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# Evaluation of the Effects of Neptune Krill Oil™ on the Management of Premenstrual Syndrome and Dysmenorrhea

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## Abstract

**PRIMARY OBJECTIVE:** To evaluate the effectiveness of Neptune Krill Oil™ (NKO™) for the management of premenstrual syndrome and dysmenorrhea. **SECONDARY OBJECTIVE:** To compare the effectiveness of NKO for the management of premenstrual syndrome and dysmenorrhea with that of omega-3 fish oil. **METHODS/ DESIGN:** Double-blind, randomized clinical trial. **SETTING:** Outpatient clinic. **PARTICIPANTS:** Seventy patients of reproductive age diagnosed with premenstrual syndrome according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R). **INTERVENTIONS:** Treatment period of three months with either NKO or omega-3 fish oil. **OUTCOME MEASURES:** Self-Assessment Questionnaire based on the American College of Obstetricians & Gynecologists (ACOG) diagnostic criteria for premenstrual syndrome and dysmenorrhea and number of analgesics used for dysmenorrhea. **RESULTS:** In 70 patients with complete data, a statistically significant improvement was demonstrated among baseline, interim, and final evaluations in the self assessment questionnaire ( $p < 0.001$ ) within the NKO group as well as between-group comparison to fish oil, after three cycles or 45 and 90 days of treatment. Data analysis showed a significant reduction of the number of analgesics used for dysmenorrhea within the

NKO group (comparing baseline vs. 45- vs. 90-day visit). The between-groups analysis illustrated that women taking NKO consumed significantly fewer analgesics during the 10-day treatment period than women receiving omega-3 fish oil ( $p < 0.03$ ). **CONCLUSION:** Neptune Krill Oil can significantly reduce dysmenorrhea and the emotional symptoms of premenstrual syndrome and is shown to be significantly more effective for the complete management of premenstrual symptoms compared to omega-3 fish oil.

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*Table 1. Diagnostic Criteria for PMS*

- A. In most menstrual cycles during the past year, symptoms occurred during the last week of the luteal phase and remitted within a few days after the onset of the follicular phase. In menstruating females, these phases correspond to the week before, and a few days after, the onset of menses. (In non-menstruating females who have had a hysterectomy, the timing of luteal and follicular phase may require measurement of circulating reproductive hormones.)
- B. At least five of the following symptoms have been present for most of the time during each symptomatic late luteal phase, at least one of the symptoms being either (1), (2), (3), or (4):
  - 1. marked affective lability, e.g., feeling suddenly sad, tearful, irritable, or angry;
  - 2. persistent and marked anger or irritability;
  - 3. marked anxiety, tension, feelings of being "keyed up" or "on edge;"
  - 4. decreased interest in usual activities, e.g., work, friends, hobbies;
  - 5. easy fatigability or marked lack of energy;
  - 6. subjective sense of difficulty in concentrating;
  - 7. marked change in appetite, overeating, or specific food cravings;
  - 8. hypersomnia or insomnia;
  - 9. other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," weight gain.
- C. The disturbance seriously interferes with work or with usual social activities or relationships with others.
- D. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depression, panic disorder, dysthymia, or a personality disorder.

Criteria A, B, C, and D are confirmed by prospective daily self-rating during at least two symptomatic cycles.

From: Spitzer RL et al. Late luteal phase dysphoric disorder and DSM-III-R. *Am J Psychiatry* 1989; 146: 892-897.

## Introduction

Premenstrual syndrome (PMS) and dysmenorrhea are characterized by a combination of cyclic symptoms that occur during the luteal phase of the menstrual cycle. Symptoms are practically absent in the follicular phase of the menstrual cycle, begin at varying points after ovulation, peak

in the late luteal phase, and subside with the onset of menses or shortly thereafter. The diagnostic criteria based on the Diagnostic and Statistical Manual of Mental Disorders (DSM III-R), Third Edition, Revised are outlined in Table 1.<sup>1</sup>

Multiple causes have been attributed to the complex interplay of neuroendocrine, chronobiological, and psychosocial interactions that comprise the symptomatology of PMS.<sup>2-8</sup> A review reveals more than 200 symptoms that have been reported to occur premenstrually.<sup>2,7</sup> Depending on the symptom, the causative factors include hormonal imbalance, psychological abnormalities, nutritional deficiency or excess, increased inflammatory prostaglandin synthesis, and neurotransmitter imbalance.<sup>2-8</sup> Nevertheless, laboratory findings vary from being completely normal in some women to an excess or deficiency of certain hormones, neurotransmitters, or nutrients in others. The most probable cause of the physical symptoms of PMS seems to be the combined interaction of hormones and essential nutrients leading to an increased inflammatory response. On the other hand, the emotional symptoms of PMS seem to be propagated by an exaggerated response of neurotransmitters to psychosocial stresses. These imbalances have been shown to differ extensively from person to person, as well as from cycle to cycle within the same person.

Evidence suggests that alpha-tocopherol can significantly reduce symptoms of PMS.<sup>2,9-16</sup> Tocopherol reduces release of arachidonic acid from phospholipids, resulting in a decrease in formation of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) (inflammatory prostaglandins).<sup>16</sup> Alpha-tocopherol, which crosses the blood-brain barrier, also has modulating effects on neurotransmitters.<sup>16</sup> Several studies suggest a beneficial effect of vitamin A for the treatment of PMS, particularly for premenstrual headaches.<sup>17,18</sup>

The balance of polyunsaturated (essential) fatty acids in the body is critical for the maintenance of healthy cell membranes and hormone regulation. During the last several decades, the average Western diet has shifted to much higher levels of omega-6 and less omega-3 fatty acid intake. Long-chain omega-6 fatty acids, such as arachidonic acid, predominating in the phospholipids of cell membranes can encourage the production of pro-inflammatory type-2 prostaglandins (PGE<sub>2</sub>), while omega-3 fatty acids promote the production of anti-inflammatory prostaglandins.<sup>19-20</sup>

Omega-6 fatty acids, mainly arachidonic acid, are released following the reduction of progesterone prior to menstruation,<sup>21,22</sup> initiating an inflammatory process by triggering a flux of inflammatory prostaglandins and leukotrienes in the uterus.<sup>21,22</sup> At the same time, cyclooxygenase metabolites of arachidonic acid, prostaglandins E<sub>2</sub> and F<sub>2</sub>, cause vasoconstriction and myometrial contractions that lead to ischemia and eventually the pain of menstrual cramps.<sup>21,22</sup>

Research has uncovered abnormal fatty acid metabolism in women with PMS. Brush and colleagues examined plasma fatty acid levels in 42 women with premenstrual syndrome. They found that although levels of linoleic acid, the body's main dietary source of omega-6 fatty acids, were significantly above normal in all the women, levels of its anti-inflammatory metabolites, including gamma-linolenic acid, were all deficient,<sup>23</sup> reinforcing the theory that one of the main causes of PMS is inflammation.

The role of long-chain fatty acids for the management of PMS has been evaluated in several studies.<sup>2,19-27</sup> Omega-3 fatty acids, mainly eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), compete with the omega-6 species for the enzyme prostaglandin synthetase. The omega-3 fatty acids trigger secretion of less potent leukotrienes and anti-inflammatory prostaglandins of the 3 series (PE<sub>3</sub>, PI<sub>3</sub>, and thromboxane A<sub>3</sub>).<sup>22,28-32</sup> The result is a decrease of myometrial contractions and uterine vasoconstriction, relieving ischemia and reducing pain. This effect may be due to an increase in sensitivity of the uterus to the relaxing effects of beta-adrenergic catecholamines.<sup>22,33-37</sup>

While prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) inhibits glucose-induced insulin secretion, a deficiency – occurring either as a result of an inadequate intake of essential fatty acids in the form of cis-linoleic acid or problems with conversion to gamma-linolenic acid (GLA) – could result in symptoms of hypoglycemia, cravings for sweets, and increase in appetite reported by many PMS patients.<sup>26,37</sup> Long-chain omega-3 fatty acids in fish oil have been shown to be effective for the control of cravings occurring prior to menstruation.<sup>2,22-32,34-36</sup>

Neptune Krill Oil™ (NKO™) is a natural health product extracted from Antarctic krill also known as *Euphausia superba*. *Euphausia superba*, a zooplankton crustacean, is rich in phospholipids and triglycerides carrying long-chain omega-3 polyunsaturated fatty acids, mainly EPA and DHA, and in various potent antioxidants including vitamins A and E, astaxanthin, and a novel flavonoid (similar to the 6,8-Di-C-glucosylluteolin, but with two or more glucose molecules and one aglycone).

### Patients, Materials, and Methods

Women of reproductive age who fulfilled the DSM-III-R diagnostic criteria for PMS were eligible for the study. Women who were pregnant or breast feeding, on concomitant anticoagulant therapy, receiving psychotherapy, experiencing alcohol or drug dependence, on sex hormones except for oral contraceptives, with a known seafood allergy, or diagnosed with dementia, pituitary disease, coagulopathy, or a serious medical condition were not eligible for enrollment. Patients taking other dietary supplements or vitamins were asked to stop supplementation for two weeks at which time they were randomized in the trial.

The study was described to potentially eligible patients by the treating physician. Once the patient agreed to participate, an “eligibility form” was completed by the physician according to the patient’s answers. If the patient (referred as “she”) was eligible, she signed a written Patient Informed Consent Form and was enrolled for randomization. Patients were randomly allocated according to a list of random numbers. Once the patient was randomized to either the NKO or an omega-3 fish oil group, she underwent a physical examination for screening purposes. If the physical examination revealed no reason for the patient to be excluded from the study, she was asked to complete an initial self-assessment questionnaire, as well as to record her usual daily consumption of analgesics (including type and frequency) for menstrual pain.

Each patient periodically answered three identical self-assessment questionnaires, at baseline and one at each of the two follow-up visits. A questionnaire was given to a patient at each

visit and she was asked to complete it on her own (no interviewer allowed) in the waiting room, prior to seeing the physician.

Each patient was asked to take two 1-gram soft gels of either NKO or omega-3 18:12 fish oil (fish oil containing 18% EPA and 12% DHA) once daily with meals during the first month of the trial. During the following two months, patients continued on a cyclic dose of two 1-gram soft gels eight days prior to and two days during menstruation. Study medication was given for three months, at which time patients were asked to record all analgesics consumed for menstrual pain. All patients were asked to follow a normal healthy diet consisting of 20-percent fat (less than 10-percent animal fat), 40-percent protein, and 40-percent carbohydrates. Patients were re-evaluated 45 and 90 days after recruitment.

The treating physician, the patient, and the epidemiologist performing the analysis were blinded until the completion of data analysis. The study was performed according to current International Conference on Harmonization guidelines on Good Clinical Practice. Reasons for withdrawal and adverse events were reported immediately. No crossover was allowed.

The primary objective of the study was to evaluate the effectiveness of Neptune Krill Oil for the management of premenstrual syndrome and dysmenorrhea. The secondary objective was to compare the effectiveness of NKO for the management of premenstrual syndrome with that of omega-3 fish oil. The study hypotheses were that Neptune Krill Oil can significantly reduce the physical and emotional symptoms of premenstrual syndrome and be significantly more effective for the management of PMS symptoms than fish oil.

Primary outcome measures were based on the scores of a self-assessment questionnaire for PMS based on the American College of Obstetricians & Gynecologists diagnostic criteria for premenstrual syndrome ranging from 0 (no symptoms) to 10 (unbearable),<sup>37</sup> and the difference in quantity of analgesic consumption for menstrual pain at baseline, 45-day, and 90-day visits. Secondary outcome measures were based on the overall treatment assessment, adverse event monitoring, and compliance checks.

**Table 2.** Summary of Scores on the Premenstrual Syndrome Self-assessment Questionnaire at each Visit

Symptom	Krill Oil					Control				
	Base-line*	45 days			Mean diff.**	Base-line*	45 days			Mean diff.**
		Score (SD)	P-value	Score (SD)			Score (SD)	P-value	Score (SD)	
Breast Tenderness	6.9	5.7(2)	<0.001	4.0(2)	0.3	5.9	4.9(2)	=0.38	5.0(2)	0.2
Overwhelmed	6.7	5.2(2)	<0.001	3.9(2)	0.3	7.0	5.9(1)	=0.06	6.7(2)	0.1
Stress	7.2	5.7(2)	<0.001	4.5(3)	0.2	6.9	5.4(2)	=0.07	6.1(2)	0.1
Irritable	6.0	5.1(2)	<0.001	3.2(2)	0.3	5.8	4.9(2)	=0.13	5.2(2)	0.1
Depression	6.9	5.4(2)	<0.001	4.2(2)	0.2	7.2	5.4(3)	=0.27	6.3(2)	0.1
Joint Pain	5.8	4.7(2)	<0.001	2.1(2)	0.5	5.2	3.7(3)	=0.18	4.0(2)	0.2
Weight Gain	7.5	5.8(2)	<0.001	5.3(3)	0.2	8.0	4.7(3)	=0.04	6.8(1)	0.2
Abdominal Pain	7.4	5.6(2)	<0.001	4.9(2)	0.2	7.0	4.9(4)	=0.04	5.6(3)	0.2
Swelling	7.6	5.6(2)	<0.001	4.8(2)	0.2	6.9	4.7(3)	=0.07	5.2(2)	0.2
Bloating	7.6	6.1(2)	<0.001	6(2)	0.1	7.1	6.0(3)	=0.08	6.4(2)	0.1

Range:0-10

\* Higher scores indicate more severe symptoms.

\*\*Mean difference refers to the mean difference observed between baseline and 90 days of treatment.

change in the efficacy measure were assessed with analysis of variance (ANOVA). The study was designed as a prospective, randomized, controlled, double-blind trial, with a 20-percent difference in the change in physical and emotional scores accepted as clinically significant, 90-percent power, and 5-percent significance. Seventy patients were enrolled in the study, randomly assigned to either the active (NKO) or the control (fish oil) group.

## Results

Of the 70 patients enrolled, all patients completed the three-month study period. Of those, 36 were randomized to the active group and 34 to the control group. The mean (SD) age of the active group patients was 33(±5) and that of the control group was 32(±7).

As illustrated in Tables 2 and 3, the scores of the self-assessment questionnaire demonstrated a statistically significant difference ( $p<0.001$ ) within the NKO group after intervals of both 45 days (first menstrual cycle) and 90 days (second and third cycle) in

both emotional and physical symptoms related to PMS. By contrast, within the fish oil group a statistically significant difference was attained after 45 days only with symptoms of weight gain and abdominal pain ( $p<0.04$ ). Other related physical

Changes over time within the same group (intragroup differences) in the efficacy measures were assessed using the paired Student's t-test. Differences between the two groups, NKO versus fish oil (intergroup variance), with respect to the

symptoms (breast tenderness, joint pain, swelling, and bloating) as well as emotional symptoms (feeling overwhelmed, stress, irritability, and depression) revealed no significant difference between baseline and 45-day follow-up visits. At the 90-day interval or third study visit of the fish oil group, significant differences were observed only with weight gain ( $p<0.01$ ), abdominal pain ( $p<0.001$ ), and swelling ( $p<0.001$ ). All other physical and emotional symptoms revealed no significant difference between baseline and 90-day follow-up visit of patients in the control group.

The analysis of data showed the types of analgesics consumed most frequently by women in both groups were ibuprofen (68%), acetaminophen (28%), and acetylsalicylic acid (4%). Analysis of variance showed no significant difference between the two groups for daily analgesic consumption during PMS as well as during menstruation, prior to initiation of study medications. The reported mean consumption prior to initiation of the trial was the same for both study groups – 1.2 g ibuprofen or 2.5 g acetaminophen. The number of pain relievers used for menstrual pain by women taking NKO was significantly reduced to a mean daily consumption of 0.9 g ibuprofen and 1.5 g acetaminophen, a decrease of 33 percent and 40 percent, respectively, during the first treatment cycle (recorded at the 45-day visit). The mean reported analgesic consumption during the following treatment cycle(s) in the NKO group at the 90-day visit was 0.6 g ibuprofen (total decrease of 50%) or 1.0 g acetaminophen (total decrease of 50%) per day. Student's t-test analysis showed a significant intra-group reduction

**Table 3. Statistical Significance of Within and Between Group Variation**

GROUP P-VALUE				
Symptom	NKO™		OMEGA-3 FISH OIL	
	45 days	90 days	45 days	90 days
Breast Tenderness	<0.001	<0.001	=0.38	=0.38
Overwhelmed	<0.001	<0.001	=0.06	=0.40
Stress	<0.001	<0.001	=0.07	=0.07
Irritable	<0.001	<0.001	=0.13	=0.13
Depression	<0.001	<0.001	=0.27	=0.27
Joint Pain	<0.001	<0.001	=0.18	=0.18
Weight Gain	<0.001	<0.001	=0.04	<0.01
Abdominal Pain	<0.001	<0.001	=0.04	<0.001
Swelling	<0.001	<0.001	=0.07	<0.001
Bloating	<0.001	<0.001	=0.08	=0.08

( $p<0.01$ ) for daily analgesic usage comparing baseline vs. 45 ( $p<0.02$ ) vs. 90-day visit ( $p=0.005$ ). Women in the fish oil group reported a similar decrease of 0.9 g ibuprofen and 1.65 g acetaminophen, a decrease of 33 and 34 percent, respectively, during the first treatment cycle. The analgesic use remained essentially constant during the second cycle, with reported daily quantities of 0.8 g ibuprofen and 1.48 g acetaminophen, a decrease of 33 and 41 percent, respectively. Student's t-test analysis showed an intra-group reduction for the fish oil group ( $p<0.02$ ) for daily analgesic usage comparing baseline to 45-day ( $p<0.02$ ) and 90-day ( $p<0.02$ ) visits. At the end of the entire study, the comparative analysis between groups illustrated that women taking NKO consumed significantly fewer pain relievers during the 10 days of treatment than women receiving fish oil ( $p<0.03$ ).



Analysis of variance showed that NKO was statistically more effective ( $p < 0.01$ ) than fish oil for the management of emotional symptoms (feeling overwhelmed, stress, irritability, and depression) ( $p < 0.01$ ); breast tenderness ( $p < 0.01$ ); and joint pain ( $p < 0.04$ ). There was no significant difference observed between NKO and fish oil for the management of weight gain, abdominal pain, and swelling ( $p < 0.5$ ).

No serious adverse events were reported during the duration of the trial. Three of the 36 women in the NKO group reported a reduction of the duration of the menstrual cycle by 3-7 days during the first month of treatment. This was no longer observed after the dose was reduced to 2 gel caps per day for 10 days per month. NKO group patients exhibited minor oiliness of the facial skin. Patients taking NKO did not experience any gastrointestinal difficulties such as regurgitation, while 64 percent of the women in the fish oil group complained of unpleasant reflux. On the contrary, the NKO subjects reported an increase of alertness, energy, and well-being.

## Discussion

Premenstrual syndrome is a complex psychoneuroendocrine disorder characterized by a combination of physiological, psychological, and social symptoms. It is estimated that 85-97 percent of women of reproductive age experience some symptoms in the premenstrual phase of the cycle and 30-40 percent of these women will seek medical advice.<sup>38</sup> For 3-5 percent of women, symptoms are severe enough to significantly disrupt their everyday life.

Given the complexity in the cause and symptomatology of premenstrual syndrome, a vast array of treatments have been suggested. A meta-analysis performed by Wyatt et al<sup>39</sup> on the annual rates of diagnoses and prescribing patterns in premenstrual syndrome during the years 1993-1998 showed a yearly decrease in the number of prescriptions linked to PMS diagnoses. Simultaneously, the meta-analysis revealed a recent increase in popularity of alternative or natural remedies.<sup>39</sup> A survey of medical herbalists in 1998 showed PMS to be the second-most common condition treated with natural health products.<sup>40</sup>

Numerous studies have shown a beneficial effect of omega-3 fatty acids on menstrual pain.<sup>41-43</sup> This is consistent with the fact that menstrual pain and cramps are caused by inflammation mediated by omega-6 fatty acid-derived eicosanoids.

Following ovulation, there is shift of fatty acid balance in the phospholipids of the cell membranes.<sup>43</sup> Prior to menstruation, excessive amounts of arachidonic acid are released, and an increase in prostaglandins and leukotrienes (LTs) is triggered in the uterus. The inflammatory response initiated by the PGs and LTs results in vasoconstriction, myometrial contractions, and ischemia that cause pain; gastrointestinal symptoms such as nausea, vomiting, and bloating; and headaches.<sup>43</sup> Supplementation with omega-3 fatty acids mediates the production of less potent PGs and LTs, resulting in a reduction in the severity of myometrial contractions and uterine vasoconstriction, a decrease in the formation of inflammatory mediators, and subsequently reduced ischemia and improved blood flow.<sup>41-43</sup>

The results of the present study indicate that Neptune Krill Oil has statistically significant and clinically marked benefits against the inflammatory dysmenorrhea symptom complex as well as on the emotional symptomatology that characterizes premenstrual syndrome (intra-group difference  $p < 0.001$ , CI 95%). When compared to omega-3 fish oil, the effect of NKO was comparable with respect to weight gain, abdominal pain, swelling, and bloating (inter-group variance ( $p < 0.5$ , CI 95%). NKO was shown to be significantly more effective than fish oil for the management of all emotional symptoms of PMS ( $p < 0.01$ , CI 95%), breast tenderness ( $p < 0.01$ , CI 95%), and joint pain ( $p < 0.04$ , CI 95%).

Evidence has shown that phospholipids of the brain have an especially high content of the long-chain omega-3 fatty acid DHA, and that these phospholipid species are centrally involved in brain function.<sup>44-46</sup> The effectiveness of NKO on emotional menstrual symptoms may thus be based on potential modulating effects on neurotransmitters that affect emotional and psychological symptoms. The synergistic effects of omega-3 fatty acids and phospholipids are specific to NKO since

the solvent-based cold extraction process used to produce this oil maintains the integrity of the phospholipids. Processes for fish oil extraction can involve conditions that irrevocably damage certain components like phospholipids.

## Conclusion

The final results of the present study suggest within a high level of confidence that Neptune Krill Oil can significantly reduce the physical and emotional symptoms related to premenstrual syndrome, and is significantly more effective for the management of dysmenorrhea and emotional premenstrual symptoms than fish oil. NKO has a unique biomolecular profile of phospholipids, omega-3 fatty acids, and diverse antioxidants that surpasses the usual fish oil profile. The association between phospholipids and long-chain omega-3 fatty acids highly facilitates the passage of fatty acid molecules through the intestinal wall, increasing their bioavailability, and ultimately improving the omega-3:omega-6 ratio. Furthermore, phospholipid molecules play a major role in membrane fluidity, which may in turn play an active role in the management of emotional symptoms. Findings from this trial raise the possibility that Neptune Krill Oil has a positive benefit to risk profile for PMS.<sup>47</sup>

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