psychotropic drugs. Total adverse events reported in patients were 4 (10.0%) in the O3FAs group and 10 (25.0%) in the placebo group. Patients had gastrointestinal symptoms as the main adverse effects in the 4 (10.0%) O3FAs group and 7(17.5%) in the placebo group. There were no significant differences in both groups in terms of adverse effects (p=0.08).[27]

The side effect profile of O3FAs in the present study (same dose range) is also in line with Frangou et al. An RCT was done for 12 weeks. BD patients (n=75) were divided into 3 groups EPA 1 g/day (n=24) and EPA 2 g/day (n=24) and placebo (n=26) as an adjunctive treatment along with psychotropic medication. Most reported side-effects were loose stools (3 (11.5%) in the placebo group, 3 (12.5%) in the 1 g/day ethyl-EPA group and 6 (25%) in the 2 g/day ethyl-EPA group) and gastrointestinal discomfort (3 (11.5%) in the placebo group, 1 (4.6%) in the 1 g/day ethyl-EPA group and 2 (8.3%) in the 2 g/day ethyl-EPA group). There were no significant differences between the groups in these side effects (p=0.59). The placebo group also reported constipation in 2 (7.6%) patients. In the 1 g/day ethyl- EPA group, flatulence in 1 (4.6%) and nausea in 1 (4.6%) patient had occurred. In the 2 g/day ethyl-EPA group unpleasant taste 1 (4.6%) was also reported.[24]

The variation in adverse effects of O3FAs observed may result from the different doses of O3FAs and different baseline drugs in different studies. In the present study, groups B and C had fewer adverse events than group A. The prevalence of general adverse effects in group C was less as compared to groups A and B. As seen in the present study, O3FAs as adjunctive treatment in a dose of 2.4 g/day had the advantage of higher efficacy, safety and tolerability along with psychotropic drugs.

Novelty of the study

This is the first study to compare the efficacy and safety of different doses of O3FAs therapy along with ongoing antipsychotic therapy in Indian BD subjects. This is the first study to assess the dietary patterns of O3FAs intake in the Punjabi (North Indian) population. This is the first study to extensively evaluate both HAM-D and MADRS scores in BD patients receiving O3FAs therapy as per the available literature search. First study of different dose comparison of both components of O3FAs i.e., EPA+DHA in the Indian population.

As with the majority of the studies, the present study is also subjected to a few limitations which are small sample size (n=90) and time constraint (3 months). Concomitant medications could potentially mask the true effects of O3FAs supplementation, although this limitation affects all clinical trials of this nature in BD. Erythrocyte O3FAs levels (performed with gas chromatography) were not assessed.

CONCLUSION

From the observations in the present study, it can be concluded that subjects had lower regular intake of O3FAs in their diet which could play a significant role in the pathogenesis of the bipolar disorder. It has been observed that a high dose (2.4 g/day) of O3FAs i.e., group C showed earlier significant improvement BD symptoms than a lower dose (1.2 g/day) of O3FAs i.e., group B and only ongoing therapy group i.e., group A. As already approved drugs for BD are good therapeutic agents, O3FAs (2.4 g/day) as adjunctive showed superior efficacy, safety and better tolerability over approved drugs.

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