

## Possible deleterious effects of adjunctive omega-3 fatty acids in post-traumatic stress disorder patients

Since anger and hostility are frequently pivotal problem behaviors in post-traumatic stress disorder (PTSD) patients and depression is a common comorbid feature of PTSD, we initiated a preliminary open trial of dietary supplementation with capsules of fish oil rich in eicosapentaenoic acid (EPA) in a group of PTSD patients with these problems. Our purpose in the present study was to examine whether EPA-rich fish oil has any effect on the symptoms of PTSD patients, especially those related to depression, anger, and hostility.

We found that we had to severely curtail the study in response to complaints by our patients, which we feel are worthy of reporting here, in spite of the open-label nature and the very small number of participants.

### Introduction

PTSD is an incapacitating clinical syndrome characterized by intrusive recollections, emotional numbing and withdrawal, cue-related responses, and a chronic state of combined psychological and physiological hyperarousal (APA 1994), often expressed as irritability and outbursts of anger, with difficulties in concentration, perpetual hypervigilance, and a grossly exaggerated startle response.

Most studies of pharmacotherapy for PTSD agree that treating the predominant core symptoms and/or the associated anxiety and depressive symptoms (Davidson 1992; Solomon et al 1992; Davidson and Colket 1997) affords considerable relief and enables therapeutic and rehabilitative efforts to be applied with greater hope of success.

There has been quite a lot of interest concerning the role of dietary supplements in controlling or affecting various medical conditions including psychiatric disorders and sequelae of myocardial infarction. Lately, there has been special interest in the role of omega-3 fatty acids in mood disorders (Stoll et al 1999; Freeman 2000; Nemets et al 2002) and chronic ischemic heart disease (CIHD) (Geleijnse et al 2002). Recent studies of CIHD-prevention have focused on emotional factors, specifically depression, anger, and

hostility, as being the most likely factors mediating the beneficial effects of  $\omega$ 3-FA in CIHD (Geleijnse et al 2002).

Omega-3 (polyunsaturated) fatty acids (FA) ( $\omega$ 3-FA) are essential long-chain polyunsaturated fatty acids that are concentrated in the central nervous system, retina, and testes in humans. Eicosapentaenoic acid (EPA-C20:5n-3) and docosahexaenoic acid (DHA-22:6n-3) are components of the  $\omega$ 3-FA found in fish oils. It has been shown that dietary intake of  $\omega$ 3-FA has a number of potentially salutary effects, including a cumulative lowering of the nonesterified FA concentration in plasma and cell membranes, and modulation of sodium, potassium, and L-type calcium channels (Geleijnse et al 2002). They may thus directly and/or indirectly influence cellular function.

### Methods

#### Subjects

Six consecutive patients fulfilling DSM-IV diagnostic criteria for PTSD (as assessed by the Structured Clinical Interview) were recruited from the population under treatment in the Trauma and Post-Trauma Clinic at the Beer-Sheva Mental Health Center, Israel, for the pilot phase of the trial. All patients suffered from moderate to significant PTSD, with marked problems in controlling anger and depressive symptoms.

The subject group consisted of three men and three women, with a mean age of 44.25 ( $\pm$ SD 17.6) years, range 23–66. Types of trauma were vehicle accident=5 and combat trauma=1. Mean time elapsed since trauma was 14.75 ( $\pm$ SD 14.4) years, range 2–31 years. All were physically healthy, did not abuse substances, and had no known head trauma.

Two patients were treated with paroxetine 20 mg/day and two were treated with citalopram 30 mg/day. After receiving full explanation of the procedures, all subjects signed a written informed consent approved by the Helsinki Ethics Committee of Ben-Gurion University.

#### Study design

The study was a by-product of a large series of studies of the effect of  $\omega$ 3-FA on mental disorders that were being performed at our center. We elected to perform the pilot study as an open-label study. After baseline physical examination and determination of blood chemistry, patients were assigned to receive ethyl EPA 2 g/day (96% pure semi-synthetic ethyl-EPA) for about 3 months. The EPA

was supplied by Dr David Horrobin, Laxdale Ltd (Stirling, UK). Fish taste and smell were minimal. No other modifications were made to the patients' diets.

Patients continued their medications and psychotherapeutic treatments without change throughout this period.

The patients were assessed at two time points—at baseline and at the end point—using the following instruments: The Symptom Check List (SCL-90-R) (Derogatis et al 1976) Impact of Event Scale (IES) (Horowitz et al 1979), State Trait Anger Scale (Spielberger et al 1983), and Impulsivity Scale (Plutchik and van Praag 1990).

## Results

Six patients entered the study. Four patients completed the trial. Two patients dropped out within the first 3–4 weeks: one man who “felt no change” and thus refused to continue and one woman who complained of “feeling greasy all over”.

Psychiatric symptoms, such as hostility, interpersonal sensitivity, somatization, depression, anxiety, phobia, obsession, paranoia, and psychoticism were evaluated. At completion, all the mean symptoms were unchanged as compared with the baseline symptoms. Assessed in terms of individual scores, three patients showed mild to moderate tendencies towards worsening in almost all items, and the remaining patient showed no change.

The only statistically significant change was a marked worsening of the avoidance subscale of the IES in all three of the four patients who demonstrated a general tendency towards worsening scores on all scales. The remaining patient was unchanged.

At completion, the specifically targeted anger and hostility symptoms remained unchanged in both questionnaires.

## Discussion

The results of this abruptly curtailed study suggest that adjunctive EPA may well be ineffective in relieving either the anger and hostility or the depressive symptoms in PTSD patients. This initial PTSD patient sample not only did not benefit from  $\omega$ 3-FA, but rather appears to have experienced somewhat deleterious effects. The study is very limited in terms of population number and composition, and in terms of being open-label, although this is the result of problematic patient responses to the preparation.

These data, however, do reinforce the results of other studies of  $\omega$ 3-FA in unipolar depression patients (Marangell et al 2003) and in obsessive-compulsive disorder patients

(Fux et al 2004) where placebo-controlled crossover trials found that EPA is virtually ineffective.

We have, however, not come across reports of deleterious effects of  $\omega$ 3-FA. Our initial results have alerted us to the possibility that further study of  $\omega$ 3-FA must be performed with awareness towards the possibility that the preparations may have potentially deleterious effects in certain patients.

## Kaplan Zeev, Matar Michael, Kamin Ram, Cohen Hagit

Ministry of Health Mental Health Center, Anxiety and Stress Research Unit, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel; email Zeev Kaplan PbeZeevK@matat.health.gov.il

## Acknowledgments

We express our thanks to Professor RH Belmaker for consultation and advice in the study.

## References

- [APA] American Psychiatric Association. 1994. Diagnostic and statistical manual of mental disorders. 4th ed (DSM-IV). Washington: APA.
- Davidson J. 1992. Drug therapy of post-traumatic stress disorder. *Br J Psychiatry*, 160:309–14.
- Davidson JR, Colket JT. 1997. The eight-item treatment-outcome post-traumatic stress disorder scale: a brief measure to assess treatment outcome in post-traumatic stress disorder. *Int Clin Psychopharmacol*, 12:41–5.
- Derogatis LR, Rickels K, Rock AF. 1976. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. *Br J Psychiatry*, 128:280–9.
- Freeman MP. 2000. Omega-3 fatty acids in psychiatry: a review. *Ann Clin Psychiatry*, 12:159–65.
- Fux M, Benjamins J, Nemets B. 2004. A placebo-controlled cross-over trial of adjunctive EPA in OCD. *J Psychiatr Res*, 38:323–5.
- Geleijnse JM, Giltay EJ, Grobbee DE, et al. 2002. Blood pressure response to fish oil supplementation: meta-regression analysis of randomized trials. *J Hypertens*, 20:1493–9.
- Horowitz M, Wilner N, Alvarez W. 1979. Impact of Event Scale: a measure of subjective stress. *Psychosom Med*, 41:209–18.
- Marangell LB, Martinez JM, Zboyan HA, et al. 2003. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry*, 160: 996–8.
- Nemets B, Stahl Z, Belmaker RH. 2002. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry*, 159:477–9.
- Plutchik R, van Praag HM. 1990. A self-report measure of violence risk, II. *Compr Psychiatry*, 31:450–6.
- Solomon SD, Gerrity ET, Muff AM. 1992. Efficacy of treatments for posttraumatic stress disorder. An empirical review. *JAMA*, 268: 633–8.
- Spielberger CD, Jacobs. 1983. Assessment of anger: The State-Trait Anger Scale. In Butcher JN, Spielberger CD, et al (eds). *Advances in personality assessment*. Volume 2: Hillside: Lawrence Erlbaum Assoc. p 159–87.
- Stoll AL, Severus WE, Freeman MP. 1999. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry*, 56:407–12.