Combination of Omega-3 Fatty Acids and Valproic Acid in Treatment of Borderline Personality Disorder: A Follow-Up Study

Combination of omega-3 fatty acids and valproic acid in treatment of borderline personality disorder: a follow-up study

Short title: Omega-3 fatty acids in BPD: a follow-up study

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Abstract

Background and Objectives. Some evidences of efficacy were found for omega-3 fatty acids in patients with borderline personality disorder (BPD). In a previous 12 weeks randomized trial we assessed the efficacy of the combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) with valproic acid, in comparison with valproic acid monotherapy, in 43 BPD outpatients. Combined therapy was superior to control group in the treatment of some BPD symptoms: impulsive-behavioural dyscontrol, outbursts of anger, and self-harm. The present study is a 24 weeks follow-up aimed to evaluate whether the differences of efficacy between the two subgroups were maintained after omega-3 fatty acids discontinuation.

Methods. Thirty-four patients who completed the 12 weeks trial entered the follow-up study. Participants were evaluated at the beginning and at the end of the follow-up period with the rating scales that showed a significant difference between groups after the 12 weeks trial with fatty acids supplementation: Borderline Personality Disorder Severity Index (BPDSI) (items "impulsivity" and "outbursts of anger"), Barratt Impulsiveness Scale-Version 11 (BIS-11), and Self Harm Inventory (SHI). Statistical analysis was performed with the ANOVA for repeated measures.

Results. At the end of the follow-up a significant difference within groups was maintained for all the four variables examined, while a significant difference between groups was maintained for the outbursts of anger. Concerning tolerability, no clinically significant adverse effects were registered during the follow-up period.

Conclusions. Combined therapy with omega-3 fatty acids showed long lasting effects after discontinuation in terms of anger control.

Trial registration:

The trial was registered in the Australian New Zealand Clinical Trials Registry (ANZCTR) and allocated the code: ACTRN12612001150831.

Key words: omega-3 fatty acids, eicosapentaenoic acid, docosahexaenoic acid, valproic acid, borderline personality disorder, follow-up.

Key points

1) Patients who had previously received combination of omega-3 fatty acids and valproic acid and patients who had previously received valproic acid monotherapy showed at the end of 24 weeks of follow-up significant within subjects effects on impulsive behavioural dyscontrol, outbursts of anger, and self-injuries.

2) Significant between subjects effects were found at the end of follow-up for the outbursts of anger, indicating that combined therapy has superior effects in term of anger control enduring after discontinuation.

3) No clinically significant adverse effects occurred during the follow-up period.

1. Introduction

Recent investigations have suggested that omega-3 polyunsturated fatty acids (PUFAs) are essential for neural development and function and a deficiency of these components in brain tissues may be implicated in a wide range of psychiatric disorders (1,2). So, the interest in the role of dietary supplementation with essential fatty acids, in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in the treatment of several psychiatric disturbances has grown. Moreover, limited side effects and beneficial effects on cardiovascular system (3) of these agents allow to treat patients of all ages and with comorbid medical conditions.

Expert opinions and systematic reviews (1,4,5) outlined that there is some evidence that EPA and DHA supplementation has beneficial effects in mood disorders, in particular in the treatment of unipolar and bipolar depression; in clinical conditions characterized by high levels of impulsivity and aggression; in borderline personality disorders; and in patients with attention deficit / hyperactivity disorder. In schizophrenia there is a considerable disagreement among the authors, while in other psychiatric disturbances, including autism spectrum disorders, anxiety disorders, obsessive-compulsive disorder, eating disorders, and substance use disorder, available data are too scarce to draw any conclusion (1). Although several investigations have tested the efficacy of omega-3 fatty acids in psychiatric disorders in short-term trials, to date few studies have evaluated the long-term effects of these agents. To our knowledge only two follow-up studies were performed: the first in the treatment of patients with substance abuse (6), the second in the prevention of psychotic disorders (7). Results suggested that the supplementation with omega-3 fatty acids could produce enduring benefits.

In a randomized controlled trial (8) we compared the efficacy of the association of omega-3 fatty acids (EPA 1.2 g/day + DHA 0.6 g/day) with valproic acid (plasma concentration range: 50-100 μg/ml) versus valproic acid monotherapy (in the same plasma concentration range) in 43 consecutive BPD outpatients. At the end of 12 weeks of treatment, the combination of

valproate and omega-3 fatty acids was found significantly superior to valproic acid monotherapy in terms of decreased severity of three BPD symptoms (impulsive behavioural dyscontrol, outbursts of anger, and self-mutilating conducts).

In the present study we prospectively investigated whether the differences of efficacy of the association of omega-3 fatty acids with valproic acid versus valproic acid monotherapy registered after 12 weeks of acute treatment were maintained after discontinuation of fatty acids during a follow-up period of further 24 weeks.

2. Methods and materials

2.1. Procedure

The present study is the follow-up of a 12 weeks controlled trial, that was published in 2014 (6). Study design, procedures, selection of participants, and evaluation scales in the short-term trial were described in detail in our previous article and are here reported in summary.

In the short-term study, 43 consecutive outpatients aged between 18 and 50 years who received a DSM-IV-TR diagnosis of BPD were recruited. Patients attended the Centre for Personality Disorders, Department of Neuroscience, University of Turin, Italy.

Psychiatric diagnosis was made by an expert clinician (S.B.) and was confirmed with the Structured Clinical Interview for DSM-IV Axis I and II Disorders (9,10). Exclusion criteria were: (1) diagnosis of dementia or other cognitive disorders, schizophrenia or other psychotic disorders, or bipolar disorders; (2) a co-occurring major depressive episode and/or substance abuse; (3) administration of psychotropic medications and/or psychotherapy in the 2 months preceding the beginning of the study. Female patients in childbearing age were also excluded if they were not using adequate birth control methods (according to the judgment of clinicians). Each patient participated voluntarily in the study after providing written informed

consent. Declaration of Helsinki guidelines were observed and Ethical Committee approval was obtained.

2.2. Treatment and measures

In the initial study (8), patients were randomly allocated to one of two treatment arms for 12 weeks: (1) valproic acid (at a dose corresponding to a plasma concentration level of 50-100 µg/ml); (2) EPA (1.2 g/day) and DHA (0.8 g/day) in combination with the same dose of valproic acid.

Thirty-four patients who completed the 12 weeks trial (18 who received EPA and DHA plus valproic acid; 16 who received valproic acid monotherapy) underwent 24 weeks of follow-up. All subjects received valpoic acid alone (with plasma concentration level ranging between 50 and 100 µg/ml) during the follow-up period.

Clinical assessment was performed at the beginning of the follow-up (data were the same collected at the end of the short-term trial) and after the 24 weeks period. We used the four rating scales that showed a significant difference between groups at the end of 12 weeks trial: the Borderline Personality Disorder Severity Index (BPDSI) (item "impulsivity" and "outbursts of anger" (11), the Barratt Impulsiveness Scale, version 11 (BIS-11) (12), and the Self Harm Inventory (SHI) (13).

2.3. Statistical analysis

Statistical analysis was performed with the analysis of variance (ANOVA) for repeated measures to calculate the within subjects effect (related to the duration of follow-up) and the between subjects effect (related to the treatment modality administered in the short-term trial) for the rating scales that had shown a significant effect between subjects (a significant difference between the two treatment arms) after the initial 12 weeks of treatment: the BIS-11,

the SHI, and the BPDSI items “impulsivity” and “outbursts of anger”. Significance level was $P \leq 0.05$. Effect size was calculated as eta squared (ɳ2).

3. Results

During the follow-up period, three subjects of the group of 34 patients dropped out (8.82%), two in the subgroup of patients who had previously received EPA and DHA combined with valproic acid, one in the subgroup of patients who had received valproic acid alone. Of the 31 patients who completed the 24 weeks of follow-up, 16 who had previously been treated with the association of omega-3 fatty acids and valproic acid received a mean dose ± SD of valproic acid of 860.2 ± 50.3 mg/day; 15 patients who had previously been treated with valproic acid monotherapy received a mean ± SD of valproic acid of 880.2 ± 45.4 mg/day (with no statistical difference at t-test).

The thirty-four subjects who entered the follow-up study had a mean age of 25 ± 6.4 years; 8 were male (23.53%) and 26 were female (76.47%). Demographic and clinical characteristics of the two groups of patients at the beginning of the follow-up are reported in Table 1. No significant differences of baseline characteristics were found between the two groups at t-test and chi-square test.

ANOVA for repeated measures produced similar results for the following three scales: the BIS-11, the SHI, and the BPDSI item “impulsivity”. For all the three scales, effects within subjects (effects of duration of the trial) were statistically significant at the end of follow-up (respectively, $P = 0.02$, $ɳ2 = 0.23$; $P = 0.032$, $ɳ2 = 0.19$; and $P = 0.032$, $ɳ2 = 0.19$), but no significant effects were calculated between subjects (effects of different treatment modalities administered in the initial trial).

A different finding was obtained for the BPDSI item "outburst of anger". At the end of follow-up, a significant value was calculated for both within subjects effect (P = 0.01, $\eta 2$ = 0.26) and between subjects effect (P = 0.02, $\eta 2$ =0.22). Results of ANOVA for repeated measures are reported in detail in Table 2.

Concerning tolerability, no new adverse effects were registered during the follow-up. No cases of weight increase ≥ 2kg were registered. The three drop-outs were due to lack of compliance.

4. Discussion

As a recent Cochrane review (14) indicated some evidence of efficacy of omega-3 fatty acids supplementation in the treatment of BPD symptoms, in 2014 we performed a twelve weeks trial aimed to compare two treatment options: the combination of omega-3 fatty acids EPA and DHA with valproic acid versus valproic acid monotherapy. Although BPD is long-lasting disorder, very few follow-up studies investigating the long-term effects of drug treatments have been conducted. In particular, no follow-up study concerned effects of omega-3 fatty acids. For this reason, we designed the present study with the aim to verify whether the benefits obtained with the addition of omega-3 fatty acids to valproic acid after 12 weeks of treatment were maintained during a follow-up period of further 24 weeks after discontinuation of omega-3 fatty acids (all patients continued to receive valproic monotherapy at the same dose).

In the short-term trial, we found that the two treatment modalities, the combined therapy of valproic acid plus EPA and DHA, and the monotherapy with valproic acid, can both be proposed as effective options for the treatment of BPD. Nevertheless, significant differences in favour of the combination of PUFAs and valproic acid were observed. In particular, the

combined therapy was significantly superior to monotherapy (as indicated by significant between subjects effects with the ANOVA) in terms of decreased severity of outbursts of anger (BPDSI item), self-injuries (SHI), and both self-rated and clinician-rated measures of impulsive-behavioural dyscontrol (BIS-11 and BPDSI item). Findings of the follow-up evaluation showed that these four measures of BPD symptoms still improved in the further period of 24 weeks (within subjects effects were significant for all the four items). Patients initially treated with the association of EPA and DHA plus valproic acid maintained a significant advantage over controls in one of the BPD core symptoms: outbursts of anger (as indicated by a significant between subjects effect). On the contrary, the advantage of the combined therapy with omega-3 fatty acids and valproic acid in terms of improvement of impulsive-behavioral dyscontrol and self-injuries was not replicated at follow-up (within subjects effects were no longer significant).

Unfortunately, it is not possible to compare these results with previous studies, as no other follow-up trials of PUFAs in BPD patients are available. Recent short-term trials of efficacy highlighted the role played by omega-3 fatty acids in clinical conditions characterized by behavioural dyscontrol, in terms of high levels of impulsivity, hostility, and anger (15-17). Concerning follow-up evaluations, only two studies have been published concerning the use of omega-3 fatty acids in other psychiatric disorders. The first study was performed by Buydens-Branchey and Branchey (6) and evaluated the efficacy of PUFAs in a group of patients with substance use disorder. The second investigation was conducted by Amminger and colleagues (7) and assessed the long-term outcome (during a period of 6.7 years) of omega-3 fatty acids in the prevention of psychotic disorders. In the study of Buydens-Branchey and Branchey, authors did not exclude patients with a diagnosis of personality disorders. So, our results can be considered partially comparable with those obtained by these authors. On the contrary, the findings of the follow-up study performed by Amminger and

colleagues cannot be compared with ours because of the sample characteristics (young people with high risk to develop psychosis) and the aim of the study (to evaluate the prevention of psychotic symptoms).

The enduring effect of the association of EPA and DHA with valproic acid on the severity of the outbursts of anger that was observed in our trial is consistent with the finding reported by Buydens-Branchey & Branchey (6). In fact, these authors found that the administration of 3 g/day of PUFAs for a period of 3 months significantly decreased feelings of anger in comparison with placebo and this result was maintained during the 3 months after treatment discontinuation. A possible explanation for the persistence of this effect of omega-3 fatty acids after treatment discontinuation proposed by Buydens-Branchey and Branchey is based on the hypothesis of a persistent central effect of these agents. In particular, it is possible that PUFAs were stored in fatty tissues and continued to be released across time. In this case, the duration of the effect after treatment discontinuation is expected to last for a limited period.

The neurobiological mechanism of the prolonged effect of omega-3 fatty acids on anger control is still unclear. However, some authors (2) suggested a link between omega-3 levels and anger control, at least partially mediated by inflammatory modulation and the impact on fluidity of neuronal membrane and function of receptors.

Outbursts of anger are an expression of affective-emotional dysregulation, a core psychopathological factor of BPD (18). In addition, high levels of anger and their negative effects on behavioural organization have significant consequences on quality of interpersonal relationships and social functioning. So, availability of new treatments that allow clinicians to manage symptoms of anger are likely to have secondary relevant effects on core psychopathology and relational functioning of BPD patients.

Concerning tolerability, omega-3 fatty acids supplementation presented in our initial trial a low risk of adverse effects (mainly dyspepsia and a mild degree of weight gain). During the

24 weeks of follow-up we did not register new adverse effects in our sample. No patients presented a weight gain ≥ 2 kg. As BPD is a long-lasting disorder and patients suffering from this disorder have a poor adherence to medications, well tolerated therapeutic agents are of particular importance.

One strength of the present study is the randomized controlled design. In addition, both self-evaluated and clinician-rated scales were used to obtain a more reliable assessment of BPD symptoms. Only 8.8% of drop-outs was registered during the 24 weeks of follow-up, that can be considered quite a low rate in samples of BPD patients.

On the other hand, this trial suffers from some limitations: (1) the relatively small size of the clinical sample; (2) the lack of a placebo controlled group; (3) the exclusion of patients with psychiatric comorbidities. Treatment with placebo of BPD patients, a clinical population characterized by severe symptoms and risks of aggressive behaviours and self-harm, was not allowed by our Ethical Committee. Exclusion of subjects with comorbid mental disorders, in particular major depression, was decided in order to avoid the effects of associated psychopathology on response to treatment. However, our patients are likely to present clinical characteristic partly different from those commonly observed in clinical practice.

5. Conclusion

In conclusion, findings of the initial twelve weeks trial indicated that both combination of omega-3 fatty acids EPA and DHA with valproic acid and valproic acid monotherapy can be considered as efficacious therapeutic options in the treatment of BPD patients, but combined therapy produced better effects on some BPD symptoms: impulsive behavioural dyscontrol, outbursts of anger, and self-injuries. After discontinuation of omega-3 fatty acids and 24 weeks of follow-up, the difference between the two treatment subgroups was maintained for a

single item: outbursts of anger. So, the lasting effect of the combination of omega-3 fatty acids was a better improvement of anger related behaviours. At the moment, other studies of follow-up in BPD patients treated with omega-3 fatty acids are not available to compare our results. Nevertheless, these initial data are promising and need to be replicated.

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Declaration of conflicting interests

Authors declare that there is no conflict of interests.

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Table 1.

Demographic and baseline clinical characteristics of the sample of 34 BPD patients who entered the 24 weeks follow-up study.

Parameter	Association of omega-3 fatty acids and valproate N= 18	Single valproate N=16
Age (mean ±SD), years	24.8 ±5.3	25.3 ± 6.3
Gender (female), n (%)	12 (46.1)	14 (53.8)
Employment (employed), n(%)	10 (55.5)	9 (56.2)
Marital status (married), n(%)	11 (61.1)	10 (62.5)
Education (mean ± SD), years	12.53 ±3.8	12.67±4.5
Previous hospitalization, n (%)	9 (50)	7 (43.7)

Table 2.

Results of ANOVA repeated measures for the BIS-11, SHI, items "impulsivity and "outbursts of anger" of BPDSI

Scale	Treatment	12 weeks Trial end point Mean±SD	24 weeks Follow-up Mean±SD	Within subjects effect (duration)	Between subjects effect (treatment)
BIS-11	**omega-3 + valproate**	64.78±12.74	61.81±10.72	P=0.02	P=0.146
	valproate	77.37±5.51	68.78±4.92	ηp2=0.23	ηp2=0.08
SHI	**omega-3 + valproate**	3.33±2.7	2.87±2.33	P=0.032	P=0.213
	valproate	5.88±1.89	4.47±2.15	ηp2=0.19	ηp2=0.07
BPDSI impulsivity	**omega-3 + valproate**	3.78±1.35	3.37±1.56	P=0.032	P=0.193
	valproate	6.25±1.61	5.31±2.11	ηp2=0.19	ηp2=0.08
BPDSI outbursts of anger	**omega-3 + valproate**	4.22±1.16	3.15±1.38	P=0.01	P=0.02
	valproate	6.75±1.61	6.50±1.82	ηp2=0.26	ηp2=0.22

ANOVA=analysis of variance; SD=standard deviation;

BIS-11=Barratt Impulsiveness Scale - Version 11;

SHI= Self Harm Inventory;

BPDSI=Borderline Personality Disorder Severity Index;

ηp2= Eta squared.