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Long chain n-3 polyunsaturated fatty acids decrease feelings of anger in substance abusers

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Abstract

It has been suggested that low levels of n-3 polyunsaturated fatty acids (PUFAs) play a role in the pathophysiology of some psychiatric disorders. In light of the existence of strong associations between high-frequency and high-severity aggressive behaviors and substance use disorders and of our observation that substance abusers have poor dietary habits, the possibility that the administration of supplements of n-3 PUFAs would decrease their anger levels was explored. A life long history of aggressive behaviors and problems with the law was obtained in 24 patients. Thirteen patients received on a daily basis capsules containing 3 g of n-3 PUFAs (EPA+DHA). Eleven patients received placebo capsules. The trial was double-blind, randomized, and lasted 3 months. An anger scale was administered at baseline and every month thereafter. Six PUFA group patients and eight placebo group patients were followed for an additional 3 months after treatment discontinuation. Four patients in each group had a history of assaultive behavior. The baseline fish and n-3 PUFA intakes of these 8 patients were significantly lower than those of the non-aggressive patients. When given for 3 months, n-3 PUFAs were superior to placebo in diminishing anger scores. These scores remained decreased for 3 months following treatment discontinuation. These data provide further support to emerging evidence indicating that supplementation with long-chain n-3 PUFAs could be beneficial in the treatment of some individuals with aggressive tendencies.

Keywords

EPA; DHA; Supplementation; Aggression

1. INTRODUCTION

Over the recent past, there has been increased interest in the role of n-3 polyunsaturated fatty acids (PUFAs) in health and disease. PUFAs are divided into two major families, the n-3 and the n-6 family. EPA (eicosapentaenoic acid, 20:5n-3) and DHA (docosahexaenoic acid, 22:6n-3) are the main long-chain derivatives of the precursor ALA (alpha-linolenic acid, 18:3n-3). AA (arachidonic acid, 20:4n-6) is the main long-chain derivative of the n-6 series precursor LA (linoleic acid, 18:2n-6). ALA and LA are essential fatty acids (EFAs) as mammals cannot synthesize them. The conversion of ALA to EPA and DHA and of LA to AA is limited in humans (Holub, 2002). However, humans can directly ingest the longer chain PUFAs from

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animals or other foods. Dietary fish and shellfish are the main sources of pre-formed EPA and DHA.

Deficiencies in n-3 PUFAs have been reported in a wide range of psychiatric disorders that have included (but are not limited to) depression, suicidal tendencies and aggressive disorders (Alessandri et al., 2004; Young and Conquer, 2005). The available evidence for associations between these disorders and the consumption of foods rich in n-3 PUFAs such as fish has been derived in part from epidemiological studies. International comparison studies have revealed a significant negative association between seafood consumption and the prevalence rates of depression and homicides (Hibbeln, 1998; Hibbeln and Salem, 2001). It could be argued, however, that these associations could be due in part to environmental, cultural or genetic differences between populations. Other types of epidemiological studies (cross-sectional, case control and cohort) have, for the most part, found a negative association between a low intake of fish or n-3 PUFAs or between low amounts of n-3 PUFAs in tissues and depression or suicide risk (Alessandri et al., 2004; Young and Conquer, 2005). These studies are observational and do not constitute absolute proof that fish or n-3 PUFAs affect behavior. Studies of the efficacy of n-3 supplements could theoretically provide stronger evidence for the beneficial role of n-3 PUFAs in psychiatric disorders.

Placebo controlled, randomized, double-blind supplementation studies have assessed the effects of fish oil, EPA or DPA in several psychiatric disorders. Three studies of depressed patients using EPA found improvements in scores on depressive rating scales (Nemets et al., 2002; Peet and Horrobin, 2002; Puri et al., 2001). In other studies, depressed patients improved after being treated with EPA and DHA (Su et al., 2003) but experienced no changes after supplementation with DHA alone (Marangell et al., 2003). The beneficial effects of n-3 PUFAs are not limited to adults but have been reported in childhood depression (Nemets et al., 2006). Treatment with n-3 PUFAs was also found to be effective in bipolar patients (Stoll et al., 1999; Frangou et al., 2006). Few studies have investigated the effects of n-3 supplements on hostility or aggression. In one study, DHA supplementation with oil capsules prevented an increase in aggression at times of stress among Japanese students (Hamazaki et al., 1996) but had no effect in non-stressful situations (Hamazaki et al., 1998). Similar findings by the same authors were reported in an elderly cohort of white-collar workers but not in rural villagers (Hamazaki et al., 2002). In another study, EPA was found to be more effective than a placebo in diminishing aggression as well as the severity of depressive symptoms in women with untreated borderline personality disorder (Zanarini and Frankenburg, 2003). Prisoners treated with supplements of vitamins, minerals and n-6 and n-3 PUFAs had fewer disciplinary incidents than those who had received a placebo but, in light of the multiple supplements, the participants in this study received, it is difficult to attribute the improvement to any supplement in particular (Gesch et al., 2002). In light of the high cost of violence to society and to the individual, more research appears to be needed to evaluate the effects of n-3 PUFAs on hostility and aggression.

We have observed that the diets of many substance abusers were less than optimal because of lack of appetite, lack of interest for food while “high” or unwillingness to spend money for food instead of alcohol or drugs (unpublished). It has also been reported that there is a high rate of comorbidity between substance use and psychiatric disorders (Merikangas et al., 1998). There are strong associations between high-frequency and high-severity aggressive behaviors and substance abuse disorders (Merikangas et al., 1998). In the present study, it was decided to assess the effect of supplements of n-3 PUFAs on hostility in a group of substance abusers. A combination of EPA and DHA was used because the bulk of the literature points to the efficacy of such a combination in improving psychiatric symptoms whereas DHA alone appears to be less effective (J.R. Hibbeln and N. Salem, 2001). It was hypothesized that patients’ consumption of long-chain n-3 PUFAs containing foods prior to the start of the study

would be below recommended intakes and that the administration of long-chain n-3 PUFA supplements would decrease their hostility levels.

2. METHODS

2.1 Patients

Patients selected for participation in this study were 24 men admitted to the New York Harbor Healthcare System (Brooklyn site) substance abuse clinics. All patients consecutively admitted were considered for enrollment after they had completed the first phase of their rehabilitation treatment that lasted 3 months. They underwent a physical examination and were administered a battery of laboratory tests. They were considered for inclusion if they did not have a major physical illness (e.g. cardiovascular, pulmonary, gastrointestinal, renal, neuromuscular, immunodeficiency or endocrine disorder or liver function tests greater than one SD above maximum normal values. Patients were interviewed by a psychiatrist. They were screened for concomitant Axis I disorder using the Structured Clinical Interview for DSM IV (SCID) (First et al., 1997). They were also administered the Addiction Severity Index questionnaire (ASI) (McLellan et al., 1992). The ASI explores the following areas: alcohol and drug use, psychiatric status, family history of alcohol, drug and psychiatric problems, family and social relationships, medical status, legal status and employment/support status. Patients were considered for inclusion if they did not present evidence of schizophrenia, major depressive disorder, bipolar disorder, mental retardation or dementia. If subjects were judged to be appropriate for enrollment, they were offered to participate and, if they accepted, a written informed consent was obtained after complete description of the study. The study was approved by the institution IRB.

2.2 Initial Assessment

The following assessments covering the year and the month preceding the study entry were obtained: nature of the substances used, amount of each substance used and frequency of use. A diet questionnaire covering the month preceding the study entry was obtained. This questionnaire was an adaptation of the National Institute of Health Diet History Questionnaire, downloaded from the National Cancer Institute web site (<http://riskfactor.cancer.gov/DHQ/forms/ncs>). Based on the results of this questionnaire, each patient's intake of Kcalories, n-6 and n-3 PUFAs were calculated, using the USDA National Nutrient Database Reference, Release 17 data downloaded from its website (<http://www.nal.usda.gov/fnic/foodcomp/Data/SR16-1/reports/sr16-1pg.htm>). A modified version of the Profiles of Mood States (POMS) (McNair et al., 1971) was administered. The POMS is a self-report questionnaire which requires subjects to rate the intensity of 65 mood items on a 5-point scale. Ratings are combined into six scores assessing vigor, depression, tension, anger, confusion and fatigue. It was modified for use in this study because we had observed that patients attending our clinics asked to make 325 choices when given the complete POMS quickly lost interest in the task and gave unreliable answers. The modified POMS version was limited to the 36 items comprising the anger, tension and depression subscales with the following two choices for each item: present or absent. This reduced the total number of choices to 72, making the questionnaire more readily acceptable. Changes in anger scores only are the topic of the present report. The following information was also obtained: history of assaultive behavior, history of criminal behaviors including thefts and burglaries, history of jail terms for drug possession or other reasons and arrests for driving while intoxicated (DWI).

2.3 PUFA and placebo treatment

The trial lasted 3 months and was double blind. Patients received either capsules containing n-3 PUFAs or placebo capsules. Assignment to the active substance group or to the placebo group was random. Both types of capsules were purchased from "Nordic Naturals" (94 Hangar

Way, Watsonville, CA 95076). The PUFA capsules contained 450 mg of EPA, 100 mg of DHA and 50 mg of other n-3 PUFAs, ALA and DPA (docosapentaenoic acid, 22:5n-3). These PUFAs were in the form of triglycerides. The placebo capsules contained soybean oil. All capsules contained vitamin E as an antioxidant and lemon oil to mask their taste. Patients were advised to take 5 capsules each day. Those taking the active substances were thus given a daily amount of 3 g of n-3 PUFAs. In order to measure compliance, patients were asked to return the capsule containers before being given new ones. They were also asked to return the containers at the end of the trial. They were considered compliant if 15% or less of the initial number of capsules was left in the containers.

2.4 Follow-up assessments

Twenty seven patients were selected for participation in the study. One patient assigned to the PUFA group and two patients assigned to the placebo group did not return after their first visit. Thirteen patients assigned to the PUFA group and 11 patients assigned to the placebo group were available for follow-up during the 3-month treatment period. One, 2 and 3 months following the start of the study, the substance use self-report, dietary questionnaire and modified POMS covering the one-month period elapsed between two interviews were administered to all patients.

A subset of six patients in the PUFA group and of eight patients in the placebo group was followed for an additional period of 3 months after treatment discontinuation and administered all the questionnaires on a monthly basis. This last group of 14 patients was thus followed for a total of 6 months. It had originally been planned to follow patients during the 3-month treatment period only but because some of the first patients seemed to respond well to the PUFA administration, it was decided to continue to follow new participants for another 3 months in order to see whether the n-3 PUFAs' beneficial effects would persist or disappear. When this decision was made, it was too late to follow the first enrollees for an extra 3 months. The 14 patients followed for 6 months were thus the last ones enrolled.

Throughout the trial, urine screens for presence of substances of abuse were performed at regular intervals.

2.5 Statistical analysis

Comparisons of the two patient groups' demographic and baseline dietary data were made with two-tailed Student's t-tests, chi square tests with Yates' continuity correction or Fisher's exact tests, as appropriate. Comparisons of fish and PUFAs intakes of patients with and without a history of assaultive behavior or with and without a history of criminal acts that did not involve violence were made with non parametric Mann-Whitney U tests.

Comparisons of the changes over time in the anger scale of the two patient groups were done with repeated measures ANCOVAs with baseline values as covariates, using the statistical software SPSS for Windows (version 11.5). This allowed the assessment of the effects of group (PUFAs vs. placebo), of time, and of the interaction of group by time. The significance level was set by default at .05 by the software program. Because of the small number of study participants and the resulting low statistical power of the analyses, effect sizes (*f*) for the differences between the two groups were also calculated. Small, medium and large effect sizes correspond to *f* values of .10, .25 and .50, respectively (Cohen, 1988). In addition, for each treatment group taken separately, the significance of the time effect was assessed with repeated measures ANOVAs and polynomial contrasts.

3. RESULTS

3.1 Patient characteristics

Patient characteristics are shown in table 1. There were no significant differences between the patients assigned to the two treatment groups in age, marital status, educational level, employment status or types of drugs used for a period of one year prior to the start of the study. Nine patients (five in the PUFA group and four in the placebo group) were maintained on doses of methadone ranging from 70 to 120 mg. These doses remained stable throughout the study. Five patients in each group were treated with antidepressants. Doses of antidepressants remained stable throughout the study.

Four patients in each group had a history of assaultive behavior and seven patients in each group had been incarcerated for offences ranging from drug possession to burglary, weapons possession, assault and DWI. When patients were divided into those who had a history of assaultive behavior, more patients in the assaultive group (six of eight or 75%) had been incarcerated than patients who had not assaulted others (eight of 16 or 50%). During the 3 or 6 months the study lasted, none of the patients reported having assaulted others, having used a weapon to try to harm others or having been arrested for non violent or violent crimes. Whether this was the case because the follow-up period was short or because participants were enrolled in a rehabilitation program is not known.

3.2 Side effects

None of the study participants reported side effects except for three patients who stated having loose stools.

3.3 Dietary data

Baseline dietary data are shown in table 2. The mean daily fish intake of the 24 study participants was 35.7 ± 18.6 g. Their mean daily total n-6 PUFA intake was 16.0 ± 8.8 g and their mean daily total n-3 PUFA intake was 1.45 ± 0.86 g. Patients consumed thus 11 times more n-6 than n-3 PUFAs. There were no significant differences between the PUFA and control groups in mean Body Mass Index, mean daily Kcalories, mean daily amounts of fish, mean daily amounts of total, short-chain or long-chain n-6 PUFAs and of total, short-chain or long-chain n-3 PUFAs consumed during the month preceding the start of the study. The fish most frequently consumed were catfish, whiting, flounder or canned tuna. Calculations of differences between the daily intake of 500 mg of long-chain n-3 PUFAs, recommended by ISSFAL, the International Society for the Study of Fatty Acids and Lipids (2004) and patients' actual daily intake did not reveal differences between the groups but showed that both groups fell short of the recommended daily intake. The PUFA group patients consumed on average 27% and the placebo group 33% of this recommended intake. There were no significant changes in PUFA intake over time in any of the two groups, as assessed by repeated measures ANOVAs.

3.4 Associations between diet and aggressive/unlawful behaviors

The baseline daily fish and long-chain n-3 PUFA intakes of patients with and without a history of assaultive behavior are illustrated in Figure 1. A Mann-Whitney U test revealed a significant difference in daily fish intake between patients who had a history of assaultive behavior and those who did not (22.7 ± 10.0 vs. 42.7 ± 18.6 g/day, $P=0.013$). A Mann-Whitney U test revealed a significant difference between these 2 groups in daily intake of long-chain n-3 PUFAs (89.6 ± 36.9 vs. 179.4 ± 106.2 mg/day, $P=0.011$). There were no differences between the groups in the consumption of short- and long-chain n-6 PUFAs and short-chain n-3 PUFAs. None of the patients who reported eating more than 42 g of fish daily reported a history of violence whereas

60% of patients who reported eating less than that amount reported having had violent encounters with others.

There were no differences in fish or long-chain n-3 PUFAs intake of patients who did and did not have a history of criminal behavior that did not involve violence or between those who did and did not have a history of jail terms that were served in the majority of cases for drug possession.

3.5 Effects of n-3 PUFAs and placebo on anger scale scores

Figure 2 illustrates the changes in the anger scale scores during the 3-month administration of n-3 PUFAs or placebo capsules. The figure shows a decline in anger scores in the PUFA group but not in the placebo group. A comparison of the two groups by repeated measures ANCOVA (with baseline values as covariates) revealed a significant difference ($F_{1,21}=5.876$, $P=0.024$) and a large effect size ($f=0.53$). The within subjects effects of time ($F_{2,42}=1.782$) and group by time interaction ($F_{2,42}=1.379$) were not significant. The within subjects effects of time, assessed with repeated measures ANOVAs separately for each treatment group did not show any significant effect of time in the 11 patients on placebo ($F_{3,30}=0.611$) but showed a significant effect of time in the 13 patients receiving PUFAs ($F_{3,36}=7.472$, $P=0.001$). The polynomial contrast showed a significant linear effect ($F_{1,12}=11.994$, $P=0.005$) but no significant quadratic effect ($F_{1,12}=0.766$) in these 13 patients.

Figure 3 illustrates the changes in the anger scale scores of the patients who were followed for 6 months. Scores remained decreased in patients assigned to the PUFA group from month 4 through month 6 following treatment discontinuation. A comparison of the two patient groups who were followed for 6 months by repeated measures ANCOVA (with baseline values as covariate) did not reach conventional statistical significance ($F_{1,11}=4.518$, $P=0.060$) but revealed a large effect size ($f=0.64$). The within subjects effects of time ($F_{5,55}=1.319$) and group by time interaction ($F_{5,55}=0.613$) were not significant. The within subjects effects of time, assessed with repeated measures ANOVAs separately for each treatment group did not show any significant effect of time in the eight patients on placebo ($F_{6,42}=0.205$) but showed a significant effect of time in the six patients receiving PUFAs ($F_{6,30}=4.006$, $P=0.005$). The polynomial contrast showed a significant linear effect ($F_{1,5}=11.118$, $P=0.021$) as well as a significant quadratic effect ($F_{1,5}=9.349$, $P=.028$) for these six patients.

4. DISCUSSION

In this study, the daily administration of 3 g of long-chain n-3 PUFAs for a period of 3 months significantly decreased feelings of anger in a population of substance abusers by comparison with the administration of a placebo. Anger scores did not return to baseline values during the 3 months that followed treatment discontinuation. These results support the observation made by others that supplements of long-chain n-3 PUFAs can diminish hostility levels in groups of non psychiatric individuals and in borderline patients (Hamazaki et al., 1996, 1998, 2003; Zamarini, 2003). The influence of n-3 PUFAs on aggression was also demonstrated in an animal model. Rats fed a diet deficient in n-3 PUFAs for 15 weeks after weaning had a significantly increased score on a test for aggression associated with a 36% reduction in DHA in brain phospholipids (DeMar et al., 2006).

In the small group of participants in the present investigation, significant associations were found between low intakes of fish and of long-chain n-3 PUFAs prior to the start of the study and a history of assaultive behavior. Sixty percent of the patients who had reported having assaulted others stated eating from 8 to 42 g of fish daily. None of the patients eating more than this amount reported a history of assaultive behavior. These data are consistent with a cross-national study showing that rates of homicides are lower in countries where the

consumption of foods rich in PUFAs such as fish is high (Hibbeln and Salem, 2001). They also give support to cross-sectional studies that reported a reduced plasma DHA level in violent male subjects with antisocial personality (Virkkunen et al., 1987), and a lower likelihood of high hostility in young adults whose dietary intake of DHA and of fish was high (Irribaren et al., 2004). If in the present study, there was a causal link between deficient diets and violence, it would imply that patients' poor dietary habits had been long-lasting. We followed for one year a group of substance abusers and observed that their diets changed little during that period (unpublished). Taken together, existing literature and the present study data suggest that the insufficient intake of long-chain n-3 PUFAs may be one of the factors contributing to increased violence in some individuals. It should, however, be noted that in this study, some patients who did not report violent behaviors, had fish and long-chain n-3 PUFAs intakes as low as those of violent patients. It may be that only some individuals are vulnerable to diverse influences, one of which could be an insufficient intake of long-chain n-3 PUFAs.

Recommendations for the intake of n-3 PUFAs necessary to cover human requirements are still in the process of being determined and will have to await the completion of additional trials. These recommendations vary from country to country and depend in part on the amount of n-6 PUFAs present in different diets because n-6 PUFAs influence tissue concentrations of n-3 PUFAs. Based on a review of major epidemiological studies conducted in the US, the daily intake of EPA and DHA recommended by ISSFAL (International Society for the Study of Fatty Acids and Lipids, 2004) for cardiovascular health is 500 mg. More recently, Hibbeln et al. (2006) have proposed that the daily dietary allowance of long-chain n-3 PUFAs that would protect the US population against both cardiovascular and major psychiatric diseases should be higher than the ISSFAL recommendation and should be as high as 3.5 g per day for a 2000 Kcal diet. Participants in the present study consumed only an average of 149 mg of long-chain n-3 PUFAs daily, or 30% of the ISSFAL recommendation and 3.7% of the Hibbeln et al.'s recommendation. Their intake of EPA and DHA was most likely even lower because in our calculations of long-chain n-3 PUFAs, DPA was included. Depending on the estimations of what amounts to healthy long-chain n-3 PUFAs consumption, the reported intakes of patients taken as a group could be rated as being either deficient or very deficient. The long-chain n-3 PUFAs intakes of patients who had assaulted others were even lower and amounted to 18% and 2.6% of the ISSFAL and Hibbeln et al.'s recommendations, respectively.

It has been suggested that n-3 PUFAs could decrease stress (Bradbury et al, 2004) and could be effective in the treatment of a wide variety of psychiatric disorders, including mood disorders, attention deficit and hyperactivity disorders, Alzheimer's disease, dementia and schizophrenia. The effects of n-3 PUFAs have been reviewed recently (Alessandri et al., 2004; Young et al., 2005; Berger et al., 2006; Parker et al., 2006; Peet, 2005). This apparent multitude of effects could be understood in light of the extraordinary complexity and diversity of actions of PUFAs (Alessandri et al., 2004; Young and Conquer, 2005). They are components of neuronal membrane phospholipids and modulate their dynamic properties. The conformation of proteins embedded in the membrane bi-layer is influenced by its lipid components. These proteins have important functions as they act as receptors and transporters and can alter the passage of ions. Neuronal membrane fluidity that can be altered by their PUFA composition can thus affect the function of neurotransmitters systems. Upon stimulation, both n-6 and n-3 PUFAs can also be cleaved from membrane phospholipids under the influence of phospholipases and can be converted via different pathways to mediators that have opposing effects. AA derived mediators are vasoconstrictive, pro-aggregant and pro-inflammatory whereas EPA derived mediators have vasodilating, anti-aggregating and anti-inflammatory actions. Finally, PUFAs and their metabolites regulate gene transcriptions. All of the actions of PUFAs have probably not yet been completely elucidated.

In light of this diversity of actions, it could be hypothesized that different mechanisms could have played a role in the decrease in anger scores observed in this study. Modifications of serotonergic neurotransmission that have been implicated in violence might be one of the modes of action of n-3 PUFA supplementation (Mann, 1995). Higher concentrations of plasma DHA were found to predict higher levels of CSF 5-HIAA in healthy controls and late onset alcoholics (Hibbeln et al., 1998). This finding suggests that increasing DHA consumption may increase brain serotonin. In the animal literature, it has been shown that modifying the PUFA composition of the diet can influence neurotransmitter level. The supplementation of AA and DHA in the diet of piglets increased the frontal cortex concentrations of 5-HT and dopamine (de la Pressa Owens and Innis, 2000). Decreasing PUFA levels was found to affect 5-HT as well. Rats fed a diet deficient in n-3 PUFAs had an increase in 5-HT receptor density in the frontal cortex with no changes in binding activity (Delion et al., 1996). These changes were similar to those reported by Stanley and Mann (1983) among suicide victims. In other studies, diets low in PUFAs induced decreased concentrations of 5-HT and 5-HIAA in several brain regions including the cortex (Olsson et al., 1998) and decreased amounts of 5-HT released during synaptic transmission (Kodas et al., 2004). Other mechanisms might be at play as well because a combination of DHA and EPA or EPA alone appear to have a greater efficacy than DHA alone (Alessandri et al., 2004). One could wonder why EPA, which is not abundant in neuronal membranes, appears more effective than DHA alone (Hibbeln and Salem, 2001). It has been suggested that EPA could play a role in brain function by counteracting the AA-mediated signaling. EPA could, for example, competitively attenuate the formation of the n-6 derived eicosanoids that mediate immune-inflammatory responses that have been linked to the pathophysiology of mood disorders (Maes and Smith, 1998; Raison et al., 2006). EPA could also counteract the vasoconstrictive effects of AA, thereby increasing blood flow in the brain.

There are few data about the eventual persistence of the behavioral effects of n-3 PUFA supplementation after the administration of the supplements has been discontinued. In this study, anger scores remained reduced for 3 months following treatment discontinuation. This could be attributed to the persistent central effects of n-3 PUFAs. It is also possible that fatty acids were stored in fatty tissues and continued to be released from these stores and thus continued to influence patients' feelings.

The present study has some limitations. The number of participants was small and some of them received medications. It should be pointed out that medication doses remained stable during the study and that a number of other studies of the efficacy of n-3 PUFAs supplementation in mood disorders involved individuals on standard medication who experienced further improvements that were attributed to the PUFA supplements.

This study, which needs to be replicated in larger samples, showed that the daily administration of 3 g of long-chain n-3 PUFAs for a period of 3 months significantly decreased feelings of anger by comparison with the administration of a placebo. This decrease appeared to persist for 3 months after treatment discontinuation. These data give support to emerging evidence that long chain n-3 PUFAs could play a role in hostility and violence. Angry feelings can lead to aggressive behaviors and in this small population sample, the group of patients who had a history of violent encounters with others reported significantly lower intakes of fish and of long-chain n-3 PUFAs than patients who had not exhibited violent behaviors. N-3 PUFAs supplements, that are both inexpensive and well tolerated, could be considered as treatment adjuncts for patients displaying aggressive behaviors. Moreover, n-3 PUFAs have been shown to be beneficial to general physical health and have been specifically recommended for the prevention of cardiovascular diseases (Kris-Etherton et al., 2002).

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Figure 1.

Baseline daily fish and long chain n-3 PUFAs intake in patients with and without a history of assaultive behavior. Circles represent individual patients. Horizontal lines represent means. Comparisons of the two patient groups with Mann-Whitney U tests revealed that patients with a history of assaultive behavior reported significantly lower fish and long chain n-3 PUFAs intakes ($P=0.013$ and $P=0.011$, respectively).

Figure 2.

Anger scale scores (Means $\pm$ SEM) of substance abusers during a 3-month administration of n-3 PUFAs or placebo. A comparison of the scores of the 2 patient groups by a repeated measures ANCOVA (with baseline values as covariates) revealed a significant difference ($P=0.025$). The effect size was large ($f=0.53$).

Figure 3.

Anger scale scores (Means ± SEM) in a subset of the initial sample of substance abusers during a 3-month administration of n-3 PUFAs or placebo and a follow-up period of 3 months. A comparison of the scores of the 2 patient groups by a repeated measures ANCOVA (with baseline values as covariates) almost reached significance ($P=0.060$). The effect size was large ($f=0.64$).

Table 1
CHARACTERISTICS OF PATIENTS TREATED WITH N-3 PUFAS AND PLACEBO

	All patients (n=24)	n-3 PUFAs (n=13)	Placebo (n=11)	<i>P</i> value
Age (years)	51.2±6.9	52.0±7.0	50.3±7.0	NS
Marital status				
Never married	25.0% (6/24)	30.8% (4/13)	18.2% (2/11)	NS
Married	16.7% (4/24)	15.4% (2/13)	18.2% (2/11)	NS
Separated/Divorced/Widowed	58.3% (14/24)	53.8% (7/13)	63.6% (7/11)	NS
Educational level (years)	12.2±1.2	12.5±0.8	12.0±1.5	NS
Employment status				
Employed	20.8% (5/24)	23.1% (3/13)	18.2% (2/11)	NS
Unemployed	79.2% (19/24)	76.9% (10/13)	81.8% (9/11)	NS
Drugs used during 1 year preceding the study [*]				
Alcohol	50.0% (12/24)	38.5% (5/13)	63.6% (7/11)	NS
Cocaine	70.8% (17/24)	69.2% (9/13)	72.7% (8/11)	NS
Heroin	45.8% (11/24)	46.2% (6/13)	45.4% (5/11)	NS

^{*} Some patients used more than one drug.

Values are Means ± SD

Comparisons between the PUFA and placebo groups were made with two-tailed Student's t-tests or chi-square tests, as appropriate.

Table 2
BASELINE DAILY CALORIES, FISH AND PUFA INTAKES OF PATIENTS TREATED WITH N-3 PUFAS AND PLACEBO

	All patients (n=24)	n-3 PUFAs (n=13)	Placebo (n=11)	P value
Body Mass Index (BMI)	25.68±3.85	26.02±3.94	25.8±3.85	NS
Kcalories	2286±1424	2305±1499	2261±1401	NS
Fish (grams)	35.7±18.6	35.9±20.9	35.5±16.4	NS
n-6 PUFAs (in grams)				
Short chain (C18)	15.7±8.7	16.7±9.0	14.5±8.6	NS
Long chain	0.239±0.232	0.208±0.191	0.280±0.282	NS
Total	16.0±8.8	16.9±9.2	14.7±8.7	NS
n-3 PUFAs (in grams)				
Short chain (C18)	1.30±0.78	1.35±0.86	1.24±0.71	NS
Long chain	0.148±0.097	0.135±0.110	0.165±0.080	NS
Total	1.45±0.86	1.48±0.96	1.40±0.78	NS
Daily intake of long chain n-3 PUFAs as % of ISSFAL recommended intake	30±19	27±22	33±16	NS

Values are Means ± SD.

Comparisons between the PUFA and placebo groups were done with two-tailed Student's t-tests or, in case of non-Gaussian distribution, with Mann-Whitney U tests.

ISSFAL is the abbreviation for "International Society for the Study of Fatty acids and Lipids".