# Omega-3 Fatty Acids in the Prevention of Interferon-Alpha-Induced Depression: Results from a Randomized, Controlled Trial

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**Background:** Interferon (IFN)-α therapy for chronic hepatitis C virus infection is frequently associated with depression. The routine prophylaxis with antidepressants might expose patients to adverse effects, hence, the need for alternative preventive interventions. Omega-3 polyunsaturated fatty acids are safe and effective essential nutritional compounds used for the treatment of depression, putatively through an anti-inflammatory action. In addition, lower erythrocyte levels of omega-3 polyunsaturated fatty acids have been associated with an increased risk of IFN-induced depression.

**Methods:** We conducted a 2-week, double-blind, placebo-controlled trial comparing eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and placebo for the prevention of IFN-α-induced depression. A total of 162 patients consented to participate and were randomized to the study. All of the patients completed the 2-week trial; 152 participants were followed throughout the 24 weeks of IFN-α treatment and were included in the analysis.

**Results:** Compared with placebo, the incident rates of IFN-α-induced depression were significantly lower in EPA-treated but not in DHA-treated patients (10% and 28%, respectively, versus 30% for placebo, $p = .037$). Both EPA and DHA significantly delayed the onset of IFN-induced depression (week of onset: 12.0 and 11.7, respectively, versus 5.3 for placebo, $p = .002$). EPA and DHA were both well tolerated in this population. EPA treatment increased both EPA and DHA erythrocyte levels, but DHA only increased DHA erythrocyte levels.

**Conclusions:** EPA is effective in the prevention of depression in hepatitis C virus patients received IFN-α therapy. Our study confirms the notion that anti-inflammatory strategies are effective antidepressants in the context of depression associated with inflammation.

**Key Words:** Chronic hepatitis C virus (HCV), clinical trial, omega-3 polyunsaturated fatty acids (n-3 PUFAs), inflammation, interferon-alpha (IFN-α), major depressive disorder (MDD)

Finding the best strategy to prevent neuropsychiatric adverse effects induced by interferon (IFN)-α will improve clinical outcome and shed light on the pathogenesis of inflammation-induced depression, but previous studies have had mixed results (see below), especially in patients who receive IFN-α for chronic hepatitis C virus (HCV) infection. Chronic HCV infection is a major public health issue and has a high rate of progression to liver cirrhosis and hepatocellular carcinoma (1,2). IFN-α is the standard therapy for HCV infection and will remain a cornerstone of therapy, even within the new combinations with ribavirin and protease inhibitors (3). However, the clinical impact of IFN-α is reduced by the common and severe neuropsychiatric adverse effects. For example, almost all the patients experience acute sickness behavior, including symptoms of fatigue, malaise, myalgia, arthralgia, anorexia, apathy, and cognitive impairment (4–7). In addition, up to 30% of patients develop IFN-α-induced depression (a major depressive episode according to DSM-IV diagnostic criteria) within the first 3 months (8–10). These neuropsychiatric side effects result in early discontinuation of IFN-α therapy and poor clinical outcome (11–13).

Because of the high rate of IFN-α-induced depression, there is an ongoing debate on the use of prophylactic antidepressant use (14). The use of antidepressants is supported by the frequently cited trial, in patients with malignant melanoma, demonstrating a significant preventive effect of paroxetine, a selective serotonin reuptake inhibitor (SSRI) (15). However, in patients with HCV infection, the prophylactic effects with SSRIs have been demonstrated by some (16–18), but not all (19–22), studies. Moreover, SSRI-induced gastrointestinal bleeding is a particular concern in patients with HCV infection (23), who may already have esophageal varices and low platelet count (24). In addition, the use of antidepressants in patients receiving IFN-α therapy has been associated with rare, but severe, adverse effects, such as retinal hemorrhaging and cotton-wool spots (15,25), bone marrow suppression, hepatotoxicity (21,26), and manic episodes (27). As most patients receiving IFN-α do not develop clinically significant depression, the routine pretreatment with antidepressant drugs might expose patients to unnecessary medications; it is thus important to find alternative strategies for the prevention of IFN-α-induced depression.

Omega-3 polyunsaturated fatty acids (ω-3 or n-3 PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential nutritional compounds with potential preventive and therapeutic effects against depression. Patients with major depressive disorder have lower levels of omega-3 PUFAs (28), and societies that consume a larger amount of omega-3 PUFAs have a lower prevalence of major depressive disorder (29,30).

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More importantly, meta-analyses and many clinical studies (31–33), if not all (34–36), have shown that omega-3 PUFAs have antidepressant effects. Taken together also with the evidence discussed below, these studies support the use of omega-3 PUFAs as an effective depression prophylactic strategy in at-risk groups, such as indeed patients taking IFN-α.

One of the hypothesized mechanisms underlying PUFAs' antidepressant effects is their neuroprotective and anti-inflammatory action (37,38). Indeed, EPA is important in regulating immune function by antagonizing membrane arachidonic acid (an n-6 PUFA), reducing prostaglandin E2 synthesis (39), and preventing the response to inflammatory stimuli (40–43). Moreover, omega-3 PUFAs have been found to have beneficial effects in animal models of cytokine-induced behavioral changes that resemble depressive behavior (44–46). Of particular relevance for the present study, we have recently demonstrated that lower DHA levels in the peripheral blood are associated with an increased risk of developing IFN-α-induced depression over the following weeks (9). We have hypothesized that this reflects less endogenous anti-inflammatory capability in those who later develop depression (9). Based on this and the other evidence discussed above, we have conducted this 2-week, double-blind, placebo-controlled trial to test the differential effects of the omega-3 PUFAs, EPA, and DHA against placebo in the prevention of IFN-α-induced depression.

We have specifically prescribed a short (2 weeks) intervention before IFN-α therapy, to potentially correct the lower omega-3 fatty acid levels that we had previously identified as a risk factor for the development of IFN-α -induced depression (9). Indeed, we also have measured the levels of PUFAs in the erythrocytes before and after the trial and correlated these with treatment response. In addition, we have chosen to test a prophylactic intervention that would be acceptable to most patients because of its brevity and because it would precede, and not overlap with, the IFN-α (and ribavirin) therapy. According to most studies, the active antidepressant component from omega-3 PUFAs is EPA (32,33), but we also wanted to test DHA because, as mentioned above, we have found that lower levels of this omega-3 PUFA predispose to IFN-induced depression (9).

## Methods and Materials

### Patient Selection

Since 2005, a psychiatric team has been working together with the hepatologists to provide an integrated care package for HCV patients referred for IFN-α therapy at the Liver Centre of China Medical University Hospital, Taichung, Taiwan, where the Institutional Review Board approved the study. In the period between July 2009 and June 2012, the hepatologists identified eligible HCV patients before they started the combination therapy with peginterferon α-2b (1.5 μg per kilogram of body weight once weekly) and ribavirin (1000–1200 mg daily). Patients were excluded from this study if they had a major depressive episode at the initial assessment; a lifetime history of psychotic disorders (e.g., schizophrenia or bipolar disorder); a history of alcohol or drug dependence within 1 year before entry into the study; and evidence of any unstable chronic medical conditions (e.g., cardiovascular, endocrine, hematological, renal, or neurological diseases). The diagnoses of psychiatric disorders were based on the structured Mini-International Neuropsychiatric Interview (47). All patients who agreed to participate in this study provided their signed written informed consent before enrollment.

### Study Design and Recruitment

Two hundred seven patients with HCV were screened, 162 of them consented to participate and were randomized to the study, and all of them completed the 2-week trial; 152 participants were followed throughout the 24 weeks of IFN-α treatment and were included in the analysis. For allocation of the participants following simple double-blind randomization procedures, a computer-generated list of random numbers was used. The identical capsules were prepacked in bottles and consecutively numbered according to the randomization schedule by an independent nutritionist.

Figure S1 in Supplement 1 provides a flow chart summarizing study recruitment. Ten subjects discontinued the IFN-α treatment; they did not differ from the completers in any demographic features, including gender, age, married status, education years, and past history of depression. While the noncompleters did have significantly higher baseline scores than completers in depressive symptoms (Hamilton Rating Scale for Depression [HAMD]: 8.6 ± 3.65 versus 4.5 ± 4.49; $p = .018$) and neurovegetative symptoms (Neurotoxicity Rating Scale [NTRS]: 52.9 ± 41.74 versus 26.9 ± 29.58; $p = .010$), they were equally distributed among the three groups (EPA, $n = 4$; DHA, $n = 3$; placebo, $n = 3$).

The subjects were randomly assigned in double-blind fashion to EPA, DHA, or placebo, administered for 2 weeks before starting IFN-α therapy. Specifically, 2 weeks before the initiation of IFN-α therapy (week –2), patients started receiving a daily treatment of five identical capsules of EPA (3.5 g/day), DHA (1.75 g/day), or placebo (high oleic oil) in single or divided administration. The experimental capsules contained concentrated EPA (700 mg), DHA (350 mg), or high oleic oil (800 mg); they weighed 1000 mg, were deodorized with orange flavor, and were supplemented with tertiary-butyl hydroquinone (.2 mg/g) and tocopherols (2 mg/g) as antioxidants. The sources of EPA, DHA, and oleic acids were, respectively, anchovy fish body oil (purchased from AK BioTech, Ulsan, Korea), algal vegetable (purchased from DSM Nutritional Products, Basel, Switzerland), and safflower oil (purchased from Aarhus Karlshamn, Hull, England).

The recruited participants were evaluated at weeks –2 (when omega-3 fatty acid prophylactic intervention started) and 0 (when the prophylactic intervention stopped and IFN-α therapy started) and during weeks 2, 4, 6, 8, 12, 16, 20, and 24 of IFN-α therapy to assess the occurrence of major depressive episode with the structured Mini-International Neuropsychiatric Interview. Sociodemographic factors, including gender, age, education, and marital status, as well as the past psychiatric history, substance use history, and family psychiatric history, were recorded at the initial assessment. Severity of depressive symptoms and of neurovegetative symptoms were measured using, respectively, the 21-item HAMD (48), rated by trained psychiatrists, and the self-administered NTRS (49), both administered at weeks –2, 0, 2, 4, 6, 8, 12, 16, 20, and 24. The NTRS is a checklist questionnaire that has been frequently used for the evaluation of neuropsychiatric symptoms related to cytokine therapy; the items are categorized into general symptoms, nonpainful somatic symptoms, and painful somatic symptoms, with each item rated from 0 to 10 on a visual analog scale, and the final score ranging 0 to 390 (15,49–51). During IFN-α therapy, allowable concomitant medications included acetaminophen and other nonsteroidal anti-inflammatory agents for pain symptoms and fever; granisetron or ondansetron for nausea; lorazepam for severe anxiety; and zolpidem for insomnia. The results of routine biochemical laboratory examinations, the occurrence of adverse effects, and any reason for IFN-α discontinuation were recorded.