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ABSTRACT

Objective: To determine if fatigue, as defined by the Piper Fatigue Scale (PFS), can be significantly relieved by use of a glycophospholipid-rich dietary supplement in a targeted sampling of the general population (mean age=50.3 years).

Methods: Adult listeners of a Los Angeles-based radio talk show on health were invited to participate in a fatigue intervention pilot study. A survey form was mailed to those participants who described a condition consistent with the definition of fatigue as defined by the self-reported Piper Fatigue Scale (PFS). The PFS has been shown to accurately reflect the multifactorial nature of fatigue through statistical factor analysis and clinical studies. Sixty-four (64) respondents were admitted to the study when their self-reported sign/symptom severity scores were converted to fatigue scores and rated as high-moderate to severe. The

requirements of the study were fulfilled by thirty four (34) respondents (mean age=50.3±10 years, range= 33-79) completing three PFS reports each, at the fourth and eighth weeks of consuming an open label study product.

Results: The Piper Fatigue Scale scores indicated a 33% reduction in fatigue after eight weeks on the supplementation product. The PFS rates fatigue from a score of 0 (no fatigue) to 10 (severe fatigue). The average initial fatigue score for the group before treatment was reported as severe (mean score=7.9± 0.82 SD, range=6.4-9.9), after four weeks rated moderate (mean=6.1±1.66 SD, range =2.6-9.5) (p<0.0001), and at eight weeks rated as moderate (mean=4.7±2.01 SD, range=1.5-9.4) (p<0.0001).

Conclusion: In this self-reported study, dietary supplementation significantly reduced fatigue as measured by the Piper Fatigue Scale. The response generated in the initial survey was significant enough to warrant further investigation in an expanded, controlled study utilizing a placebo.

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INTRODUCTION

Most researchers view fatigue as a multidimensional sensation with many possible causes. There is, however, no universally accepted definition of fatigue. Instead researchers have assessed components associated with the complaint of fatigue, such as behavioral, affective, sensory,

and cognitive changes. Piper *et al.*¹ were among the first to propose a multifactorial measurement model for fatigue that combined multiple fatigue-associated elements into an overall fatigue score.

Disease and the complaint of fatigue or loss of energy often precede clinical diagnosis by a considerable length of time. Bland states, "In a sense, fatigue is the body's statement that it cannot manufacture and control adequate energy to meet its needs. Fatigue of the brain leads to confusion, while muscle fatigue leads to exhaustion. Fatigue of the immune system results in an increased susceptibility to infection and/or increased autoimmunity."²

A cell's functional capacity can be measured, in part, by the fluidity of its membranes and its cell-to-cell communication capacity. One of the most common forms of cell damage is created by free radicals, which reduce membrane fluidity, cell communication, and cell to cell function. Protecting cell membrane integrity is thought to enhance cellular health, energy and efficient metabolism.

Preventing loss of membrane integrity due to damaged components and the resultant loss of cellular energy may be accomplished, in part, by replacement of damaged lipids. Among the important cell membrane lipids, polyunsaturated phosphatidylcholine (PPC) molecules are essential for the structure, function, and regeneration of all biological membranes.^{3,4} As cell membranes will incorporate exogenous PPC (derived from soybean semen), dietary supplementation is a logical first step in the restoration process. Such processes may play an important part in preventing disease, in general, and certainly fatigue.⁵⁻⁶

Several clinical and pharmacological trials have shown the relationship between loss of membrane phospholipids, membrane damage, and disease. PPC administration as a dietary supplement has resulted in enhancement of cognitive performance of the aging brain, improvement of coronary, peripheral and cerebral blood flow, activation of liver metabolism, and detoxification and gastrointestinal function through mucosal restoration.⁸

The product used in this pilot study, Propax™ with NT Factor™ (PNTF), is a dietary supplement rich in phospholipids, particularly polyunsaturated phosphatidylcholine. PNTF provides moderate doses of multivitamins, minerals, antioxidants and essential fatty acids that the body uses to repair itself, resulting in a substantial positive impact on fatigue, nausea, diarrhea and other quality of life indicators. The effect of PNTF has been documented in a double-blind, crossover placebo-controlled, randomized study on cancer patients undergoing chemotherapy.¹⁷ Seidman⁷ conducted a pilot study with rats and found that PNTF elevated mitochondrial membrane activity, as determined by rhodamine 123 metabolic dye uptake and reduction in mitochondria measured by fluorescence flow cytometry, compared to the activity of mitochondria isolated from control animals on an

identical diet without the PNTF supplement. The increase in mitochondrial activity of rats fed PNTF was statistically significant ($p < 0.05$) compared to control animals, demonstrating its protective effect on mitochondrial membrane function. Additionally, brainstem auditory responses were recorded for the two groups at the onset and conclusion of this six-month study. Preservation of hearing was noted in the treated rats at all frequencies examined, suggesting substantial protection of auditory nerve function. In contrast, the control group showed continuing age-related hearing loss at all examined frequencies. Differences between test and control groups were significant ($p < 0.005$).⁷ The rats were euthanized to obtain tissue samples from brain and cochlear sites to study mitochondrial DNA deletions associated with aging. Quantitative determination⁸ revealed a significantly lower ratio of this common age-associated phenomenon in the experimental group compared to control rats, indicating that PPC as a dietary supplement had a protective effect on mitochondrial DNA damage.

As an important part of membrane structures, phospholipids maintain membrane integrity, and through changes in membrane fluidity regulate mitochondrial enzyme activities and membrane transport processes.^{3,5} Phospholipids have other specific functions. The choline portion of PPC may be used in neural tissue for the synthesis of acetylcholine, a neurotransmitter. Oral administration of choline has been shown to increase plasma and neuronal concentrations of PPC, which stimulates the release of acetylcholine in neuro-muscular systems. Physical stress depresses plasma choline concentrations as evidenced by a decline in muscle function.⁹⁻¹¹ This was noted through the examination of individuals in the Boston Marathon where a 40% decrease in plasma choline levels were found during the race.¹¹ It has been established that providing PPC prior to exercise can compensate for these choline losses.¹²⁻¹⁵

SUBJECTS AND METHODS

Subjects: Participants were prescreened on the basis of an initial phone conversation to determine whether their symptoms were consistent with persistent, intractable fatigue, or merely an intermittent "tiredness" linked to work or lifestyle. Those who described a condition consistent with the definition of fatigue as defined in the Piper Fatigue Scale, "an unusual sense of tiredness that is not usually relieved by either a good night's sleep or by rest", were mailed a survey. The completed surveys were scored as described previously.^{1,16} After the initial survey, participants aged 20 years and older with a Piper Fatigue Scale score of 6 to 10 were admitted to the study. This corresponded to having high-moderate to severe fatigue (0 = no fatigue, 1-3 = mild fatigue, 4-6 = moderate fatigue, 7-10 = severe fatigue).

Thirty-four (34) respondents with a mean age of 50.3 completed the study: 21 (61.8%) were women ranging in

age from 33 to 62 at an average of 47.0 years, and 13 men ranging in from 38 to 79, at an average of 54.2 years. Thirty-one were from California, and one each was from Ohio, Connecticut and New York. The majority of Californians resided in the greater Los Angeles metropolitan area.

To gain insight into the type of respondent who was over 21 years old and had a PFS score of 6 or higher, (moderately to severe fatigue) we telephoned 24 of the 34 respondents who completed the study. They were asked what, if any, prescription medications they used, and were asked to confirm the length of their fatigue and to discuss any preexisting medical conditions. Seven (29%) reportedly experienced fatigue, as defined above, lasting over a month, and 17 (71%) experienced fatigue lasting over a year. A variety of diagnoses were represented in the study group (Table 1), and 50% (5 males, 7 females) were on prescription medications. Table 2 presents the category of medications by class and the number of individuals using them. Overlap occurs in Tables 1 and 2, as some respondents reported more than one condition and/or used more than one medication. However, of the 9 subjects in Table 1 who indicated persistent, intractable fatigue, only two used medication. All five who listed depression as a diagnosis were on antidepressants, and the two hypothyroid respondents were on Armour Thyroid supplementation.

Study Design: Subjects admitted into the study with severe fatigue (7-10 on the Piper Fatigue Scale) were given a 4-week supply of PNTF and instructed to use 3 packets daily; those with high-moderate fatigue (6 on the PFS) were instructed to use two packets per day. No one was admitted to the study with a PFS score less than 6. All respondents were told to repeat the PFS self-assessment at the end of three weeks and return the survey to Nutritional Therapeutics, Inc., Hauppauge, NY. All PFS scores were then verified for accuracy and completion. Based on their their new scores participants were instructed to use three

Table 1. Diagnoses of Participants in the Study

| | |
|-------------------------------------|----------------------------|
| Depression: | 5 (all on antidepressants) |
| Hypothyroid: | 2 (all on Armour Thyroid) |
| Malignancy: | 2 |
| Anemia: | 3 |
| Asthma/allergies: | 4 |
| HTN/CVD: | 1 |
| General Fatigue: | 9 |
| Paralysis/Spinal Cord Injury: | 1 |
| Narcolepsy: | 1 |
| Glaucoma: | 1 |
| Fibromyalgia: | 2 |
| Candida/Viral: | 1 |
| Pregnant: | 1 |
| Restless Leg Syndrome: | 1 |
| DJD/OA: | 2 |

packs of PNTF per day for PFS scores of 7-10, two packs per day for scores of 4-6, and one pack daily for scores of 1-3. Subjects were supplied with PNTF for four more weeks, at which time participants completed and mailed in their third and final PFS questionnaire for verification and completion of scoring accuracy.

Table 2. Medications used by study participants (n=24)

| Medications Represented by Category | |
|--|---|
| Anti seizure: | 2 |
| Asthma/allergies: | 2 |
| Anti inflammatory/Non Steroidal: | 2 |
| Thyroid replacement: | 2 |
| Female hormone replacement: | 1 |
| Anti depressant: | 5 |
| Anti acids/H2-blocker: | 2 |
| Anti hypertensive: | 1 |
| Pain meds: | 1 |

Table 3. Factor Loading for Items on the Four Piper Fatigue Scale Subscales

| <u>Subscale and Items</u> | <u>Factor Loading</u> |
|--|-----------------------|
| I. Behavioral/Severity | |
| 1. Fatigue distress | 0.658 |
| 2. Interference with work/school | 0.710 |
| 3. Interference with socializing with friends | 0.775 |
| 4. Interference with sexual activity | 0.528 |
| 5. Overall interference with enjoyable activities .. | 0.840 |
| 6. Fatigue intensity/severity | 0.730 |
| II. Affective meaning | |
| 1. Pleasant/unpleasant | 0.704 |
| 2. Agreeable/disagreeable | 0.815 |
| 3. Protective/destructive | 0.838 |
| 4. Positive/negative | 0.953 |
| 5. Normal/abnormal | 0.705 |
| III. Sensory | |
| 1. Strong/weak | 0.614 |
| 2. Awake/sleepy | 0.812 |
| 3. Lively/listless | 0.745 |
| 4. Refreshed/tired | 0.844 |
| 5. Energetic/unenergetic | 0.812 |
| IV. Cognitive/mood | |
| 1. Patient/impatient | 0.788 |
| 2. Relaxed/tense | 0.847 |
| 3. Exhilarated/depressed | 0.552 |
| 4. Ability to concentrate | 0.648 |
| 5. Ability to remember | 0.547 |
| 6. Ability to think clearly | 0.566 |

Materials and Methods: In its current form, the PFS survey form is composed of 22 questions rated from "0", no fatigue, to "10", the most fatigue. Each question has word anchors that vary from the generic (*none to a great deal*) to the specific (such as: *able to concentrate to unable to concentrate*). These items measure four dimensions of subjective fatigue: behavioral/severity (6 items), affective meaning (5 items), sensory (5 items), and cognitive/mood (6 items). Answers are used to calculate four sub-scale/dimensional scores and total fatigue scores. The Severity Code scoring the degree of fatigue is as follows:

0 = NONE 1-3 = MILD 4-6 = MODERATE 7-10 = SEVERE

Table 3 displays the factors and subscales with their respective factor loading values.¹⁶ The standardized alpha (Cronbach's alpha) did not drop below 0.92 for any subscale, and the standard alpha for the entire scale of 22 questions was 0.97, indicating excellent reliability for an established instrument.^{16,17} The study product, (PNTF) is a proprietary nutrient complex (Table 4).

RESULTS

The total PFS group average (mean) score, 7.9, improved 33% from the initial survey before taking PNTF to 6.1 after four weeks, and to 4.7 after eight weeks. By sex, the group mean final score improved 35% for women and 29% for men. Age was not associated with the degree of change in fatigue. Table 5 shows the clustering of values for the degrees of change in the PFS scores, before and after supplement usage.

By PFS subscale, respondent's Behavioral/Severity scores improved an average of 37% for the entire group after PNTF (women 39%, men 33%). The Affective Meaning subscale responses improved by an average of 31% (women 36%, men 24%). The Sensory subscale revealed a 34% average improvement (women 33%, men 35%). The Cognitive/Mood subscale showed an average improvement of 27%, (women 30%, men 23%).

Summary scores on the PFS showed women improving by 35% and men by 29%. The difference in the improvement in for the entire group was significant ($p < 0.0001$).

DISCUSSION

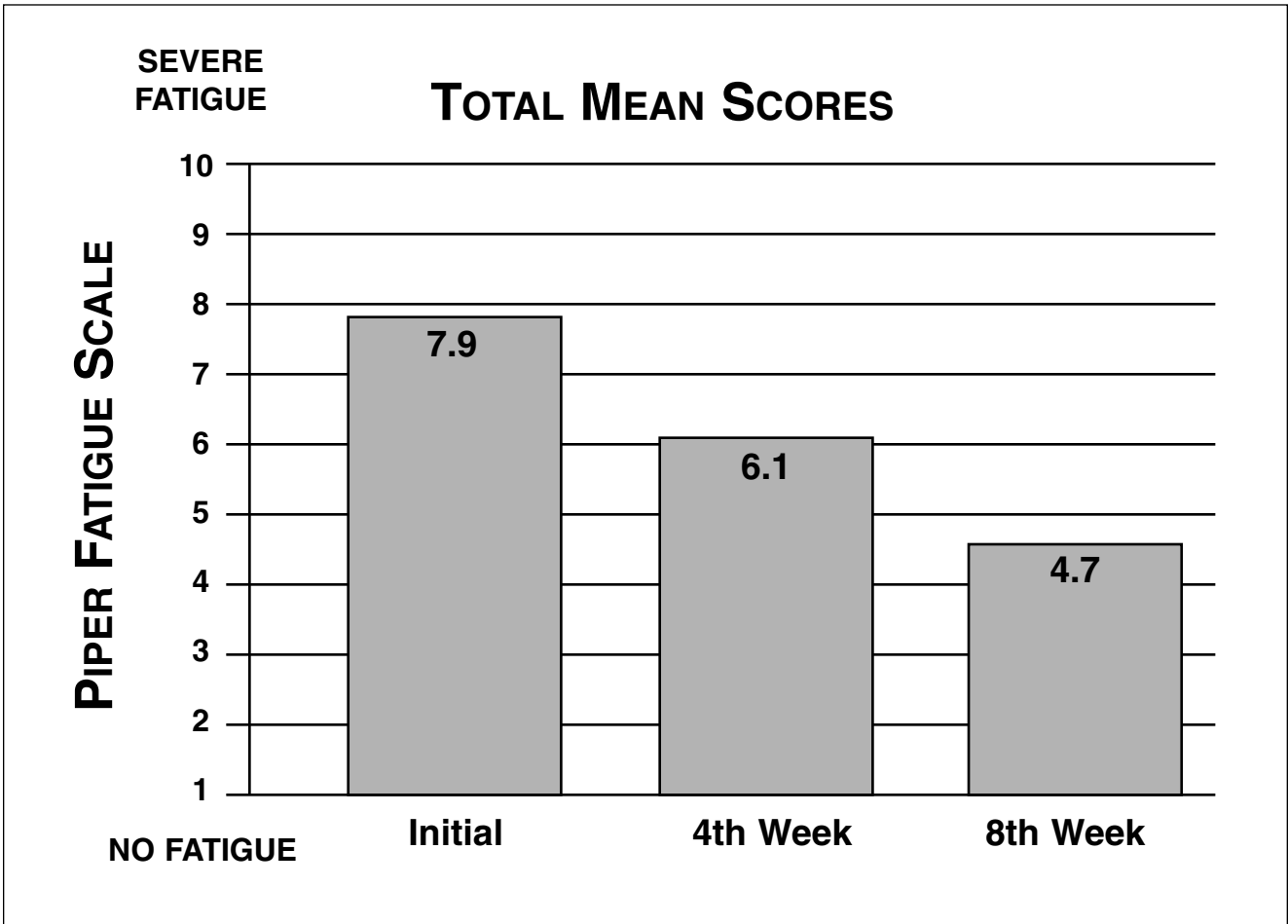
The pilot study sampled a general population of predominantly older subjects from the Los Angeles metropolitan area who were listening to a health talk radio show on the subject of fatigue. The only admission criteria was that subjects had to be 20 years old or more and have moderately high or severe fatigue corresponding to a score of 6-10 on the Piper Fatigue Scale. The only intervention was the use of the phospholipid-rich nutrient complex PNTF. After eight weeks on this dietary supplement product, all but one of the 34 respondents showed improvement in their fatigue. The

Table 4. Contents of Propax™ with NT Factor™

Each serving pack (4 tablets and 1 softgel capsule) provide the following nutrients

| | |
|---|--|
| Vitamin A (as acetate)..... | 4375 IU |
| Vitamin A (as natural beta-carotene) | 3750 IU |
| Vitamin C (as calcium ascorbate)..... | 150 mg |
| Vitamin D-3 (as cholecalciferol) | 32 IU |
| Vitamin E (as d-alpha tocopherol) | 145 IU |
| Vitamin K (as phytonadione) | 2.5 mcg |
| Vitamin B-1 (thiamin HCl)..... | 6.25 mg |
| Vitamin B-2 (as riboflavin/ribose-5-phosphate)..... | 30 mg |
| Vitamin B-3 (as niacinamide)..... | 60 mg |
| Vitamin B-6 (as pyridoxine/P-5-P)..... | 40 mg |
| Folic Acid (as folate) | 200 mcg |
| Vitamin B-12 (cyanocobalamin)..... | 25 mcg |
| Biotin | 25 mcg |
| Pantothenic Acid (as d-calcium pantothenate)..... | 25 mg |
| Calcium..... | 360 mg (as phosphate, ascorbate, citrate, sulfate, borogluconate) |
| Iodine (as kelp) | 18.75 mcg |
| Magnesium | 160 mg (as carbonate, oxide, glycinate, sulfate) |
| Zinc (as methionate) | 12.5 mg |
| Selenium (as selenomethionate) | 75 mcg |
| Copper (as tyrosinate)..... | 300 mcg |
| Manganese (as glycinate) | 2.5 mg |
| Chromium (as nicotinate) | 50 mcg |
| Molybdenum (as glycinate) | 20 mcg |
| Potassium (as citrate) | 12.8 mg |
| Bioflavonoids | |
| (as citrus, rutin, rosehips, quercetin) | 165 mg |
| Boron (as calcium borogluconate) | 500 mcg |
| L-Carnitine Tartrate | 160 mg |
| Grape Seed Extract (proanthocyanidins) | 5 mg |
| Inositol (inositol/inositol nicotinate)..... | 25 mg |
| Lactoferrin..... | 4 mg |
| Pantethine (as coenzyme A precursor) | 70 mg |
| Vanadium (as vanadyl sulfate) | 12.5 mcg |
| Alpha-Keto Glutarate | 125 mg |
| Glutathione (as reduced)..... | 5 mg |
| L-Tyrosine..... | 60 mg |
| N-Acetyl-L-Cysteine..... | 25 mg |
| Taurine | 110 mg |
| Green Tea Extract | 50 mg |
| Horsetail (as silica) | 12.5 mg |
| Phosphoglycolipids | 160 mg |
| EPA (as eicosapentaenoic acid) | 180 mg |
| DHA (as docosahexanoic acid)..... | 120 mg |
| NT Factor (as tablet base)..... | 1400 mg |
| Components of NT Factor™ | |
| Defatted rice bran, arginine, beet root fiber, black strap molasses, glycine, magnesium sulfate, enriched polyunsaturated phosphatidylcholine (phospholipids), saponin (glycolipids), para-amino-benzoate, leek, pantethine (bifidus growth factor), taurine, garlic, calcium borogluconate, omega-6 essential fatty acids, omega-03 essential fatty acids, artichoke, potassium citrate, calcium sulfate, spirulina, bromelain, natural vitamin E, calcium ascorbate, alpha-lipoic acid, oligosaccharides, B-6, niacinamide, riboflavin, inositol, niacin, calcium pantothenate, thiamin, B-12, bifidus, acidophilus, folic acid, chromium picolinate. | |

Table 5.



one respondent who did not improve, was contacted by the study's principal investigator to confirm their diagnosis and medications use and this was one of two participants who had a malignancy and was currently on five different medications. Although the number of subjects sampled was small, the statistical difference in the results ($p < 0.0001$) were significant. This suggests that further studies need to be conducted that control for disease or diagnosis, medication use, and potential changes in lifestyle or nutrient use.

The integrity of cellular and intracellular membrane structures is critical to cell function and energy production.^{3,5} Previous animal studies using the phospholipid nutrient complex in PNTF suggested that maintenance of membrane integrity with appropriate phospholipids improved mitochondrial function. In addition, in clinical trials on chemotherapy patients using the multivitamin and mineral supplement PNTF, the ability to reduce fatigue was demonstrated in this most challenging class of patients.¹⁷ In the pilot study presented here where fatigue alone was analyzed, the results suggest that directing dietary support at the cellular and intracellular membrane level with the phospholipid-rich sup-

plement PNTF may provide the cell membrane structural repair components needed for restoration and maintenance of cell and mitochondrial function. This, in turn, may improve cellular energy and eventually reduce fatigue.

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