

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

**Efficacy of omega-3 fatty acids in the treatment of borderline personality disorder: a study of the association with valproic acid**

**This is the author's manuscript**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/141922> since 2022-01-13T12:16:41Z

*Published version:*

DOI:10.1177/0269881113510072

*Terms of use:*

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

This is the author's final version of the contribution published as:

S. Bellino; P. Bozzatello; G. Rocca; F. Bogetto. Efficacy of omega-3 fatty acids in the treatment of borderline personality disorder: a study of association with valproic acid. JOURNAL OF PSYCHOPHARMACOLOGY. 28 (2) pp: 125-132.

When citing, please refer to the published version.

Link to this full text:

<http://hdl.handle.net/2318/141922>

**Efficacy of omega-3 fatty acids in the treatment of borderline personality disorder: a study of association with valproic acid**

**Running title: Omega-3 fatty acids and valproate in BPD**

Silvio Bellino<sup>1</sup>, Paola Bozzatello<sup>1</sup>, Giuseppe Rocca<sup>2</sup>, Filippo Bogetto<sup>3</sup>

Psychiatric Clinic 1, Department of Neuroscience, University of Turin, Italy

<sup>1</sup>Centre for Personality Disorders, Psychiatric Clinic 1, Department of Neuroscience, University of Turin, Italy

<sup>2</sup>Clinical Methodology Unit, Department of Neuroscience, University of Turin, Italy

<sup>3</sup>Psychiatric Clinic 1, Department of Neuroscience, University of Turin, Italy

**Corresponding author:**

Silvio Bellino, M.D.

Centre for Personality Disorder, Psychiatric Clinic 1

Department of Neuroscience, University of Turin

Via Cherasco 11, 10126 Turin, Italy

Tel. 0039-011-6634848; fax 0039-011-673473

e-mail: [silvio.bellino@unito.it](mailto:silvio.bellino@unito.it)

## **Abstract**

Omega-3 fatty acids have received increasing interest for their effects in stabilizing plasmatic membranes and regulating cell signalling. Authors have studied the efficacy of omega-3 fatty acids in psychiatric disorders, in particular mood disorders. Two trials on eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the treatment of borderline personality disorder (BPD) are available. The present 12-week controlled trial is aimed to assess the efficacy of the association of EPA and DHA with valproic acid, compared to single valproic acid in 43 BPD consecutive outpatients. Participants were evaluated at baseline and after 12 weeks with: CGI-S, HAM-D, HAM-A, SOFAS, BPDSI, BIS-11, MOAS, SHI, and DOTES. Nine subjects discontinued treatment: 2 for symptoms of dyspepsia, 7 for lack of compliance. Results indicated that monotherapy with valproate and combination of valproate and omega-3 fatty acids had a similar efficacy on global symptoms, symptoms related to BPD, anxiety and depressive symptoms, and social functioning. The association of DHA and EPA with valproate was significantly superior to single valproate in reducing severity of impulsive behavioural dyscontrol, outbursts of anger, and self-mutilating conducts. Mild to moderate adverse effects were registered: dyspepsia, nausea, and weight gain < 2 kg.

**Key words:** omega-3 fatty acids, eicosapentaenoic acid, docosahexaenoic acid, mood stabilizers, valproic acid, psychiatric disorders, borderline personality disorders, efficacy, tolerability.

## **Introduction**

According to current diagnostic criteria, borderline personality disorders (BPD) is a severe psychiatric disturbance characterized by a pervasive pattern of instability in affect regulation, impulse control, interpersonal relationships, and self-image. Clinical hallmarks include emotional dysregulation, impulsivity and aggressiveness, repeated self-injury, and chronic suicidal tendencies.

Because clinical response to traditional drugs in heterogeneous disorders such as BPD is often partial and limited to few symptoms, the identification of new agents is required to improve and extend treatment results in these patients. Together with second-generation antipsychotics and mood stabilizers, the up-to-date systematic review by Stoffers and colleagues (Cochrane Collaboration, 2010) indicated some beneficial effects in the treatment of BPD with supplementation of long-chain omega-3 fatty acids.

Polyunsaturated fatty acids (PUFAs) have long been investigated for their cardioprotective and anti-inflammatory action, leading to an increased use as dietary supplements. In recent years, a growing number of clinical trials on omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosaexaenoic acid (DHA), have got promising results supporting their employment in several psychiatric disorders. Based on findings of decreased level of PUFAs in individuals with psychosis, mood disorders and clinical conditions with high impulsivity and aggression, it has been argued that dysfunctional fatty acids metabolism could be involved in the aetiology of these disorders (Horrobin et al., 1994; Ross et al., 2007; Garland et al., 2007). Recent contributions have confirmed the central role of PUFAs in the mechanisms of brain cell signalling, including dopaminergic and serotonergic pathways, receptor properties, and activation of signal transduction by receptors (Hallahan and Garland, 2005; Ross et al., 2007; Sinn et al., 2010). Omega-3 fatty acids are also retained to influence

gene expression of a range of enzymes required for important neural functions and to increase the turnover of all major cortical monoamines (De la Pressa and Innis, 1999; Assisi et al., 2006).

There is a considerable number of randomised controlled trials testing the efficacy of essential fatty acids, in particular EPA and DHA, in the therapy of several psychiatric conditions. Results of most of these trials are controversial and inconclusive. There is some evidence to support the use of omega-3 fatty acids in the treatment of schizophrenia and of patients with impulsive behaviors and aggression. The most convincing findings are in favour of the efficacy of these agents for mood disorders, especially unipolar and bipolar depression (but not mania) (Stoll et al., 1999; Chiu et al., 2005; Keck et al., 2006; Garland and Hallahan, 2006; Frangou et al., 2006; Montgomery and Richardson, 2008; Sinn et al., 2010; 2012; Krawczyk and Rybakowski, 2012; Mossaheb et al., 2012).

As disturbances in regulation of mood and impulsivity are core features of borderline personality disorder, EPA and DHA may represent a potential tool for the treatment of this clinical population. To date, there is a paucity of data on the therapeutic use of omega-3 fatty acids in BPD patients. Zanarini and Frankenburg (2003) have conducted an 8 week placebo controlled, double blind study to compare the efficacy of ethyl-EPA (dose: 1g/day) and placebo in 30 female patients with a diagnosis of BPD and showed a significant beneficial effect of ethyl-EPA in reducing aggressive behaviors and depressive symptoms. Another 12 week RCT (Hallahan et al., 2007) included 35 patients who received a diagnosis of BPD and found a significant improvement of depressive symptoms, suicidality, and reaction to daily stresses in the group using EPA (1.2 g/day) and DHA (0.9g/day) in addition to standard psychiatric care.

In order to further investigate the role of omega-3 fatty acids in the therapy of BPD patients, the present study is aimed to assess the efficacy of the association of EPA and DHA with the mood stabilizer valproic acid, compared to valproic acid as single therapy.

## **Methods and Materials**

Forty-three consecutive outpatients aged between 18 and 50 years who received a DSM-IV-TR (APA, 2000) diagnosis of BPD were recruited. Patients attended the Centre for Personality Disorders of the Psychiatric Clinic 1, 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 (First et al., 1997). Exclusion criteria considered: (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 disorder and (3) administration of psychotropic medications and/or psychotherapy in the 2 months preceding the beginning of the study.

Because of the potential teratogenic effects of valproate, female patients in childbearing age were 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. Ethical Committee approval was obtained. The trial was registered in the Australian New Zealand Clinical Trials Registry (ANZCTR) and allocated the code: ACTRN12612612001150831.

Patients were randomly assigned to one of two treatment arms for 12 weeks: (1) valproic acid (at a dose corresponding to a plasma 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.

Valproic acid is a largely used antiepileptic and mood stabilizer, with an official indication for treating and preventing manic episodes of bipolar disorder. It has been tested in several studies of BPD patients showing significant effects of symptoms like depression, irritability, anger/aggressiveness, and impulsivity (Hollander et al., 2001; 2003; 2005; Townsend et al., 2001; Frankenburg and Zanarini, 2002; Simeon et al., 2007).

Patients were assessed at baseline and after 12 weeks (at endpoint) with the following assessment instruments:

- 1) the Clinical Global Impression Scale, Severity item (CGI-S) (Guy, 1976),
- 2) the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1959),
- 3) the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1960),
- 4) the Social Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992),
- 5) the Borderline Personality Disorder Severity Index (BPDSI) (Arntz et al., 2003),
- 6) the Barratt Impulsiveness Scale, version 11 (BIS-11) (Barratt et al., 1965),
- 7) the Modified Overt Aggression Scale (MOAS) (Kay et al., 1988),
- 8) the Self Harm Inventory (SHI) (Sansone et al., 1998).

Adverse effects were evaluated with the Dosage Record and Treatment Emergent Symptom Scale (DOTES) (Guy, 1976).

The BPDSI is a semi-structured clinical interview assessing frequency and severity of BPD related symptoms. The interview consists of eight items scored on 10-point frequency scales (0=never; 10=daily), including 'abandonment', 'interpersonal relationships', 'impulsivity', 'parasuicidal behavior', 'affective instability', 'emptiness', 'outbursts of anger', 'dissociation and paranoid ideation', and one item scored on a 4-point severity scale, concerning 'identity'. The BPDSI showed excellent reliability coefficients and good validity indices in two studies performed by Arntz et al. (2003).



The BIS-11 is a 30-item self-report questionnaire measuring the trait of impulsivity on a 4-point Likert scale (Barratt, 1994). Higher scores for each item indicate higher levels of impulsivity. Twelve items are reverse-scored, in order to avoid response sets. The BIS-11 showed adequate reliability and construct validity in both USA (Patton et al., 1994) and Italian (Fossati et al., 2001) samples.

The MOAS is a clinician-rated scale consisting of four subscales for different types of aggression (verbal aggression, aggression against objects, aggression against others, and self-aggression). The subscales are rated on a 5 point scale (score 0-4). Higher scores for each subscale reflect higher severity of aggressiveness (Kay et al., 1988, Margari et al., 2005).

The SHI is a brief, self-report instrument and provides informative data about clinically-relevant self-harm behaviors. Although not considered in the scoring, many of the SHI items provide additional information regarding the number of times a patient has engaged in a self-destructive act, as well as how recently he or she has done so. The scoring of the instrument is easily determined by counting the number of endorsed self-harm behaviors (Sansone et al., 2003; 2010).

For all instruments except the SOFAS, a decrease of scores indicates an improvement of symptoms. In the case of SOFAS, the improvement of the social functioning corresponds to higher scores.

Assessment was performed by an investigator (P.B.) who received training session on psychometric instruments prior to start investigation.

Statistical analysis evaluated patients who completed the 12 weeks of the trial. Baseline mean score of each rating scale were compared between the two treatment subgroups with one way analysis of variance (ANOVA). Comparison of score change after 12 weeks between treatment subgroups was performed on each rating scale with the analysis of variance (ANOVA) repeated measures.

In order to investigate if cases of drop-out had significant effects on the results of statistical analysis, we calculated for the rating scales with a significant difference between treatment subgroups the number of responders (patients with a reduction of scale score  $\geq 50\%$  after 12 weeks). Cases of drop-out were considered as non-responders. Difference in the rate of responders between subgroups was estimated for each scale with two chi-square tests: in the first test only completers were considered, while in the second cases of drop-out were also included.

Statistics were calculated with the software system SPSS Statistics, version 19.0, SPSS Inc., 2010. *P* values were considered significant when  $\leq 0.05$ .

## **Results**

Forty-three patients were randomly assigned to (1) EPA + DHA in combination with valproic acid (N=23, 53.49%) or to (2) monotherapy with valproic acid (N= 20, 46.51%). The required plasma level of valproate was achieved with a dose ranging from 800 mg/day to 1300 mg/day. Thirty-four of the 43 patients (79.07%) completed the 12 weeks of the trial: 18 patients (52.94% of the completers) received the association of fatty acids and valproate, while 16 patients (47.06%) were in monotherapy. Nine patients (20.93%) discontinued treatment in the first four weeks: five taking omega-3 in association with valproic acid, and four receiving valproic acid in monotherapy. The final sample of 34 patients had a mean age of  $25.2 \pm 6.4$  years; they were 8 males (23.53%) and 26 females (76.47%).

Results of the ANOVA calculated for baseline mean scores of rating scales are displayed in tables 1 and 2. No significant differences were found between the two treatment arms.

Results of the ANOVA repeated measures to evaluate the effect of trial duration (effect within subjects) and of treatment modality (effect between subjects) on score changes after 12 weeks are reported in tables 3, 4, and 5.

A significant effect within subjects (trial duration) was observed for all rating scales ( $P=0.001$ ), with the exception of the MOAS ( $P=0.068$ ) and of three items of the BPDSI, “identity disturbance” ( $P=0.452$ ), “parasuicidal behaviors” ( $P=0.073$ ), and “dissociation/paranoid ideation” ( $P=0.180$ ).

A significant effect between subjects (treatment modality) was found for four rating scales: the BIS-11 ( $P=0.031$ ), the SHI ( $P=0.042$ ), and items “impulsivity” ( $P=0.031$ ) and “outbursts of anger” ( $P=0.001$ ) of the BPDSI. The change of severity of the four rating scales in the two treatment subgroups is shown in figures 1 and 2.

Results of the chi-square test calculated for the four rating scales BIS-11, SHI, BPDSI “impulsivity”, and BPDSI “outbursts of anger” demonstrated significant differences in the rate of responders between treatment subgroups ( $P\leq 0.05$ ). The differences were found for all the four scales in the sample of 34 patients completing the trial and were confirmed in the group of 43 subjects including the cases of drop-out.

Of the 9 patients who discontinued their participation, only two subjects (1 with combined therapy and 1 with single medication) stopped drugs due to an adverse effect: dyspepsia. The other seven drop-outs were due to lack of compliance with trial prescriptions.

Other adverse effects observed in the two groups were of mild intensity. Two of the 18 patients receiving the combined treatment suffered from nausea. Three patients from each group referred a weight increase  $< 2\text{kg}$ .

## **Discussion**

Our study tested the efficacy and tolerability of omega-3 fatty acids (EPA and DHA) in combination with valproic acid in the treatment of BPD. We included patients without Axis I or II co-diagnoses to examine the effects of fatty acids on BPD symptoms, without any interference of comorbid psychopathology.

Considering that patients with BPD have a severe clinical picture, we decided that omega-3 fatty acids, a new and sparsely tested agent in personality disorders, could be administered only providing an associated therapy with a drug of proven efficacy in these patients. For this reason we chose to associate valproic acid, that has been evaluated in several studies of BPD patients, has shown its efficacy on depressive symptoms, irritability, impulsivity, and aggression, and is recommended by the treatment guidelines of the American Psychiatric Association (Hollander et al., 2001; 2003; 2005; Townsend et al., 2001; Frankenburg and Zanarini, 2002; Simeon et al., 2007; Oldham, 2005).

Only two preceding studies evaluated omega-3 fatty acids in BPD patients (Zanarini and Frankenburg, 2003; Hallahan et al., 2007). In the first investigation (Zanarini and Frankenburg, 2003) omega-3 fatty acids were tested in monotherapy versus placebo. Authors found a beneficial effect on depressive symptoms and aggressiveness. In the second study (Hallahan et al., 2007) EPA and DHA were associated with other psychiatric medications (antidepressants and benzodiazepines) and were found efficacious on depressive symptoms, self-injuries and reaction to daily stresses .

Results of our study suggested that the two treatment modalities, (1) valproic acid plus EPA and DHA and (2) single therapy with valproic acid, can both be proposed as efficacious options for the treatment of BPD. In fact, monotherapy with valproic acid and association of valproic acid and fatty acids had a similar efficacy on global symptoms, symptoms related to BPD psychopathology, symptoms of anxiety and depression, and social and occupational functioning. However, the two treatment groups presented significant differences in relevant symptom domains, as symptoms of impulsivity and anger and self-mutilating conducts.

In particular, our findings showed that combined therapy with omega-3 fatty acids and valproic acid was significantly superior to single therapy with valproic acid in reducing severity of self-rated and clinician-rated symptoms of impulsivity and outbursts of anger, as

indicated by score changes of the BIS-11 and of the BPDSI items “impulsivity” and “outbursts of anger”. Considering the difference in score change between the two treatment subgroups (a mean of 11 points for the BIS-11 and of 3 points for the two BPDSI items), we can conclude that the increase of clinical effects due to association of PUFAs with valproate was clinically meaningful after 12 weeks.

Efficacy of omega-3 fatty acids in the treatment of impulsive behavioral symptoms can be explained with the large body of evidences indicating that low plasma levels of these compounds were associated with dysregulation of impulsivity and that dietary supplementation improved impulsive behaviors (Vikkunen et al., 1987; Hamazaki et al., 1996; Buydens-Branchey et al., 2003; Garland and Hallahan, 2006). However, our findings on this topic cannot be compared with preceding studies of BPD samples. Zanarini and Frankenburg (2003) did not use in their trial any measure of impulsive symptoms. On the other hand, Hallahan et al. (2007) did not find a significant change of impulsivity, but evaluated these symptoms with a different type of instrument, consisting of two tests of cognitive performance (immediate and delayed memory tasks).

A significant effect of omega-3 fatty acids EPA and DHA in reducing levels of anger was previously reported in a placebo controlled study of substance abusers (Buydens-Branchey et al., 2008).

Association of omega-3 fatty acids and valproic acid was found more effective than valproate alone on the SHI measure of self-mutilating conducts. This result is consistent with previous data (Hallahan et al., 2007) indicating that EPA and DHA supplementation has positive effects in BPD patients with high level of self mutilating behaviors.

When taking into account other parameters of clinical response, findings from different studies are not in accordance. For example, Zanarini and Frankenburg (2003) registered in their patients a significant decrease of MOAS score corresponding to a considerable

amelioration of aggression. Both our results and data by Hallahan et al. (2007) did not confirm this finding, as no significant differences of MOAS score were registered. In our sample, a possible explanation of this difference is that values of MOAS score at baseline are considerably lower than in Zanarini's patients.

The effect of combining omega-3 fatty acids and valproic acid on mood depression was not significantly superior to single valproic acid. So, our findings did not confirm the antidepressant action of PUFAs reported in previous investigations of BPD patients. However, some differences in sample characteristics and treatment choices must be considered. We excluded subjects with a concomitant major depressive episode. The consequence was a rather low level of depressive symptoms in our patients, that can have an influence on treatment response. In addition, Hallahan et al. (2007) used an association of fatty acids with antidepressants to treat their patients. Thus, a stronger effect on depressed mood can be expected in their sample.

Concerning tolerability, both treatment modalities were well tolerated, with only mild side-effects. More common adverse effects in patients who received EPA and DHA in association with valproic acid were gastrointestinal disturbances, in particular nausea and dyspepsia. Only two drop-outs were due to an adverse effect (dyspepsia). In both treatment groups a modest weight gain (less of 2 kg) was registered. These results on tolerability replicated previous data concerning omega-3 fatty acids in psychiatric patients (Stensby, 1969; Topliss et al., 2002; Hallahan et al., 2007; Emsley et al., 2008; Amminger et al., 2010).

We had a rather high rate of drop-outs (almost 20%) in our study, in accordance with the majority of preceding trials and with the trend of patients with BPD to a low level of adherence to any treatment intervention (Martino et al., 2012). A relevant question was whether cases of drop-out could affect the results of the study. We performed two different chi-square tests to compare the rate of responders in the two treatment subgroups. Patients

were classified as responders if they had a score decrease  $\geq 50\%$  in the four rating scales that showed a significant treatment effect with the ANOVA (BIS-11, SHI, BPDSI “impulsivity”, and BPDSI “outbursts of anger”). The first test considered only subjects who completed the trial. The second test included also the nine drop-outs, classified as non-responders. As both chi-square tests found significant differences between treatments for all the four rating scales, we concluded that our findings were unchanged if drop-outs were considered.

In conclusion, results of this randomized controlled study indicated that monotherapy with valproate and combination of valproate and omega-3 fatty acids can both be proposed as valid therapeutic options for the treatment of BPD: they have a similar efficacy on severity of global symptoms, BPD related symptoms, anxiety and depressive symptoms, and social functioning. However, our data provided an initial evidence that the association of fatty acids with valproate is useful to increase the clinical response of these patients. In particular, combination of fatty acids produced significant effects in reducing severity of characteristic BPD symptoms, as impulsive behavioural dyscontrol, outbursts of anger, and self-mutilating conducts. Adverse effects were only mild dyspepsia, nausea, and weight gain and were similar in the two subgroups, suggesting that association of EPA and DHA with valproate is a well-tolerated intervention.

For the present, the scarcity of published investigations about omega-3 fatty acids in the treatment of BPD does not allow a reliable comparison of our data of either efficacy or tolerability. Nevertheless, these initial findings are encouraging and should stimulate further investigations on larger samples.

The present study suffers from some limitations that should be considered: (1) the small sample size, (2) the lack of a placebo controlled group, (3) the exclusion of patients with Axis I co-diagnosis. Treatment with placebo of BPD patients, a clinical population characterized by severe symptoms and risks of aggression and self-harm, was not allowed by our Ethical

Committee. Exclusion of subjects with comorbid mental disorders, in particular major depression, was determined by the concern to avoid the effects of associated psychopathology on response to treatment. However, our patients are likely to present clinical characteristic partly different from those of clinical practice.

A further limit is that medications and psychotherapies received by our subjects before entering the trial were not considered and compared between groups. This limit was only partly corrected excluding patients who had received pharmacotherapy or psychotherapy in the two months before being enrolled.

### **Aknowledgement**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.



## References

Amminger G P, Schäfer M R, Papageorgiou K , Klier C M, Cotton S M, Harrigan S M, et al. (2010) Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: A randomized, placebo-controlled trial. *Arch Gen Psychiat* 67(2): 146-154

Arntz A, Van den Hoorn M, Cornelis J, Verheul R, Van den Bosch W M, De Bie A J (2003) Reliability and validity of the borderline personality disorder severity index. *J Personal Disord* 17: 45-59

Assisi A, Banzi R, Buonocore C, Capasso F, Di Muzio V, Michelacci F et al. (2006) Fish oil and mental health: the role of n-3 long-chain polyunsaturated fatty acids in cognitive development and neurological disorders. *Int Clin Psychopharmacol* 21(6): 319-336

Barratt E S (1965) Factor analysis of some psychometric measures of impulsiveness and anxiety. *Psychol Rep* 16: 547-554

Buydens-Branchey L, Branchey M, McMakin D L, Hibbeln J R (2003) Polyunsaturated fatty acid status and relapse vulnerability in cocaine addicts. *Psychiatry Res* 120(1): 29-35

Buydens-Branchey L, Branchey M (2008) Long chain n-3 polyunsaturated fatty acids decrease feelings of anger in substance abusers. *Psychiatry Res* 157(1-3): 95-104

Chiu C C, Huang S Y, Chen C C (2005) Omega-3 fatty acids are more beneficial in the depressive phase than in the manic phase in patients with bipolar I disorder. *J Clin Psychiatry* 66 (12): 1613-1614

De la Pressa O S, Innis S M (1999) Docosahexanoic and arachidonic acid prevent a decrease in dopaminergic and serotonergic neurotransmitters in frontal cortex caused by a linoleic and alpha-linolenic acid deficient diet in formula-fed piglets. *J Nutrition* 129: 2088-2093

Emsley R, Niehaus D J, Oosthuizen P P, Koen L, Ascott-Evans B, Chiliza B, et al. (2008) Safety of the omega-3 fatty acid, eicosapentaenoic acid (EPA) in psychiatric patients: Results from a randomized, placebo-controlled trial. *Psychiat Res* 161(3): 284-291

First M B, Spitzer R L, Gibbon M (1997) Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Washington (DC): American Psychiatric Press

First M B, Gibbon M, Spitzer R L (1997) Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II). Washington (DC): American Psychiatric Press

Frangou S, Lewis M, McCrone P (2006) Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. *Br J Psychiatry* 188 (1): 46-50

Frankenburg F R, Zanarini M C (2002) Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. *J Clin Psychiatry*, 63: 442-446

Fossati A, Di Ceglie A, Acquarini E, Barratt E S (2001) Psychometric properties of an Italian version of the Barratt Impulsiveness Scale-11 (BIS-11) in nonclinical subjects. *J Clin Psychol* 57: 815-28

Garland M R, Hallahan B (2006) Essential fatty acids and their role in conditions characterised by impulsivity. *Int Rev Psychiat* 18(2): 99-105

Garland M R, Hallahan B, McNamara M, Carney P A, Grimes H, Hibbeln J R, et al. (2007) Lipids and essential fatty acids in patients presenting with self-harm. *Br J Psychiatry* 190: 112-117

Goldman H H, Skodol A E, Lave T R (1992) Revising Axis V for DSM-IV: a review of measures of social functioning. *Am J Psychiatry* 149: 1148-1156

Guy W (1976) Clinical global impression (C.G.I.). *Ecdeu Assessment Manual for Psychopharmacology*. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health, 218-222.

Guy W (1976) Dosage Record and Treatment Emergent Symptoms scale (DOTES). *ECDEU Assessment Manual for Psychopharmacology — Revised*. DHEW Publication No. ADM 76-338. NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, Alcohol, Drug Abuse, and Mental Health Administration, Public Health Service, US Department of Health, Education, and Welfare, Rockville, MD, pp. 223–44

Hallahan B, Garland M R (2005) Essential fatty acids and mental health. *Br J Psychiatry* 186: 275-277

Hallahan B, Hibbeln JR, Davis JM, Garland MR (2007) Omega-3 fatty acid supplementation in patients with recurrent self-harm. Single-centre double-blind randomised controlled trial. *Br J Psychiatry* 190:118-122

Hamazaki T, Sawazaki S, Itomura M, Asaoka E, Nagao Y, Nishimura N, Yazawa K, Kuwamori T, Kobayashi M (1996) The effect of docosahexaenoic acid on aggression in young adults. A placebo-controlled double-blind study. *J Clin Invest* 97(4): 1129-1133.

Hamilton M (1959) The assessment of anxiety states by rating. *Br J Med Psychology* 32:50

Hamilton M (1960) A rating scale for depression. *J Neurol, Neurosurg Psychiatry* 23: 56-62

Hollander E, Allen A, Lopez R P, Bienstock C A, Grassman R, Siever L J (2001). A preliminary double-blind, placebo-controlled trial of divalproex sodium in borderline personality disorder. *J Clin Psychiatry* 62: 199-203

Hollander E, Tracy K A, Swann A C, Coccaro E F, McEloray S L, Worniak P, et al. (2003) Divalproex in the treatment of impulsive aggression: efficacy in cluster B personality disorders. *Neuropsychopharmacol* 28: 1186-1197

Hollander E, Swann A C, Coccaro E F, Jang P, Smith T B, et al. (2005) Impact of trait impulsivity and state aggression on divalproex versus placebo response in borderline personality disorder. *Am J Psychiatry* 162: 621-624

Horrobin D F, Glen A I, Vaddadi K (1994) The membrane hypothesis of schizophrenia. *Schizophr Res* 13(3): 195-207

Kay S R, Wolkenfelf F, Murrill L M (1988) Profiles of aggression among psychiatric patients: I. Nature and Prevalence. *J Nerv Ment Dis* 176: 539-546

Keck P E, Mintz J, McElroy S L (2006) Double-blind randomised placebo-controlled trials of ethyl-eicosapentaenoate in the treatment of bipolar depression and rapid-cycling bipolar disorder. *Biol Psychiatry* 60(9): 1020-1022

Krawczyk K, Rybakowski J (2012) Augmentation of antidepressants with unsaturated fatty acids omega-3 in drug-resistant depression. *Psychiatr Pol* 46(4): 585-598

Margari F T, Matarazzo R, Casacchia M (2005) Italian validation of MOAS and NOSIE: a useful package for psychiatric assessment and monitoring of aggressive behaviours. *Int J Methods Psychiatr Res* 14: 109-118

Martino F, Menchetti M, Pozzi E, Berardi D (2012) Predictors of dropout among personality disorders in a specialist outpatients psychosocial treatment: a preliminary study. *Psychiatry Clin Neurosci* 66(3): 180-186

Montgomery P, Richardson A J (2008) Omega-3 fatty acids for bipolar disorder. *Cochrane Database Syst Rev* 6 (2):CD005169. doi: 10.1002/14651858

Mossaheb N, Schloegelhofer M, Schaefer M R, Fusar-Poli P, Smesny S, McGorry P et al. (2012) Polyunsaturated fatty acids in emerging psychosis. *Curr Pharm Des* 18(4): 576-591

Oldham J M (2005) *Guideline Watch: Practice Guideline for The Treatment of Patients with Borderline Personality Disorder*. Arlington, VA: American Psychiatric Association

Patton J H, Stanford M S, Barratt E S (1994) Factor structure of the Barratt Impulsiveness Scale. *J Clin Psychol* 51: 768–774

Ross B M, Seguin J, Sieswerda L E (2007) Omega-3 fatty acids as treatments for mental illness: which disorders and which fatty acid?. *Lipids in Health and Disease* 6: 21

Sansone R A, Wiederman M W, Sansone L A (1998) The Self-harm Inventory (SHI): development of a scale for identifying self-destructive behaviors and borderline personality disorder. *J Clin Psychol* 54: 973-983

Sansone R A, Sansone L A (2010) Measuring self-harm behavior with the self-harm inventory. *Psychiatry (Edgmont)* 7(4): 16-20

Simeon D, Baker B, Chaplin W, Braun A, Hollander E, et al., (2007) An open-label trial of divalproex extended-release in the treatment of borderline personality disorder. *CNS Spectr* 12: 439-443

Sinn N, Milte C, Howe P R (2010) Oiling the brain: a review of randomized controlled trials of omega-3 fatty acids in psychopathology across the lifespan. *Nutrients* 2(2): 128-170

Sinn N, Milte C M, Street S J, Buckley J D, Coates A M, Petkov J, et al. (2012) Effects of n-3 fatty acids, EPA v. DHA, on depressive symptoms, quality of life, memory and executive function in older adults with mild cognitive impairment: a 6-month randomised controlled trial. *Br J Nutr.* 107(11): 1682-1693

Stensby N E (1969) Nutritional properties of fish-oils. *World Rev Nutr Diet* 11: 46-105

Stoffers J, Völm B A Rücker G, Timmer A, Huband N, Lieb K (2010) Pharmacological interventions for borderline personality disorder. *Cochrane Database Syst Rev* 16 (6)

Stoll A L, Severus W E, Freeman M P, Rueter S, Zboyan H A, Diamond E, et al. (1999) Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 56(5): 407-412

Topliss J G, Clark A M, Ernst E (2002) Natural and synthetic substances related to human health (IUPAC Technical Report). *Pure Appl Chem* 74: 1957-85

Townsend M H, Cambre, K M, Barbee J G (2001) Treatment of borderline personality disorder with mood instability with divalproex sodium: series of ten cases. *J Clin Psychopharmacol* 21: 249-251

Virkkunen M E, Horrobin D F, Jenkins D K, Manku M S (1987) Plasma phospholipid essential fatty acids and prostaglandins in alcoholic, habitually violent, and impulsive offenders. *Biol Psychiatry* 22(9):1087-1096.

Zanarini M C, Frankenburg F R (2003) Omega-3 Fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. *Am J Psychiatry* 160: 167-169



**Table 1.**

**Comparison of baseline values of symptom and functioning rating scales between the two treatment subgroups**

<b>Scale</b>	<b>Valproate (N= 16) Mean±SD</b>	<b>Omega-3 + valproate (N= 18) Mean±SD</b>	<b>ANOVA <i>P</i></b>
<b>CGI-S</b>	3.75±0.683	3.89±0.758	0.581
<b>HAM-A</b>	19.38±2.363	19.33±3.662	0.969
<b>HAM-D</b>	14.38±0.885	14.89±1.231	0.177
<b>SOFAS</b>	66.50±9.352	65.22±9.226	0.691
<b>BIS-11</b>	81.13±5.965	80.22±9.302	0.742
<b>MOAS</b>	4.00±2.309	3.33±2.275	0.403
<b>SHI</b>	7.00±2.066	6.11±2.847	0.311

**SD=standard deviation; ANOVA=analysis of variance;**

**CGI-S=Clinical Global Impression scale – Severity item;**

**HAM-A=Hamilton Anxiety Rating Scale; HAM-D=Hamilton Depression Rating Scale;**

**SOFAS=Social Occupational Functioning Assessment Scale;**

**BIS-11=Barrett Impulsiveness Scale – version 11;**

**MOAS=Modified Overt Aggression Scale; SHI=Self Harm Inventory.**

**Table 2.**

**Comparison of baseline values of BPDSI total score and items between the two treatment groups**

<b>Scale</b>	<b>Valproate (N= 16) Mean±SD</b>	<b>Omega-3 + valproate (N= 18) Mean±SD</b>	<b>ANOVA <i>P</i></b>
<b>BPDSI total score</b>	47.45±6.32	48.09±5.85	0.762
<b>Abandonment</b>	6.50±1.46	6.67±1.53	0.749
<b>Interpersonal relationships</b>	6.75±1.12	6.67±0.84	0.807
<b>Identity</b>	4.95±1.41	4.31±1.52	0.214
<b>Impulsivity</b>	6.87±1.89	7.44±1.20	0.297
<b>Parasuicidal behaviors</b>	1.37±1.15	1.00±1.61	0.445
<b>Affective instability</b>	7.2±1.24	8.11±0.58	0.083
<b>Outbursts of anger</b>	7.00±1.26	6.44±1.29	0.216
<b>Emptiness</b>	5.37±1.15	6.00±1.75	0.233
<b>Dissociation/ Paranoid ideation</b>	1.37±1.63	1.44±1.95	0.912

**SD=standard deviation; ANOVA=analysis of variance;**

**BPDSI=borderline personality disorder severity index.**

**Table 3.**

**Results of ANOVA repeated measures for the CGI-S, HAM-A, HAM-D, and SOFAS**

Scale	Treatment	Baseline Mean±SD	12 weeks Mean±SD	Effect within subjects (duration) <i>P</i>	Effect between subjects (treatment) <i>P</i>
CGI-S	omega-3 + valproate valproate	3.89±0.76 3.75±0.68	3.33±0.84 3.38±0.72	0.001	0.844
HAM-A	omega-3 + valproate valproate	19.33±3.66 19.38±2.36	17.34±6.15 18.25±2.82	0.001	0.419
HAM-D	omega-3 + valproate valproate	14.89±1.23 14.38±0.88	12.33±2.47 13.63±1.26	0.001	0.436
SOFAS	omega-3 + valproate valproate	65.22±9.23 66.50±9.35	71.13±11.11 70.25±9.98	0.001	0.715

**ANOVA=analysis of variance; SD=standard deviation;**

**CGI-S=Clinical Global Impression scale – Severity item;**

**HAM-A=Hamilton Anxiety Rating Scale; HAM-D=Hamilton Depression Rating Scale;**

**SOFAS=Social Occupational Functioning Assessment Scale.**

**Tables 4. Results of ANOVA repeated measures for the MOAS, BIS-11, and SHI**

Scale	Treatment	Baseline Mean±SD	12 weeks Mean±SD	Effect within subjects (duration) <i>P</i>	Effect between subjects (treatment) <i>P</i>
MOAS	omega-3 + valproate valproate	3.33±2.27 4.00±2.31	2.78±2.10 3.38±2.12	0.068	0.376
BIS-11	omega-3 + valproate valproate	80.22±9.30 81.13±5.96	64.78±12.74 77.37±5.51	0.001	0.031
SHI	omega-3 + valproate valproate	6.11±2.85 7.00±2.07	3.33±2.74 5.88±1.89	0.001	0.042

**ANOVA=analysis of variance; SD=standard deviation;**

**MOAS=Modified Overt Aggression Scale;**

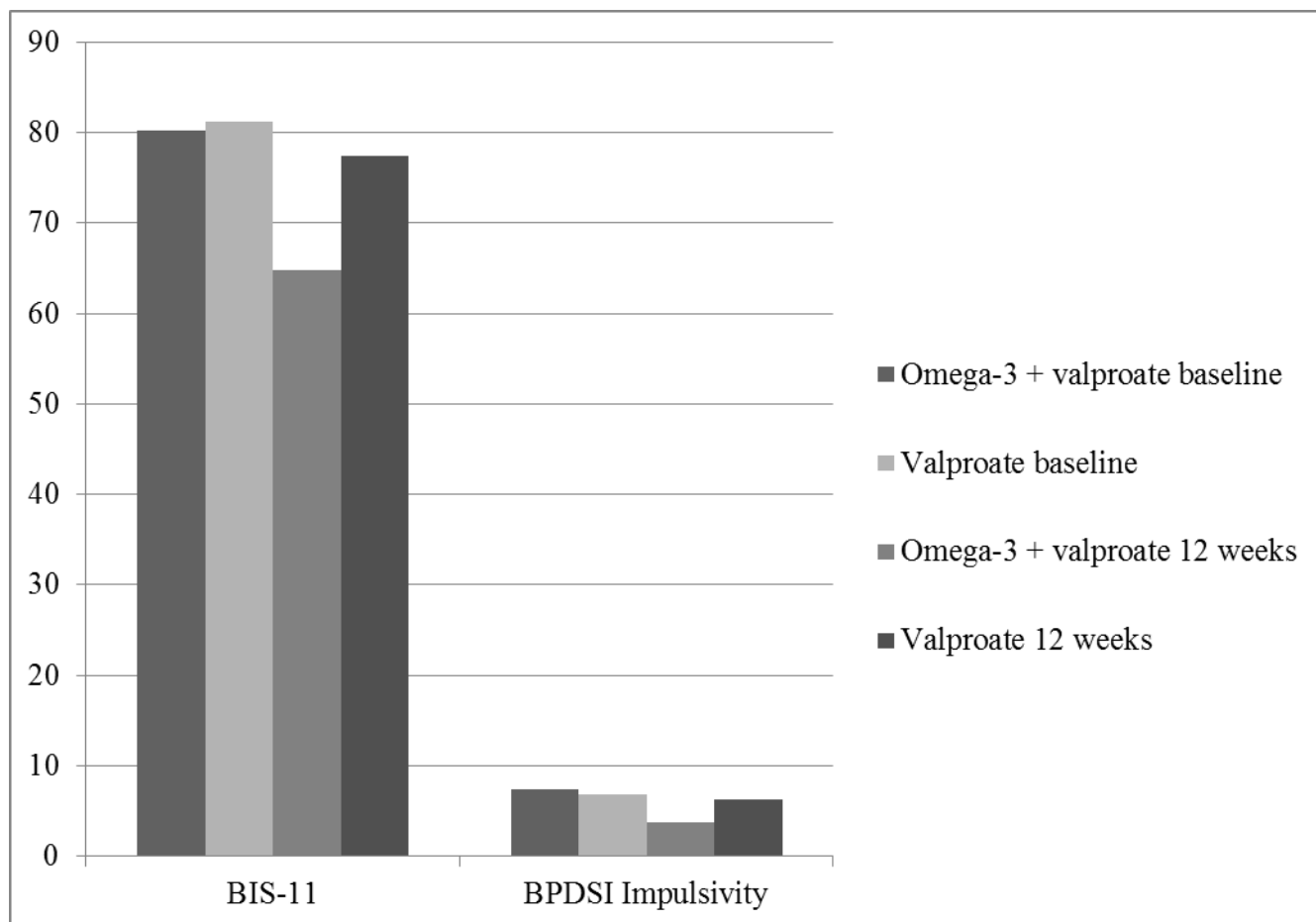
**BIS-11=Barrett Impulsiveness Scale – version 11; SHI=Self Harm Inventory.**

**Table 5. Results of ANOVA repeated measures for the BPDSI domains and total score**

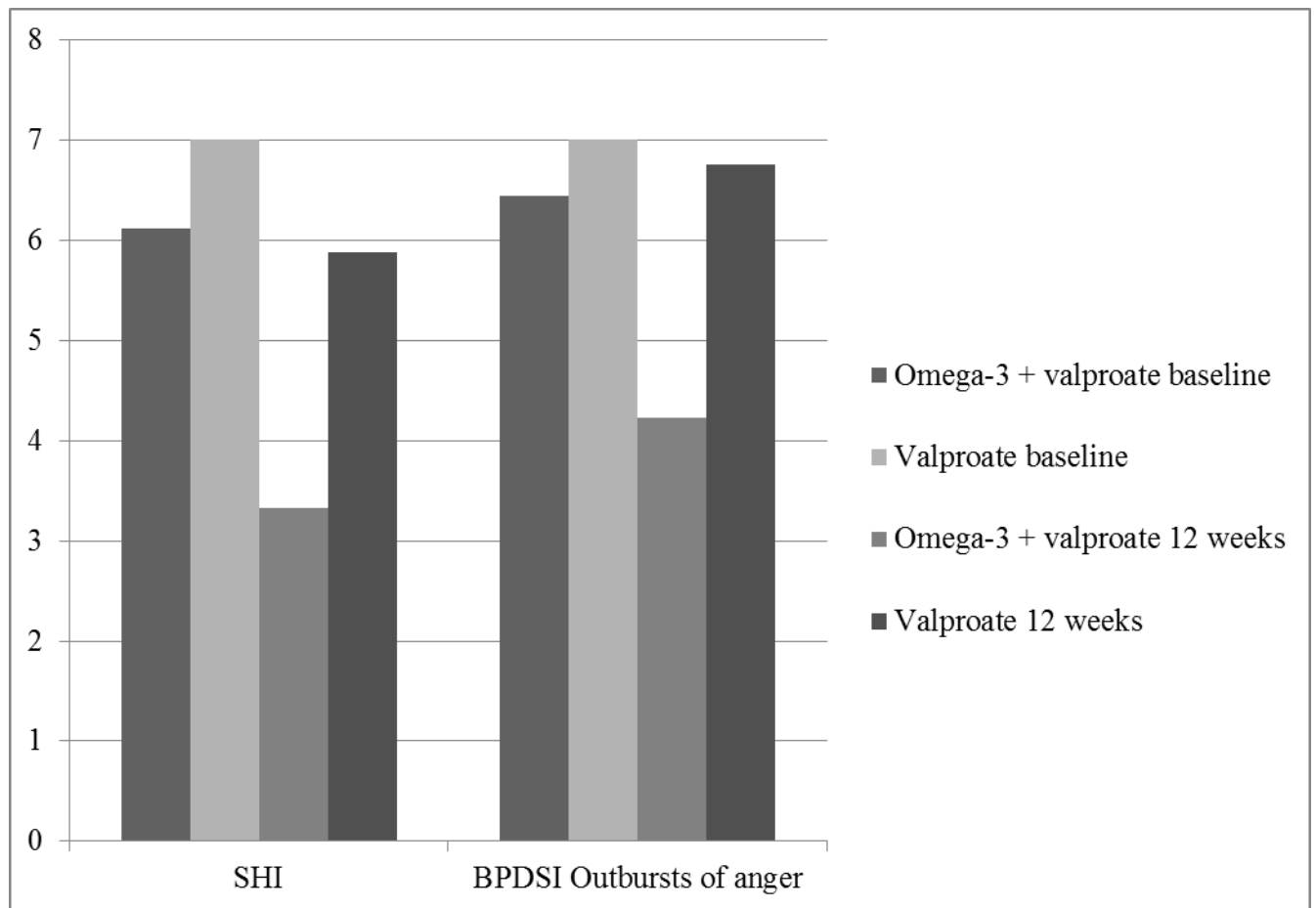
Scale	Treatment	Baseline Mean±SD	12 weeks Mean±SD	Effect within subjects (duration) <i>P</i>	Effect between subjects (treatment) <i>P</i>
<b>BPDSI total score</b>	<b>omega-3 + valproate valproate</b>	48.09±5.85 47.45±6.32	36.09±8.57 44.57±6.53	0.001	0.097
<b>Abandonment</b>	<b>omega-3 + valproate valproate</b>	6.66±1.53 6.50±1.46	6.11±1.41 6.12±1.09	0.001	0.871
<b>Interpersonal relationships</b>	<b>omega-3 + valproate valproate</b>	6.67±0.84 6.75±1.12	5.78±1.26 6.25±1.34	0.001	0.464
<b>Identity disturbance</b>	<b>omega-3 + valproate valproate</b>	4.31±1.52 4.95±1.41	4.20±1.56 4.90±1.53	0.452	0.176
<b>Impulsivity</b>	<b>omega-3 + valproate valproate</b>	7.44±1.20 6.88±1.89	3.78±1.35 6.25±1.61	0.001	0.031
<b>Parasuicidal behaviors</b>	<b>omega-3 + valproate valproate</b>	1.00±1.61 1.37±1.15	0.89±1.57 1.12±1.31	0.073	0.532
<b>Affective instability</b>	<b>omega-3 + valproate valproate</b>	8.11±0.58 7.25±1.24	4.78±1.44 6.50±1.63	0.001	0.283
<b>Outbursts of anger</b>	<b>omega-3 + valproate valproate</b>	6.44±1.29 7.00±1.26	4.22±1.16 6.75±1.61	0.001	0.001
<b>Emptiness</b>	<b>omega-3 + valproate valproate</b>	6.00±1.75 5.37±1.15	5.22±1.73 5.25±1.24	0.001	0.560
<b>Dissociation/ Paranoid ideation</b>	<b>omega-3 + valproate valproate</b>	1.44±1.95 1.37±1.63	1.33±2.00 1.36±1.28	0.180	0.982

**ANOVA=analysis of variance; SD=standard deviation;**

**BPDSI=borderline personality disorder severity index.**



**Figure 1. Mean scores of BIS-11 and BPDSI “Impulsivity” in the two subgroups treated with omega-3 fatty acids plus valproate or single valproate at baseline and after 12 weeks.**



**Figure 2. Mean scores of SHI and BPDSI “Outbursts of anger” in the two subgroups treated with omega-3 fatty acids plus valproate or single valproate at baseline and after 12 weeks.**