

**RESEARCH CLINICAL SURVEY**

# **Lipid Replacement Therapy with a Glycophospholipid-Antioxidant-Vitamin Formulation Significantly Reduces Fatigue Within One Week**

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# Lipid Replacement Therapy with a Glycophospholipid-Antioxidant-Vitamin Formulation Significantly Reduces Fatigue Within One Week

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## ABSTRACT

Fatigue occurs naturally during aging and in most degenerative diseases, and is the most common complaint of patients seeking general medical care. Lipid Replacement Therapy administered using an all-natural nutritional supplement containing membrane glycophospholipids and antioxidants can reduce or prevent fatigue. Recent clinical trials using patients with chronic fatigue have shown the benefit of Lipid Replacement Therapy in restoring mitochondrial electron transport function and reducing moderate to severe chronic fatigue. In the current preliminary study, an online survey on fatigue was used to assess the effects of a membrane glycophospholipid-antioxidant-vitamin mixture on fatigue. Fatigue was reduced within one week by a mean of 36.8% ( $p < 0.001$ ) in a group of 67 subjects of mean age 57.3 years with various fatigue

levels. There was no difference between the response of males and females to the supplement, and no adverse events occurred during the study.

## INTRODUCTION

Chronic or intractable fatigue that is not reversed by sleep is the most common complaint of patients seeking medical care.<sup>1,2</sup> It occurs naturally during aging, and is also an important secondary condition in many degenerative diseases.<sup>1</sup> The phenomenon of fatigue has been defined as a multidimensional sensation, and clinical studies have determined the extent of fatigue in aging and in various medical conditions.<sup>3-5</sup> Many diseases are associated with fatigue, including neurological, respiratory, coronary, musculoskeletal, metabolic and gastrointestinal diseases, as well as infections and cancer.<sup>2-7</sup>

Most people understand fatigue as a loss of overall energy and inability to perform even simple tasks without exertion. At the cellular level, fatigue is related to cellular energy systems found primarily in the cells' mitochondria. Damage to mitochondrial components, especially mitochondrial membranes, occurs mainly by oxidation, and this can result in increased ion leakage across mitochondrial membranes and impair the ability of mitochondria to produce high-energy molecules needed for survival and growth.<sup>8</sup> During aging and most chronic diseases, the production of oxidative molecules such as Reactive Oxygen and Nitrogen species (ROS/RNS, oxidative and free radical

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oxygen- and nitrogen-containing molecules such as nitric oxide, oxygen and hydroxide radicals and other molecules<sup>9</sup>), can cause oxidative stress and cellular damage, resulting in oxidation of lipids, proteins and DNA.<sup>9-11</sup> When oxidized, these molecules are structurally and sometimes functionally changed.<sup>12,13</sup> Important targets of ROS/RNS damage are mitochondria and cell membranes, mainly their phospholipids components.<sup>9-11</sup> Similar damage occurs in fatiguing illnesses such as chronic fatigue syndrome (CFS), whereby patients have intractable fatigue for at least six months and show increased susceptibility to oxidative stress and peroxidation.<sup>14,15</sup>

Recent clinical trials have shown the effectiveness of lipid replacement therapy (LRT) plus antioxidants in the treatment of certain clinical disorders and conditions such as chronic fatigue.<sup>6,7</sup> LRT results in the actual replacement of damaged cellular lipids with undamaged (unoxidized) lipids to ensure proper function of cellular structures, mainly cellular and organelle membranes.<sup>6,7</sup> LRT can result in the cellular delivery of unoxidized, undamaged membrane glycopospholipids in order to replace damaged lipids and restore function to oxidized cellular membranes. Combined with antioxidant supplements, LTR has proven to be an effective method to prevent ROS/RNS-associated changes in cellular activities and functions and for use in the treatment of various clinical conditions.<sup>7</sup>

In this study, we tested the results of using a formulation of glycopospholipids plus antioxidants and B-complex vitamins on suppression of fatigue during a one week trial.

## SUBJECTS AND METHODS

**Subjects:** Participants were prescreened on the basis of an initial phone conversation to determine if their symptoms were consistent with persistent, intractable fatigue, or merely an intermittent condition linked to their work or lifestyles. Those who described a condition consistent with the definition of fatigue as defined in the Piper Fatigue Scale (PFS)<sup>4</sup> were directed to take an online survey. This instrument defines fatigue as an unusual sense of tiredness that is not usually relieved by either a good night's sleep or by rest. Subjects were asked if they used any prescription medications to see if this might exclude them from the study.<sup>16</sup> The completed online surveys were scored as described previously.<sup>16,17</sup>

After the initial PFS survey, 75 participants with an overall PFS fatigue score greater than 3 were admitted to this pilot study if their fatigue could not be explained by a pre-existing clinical condition. There were 67 respondents who fully completed the study with an average age of 57.3 ± 1.5, and a range of 24 - 87.

**Study Design:** Subjects signed an online informed consent document and were admitted into the study with

measurable fatigue (3-10 on the PFS). Each participant was given instructions to use five tablets of the glycopospholipid supplement containing antioxidants and vitamins daily (Table 1). All subjects repeated the online PFS assessment at the end of the first week without access to their previous scores. After the participants completed their PFS questionnaires, all of the electronic forms were checked for verification, completion and scoring accuracy.<sup>16</sup>

**Materials and Methods:** The supplement product, NT Factor<sup>®</sup> Advanced Physicians Formula with B-Vitamin Complex (Nutritional Therapeutics, Inc., Commack, NY), is a patent-pending proprietary vitamin, mineral and nutrient complex containing an exogenous source of polyunsaturated phosphatidylcholine and other membrane phospholipids (Table 1). The participants took the suggested daily dose (3 tablets in the morning and 2 at night) for one week.

The PFS is composed of 22 numerically scaled questions rated from 0 (no fatigue) to 10 (severe) fatigue. These items measure four dimensions of subjective fatigue: behavioral/severity (6 items); affective/meaning (5 items); sensory (5 items); and cognitive/mood (6 items). These answers are used to calculate the four sub-scale/dimensional scores and the total fatigue scores. The standardized alpha (Cronbach's alpha) did not drop below 0.90 for any of the subscales, and the standard alpha for the entire scale of 22 questions was 0.96, indicating excellent reliability for an established instrument.<sup>18</sup>

## RESULTS

The glycopospholipid-antioxidant-vitamin supplement used in this study (Table 1) improved the overall fatigue scores of moderately fatigued subjects as measured by the PFS (Table 2). The initial PFS group average (mean ± standard error mean) total fatigue score was 9.56 ± 0.36, and after one week of supplement this score improved to 6.02 ± 0.295 or a 36.8% reduction in fatigue. The mean decrease in fatigue value was significant by t-test ( $p < 0.001$ ) and Wilcoxon signed-rank ( $p < 0.001$ ) analyses. There were no adverse events during the course of the study. We examined participants' data to see if there was any difference between males and females. There was no statistical significance between the response in males and females (Table 2).

The Piper Fatigue Scale can be further dissected into subcategories that include overall fatigue, behavior/severity, affective meaning, sensory and cognitive/mood (Table 3). All of these subcategories showed reductions of 34.6% to 40.6% at the end of the one-week trial, indicating that there were improvements in all subcategories of fatigue.

**Table 1.** Test Supplement (NT Factor® Advanced Physician's Formula with B-Vitamin Complex).

Component	Amount Per Serving	% Daily Value*
Vitamin E (as D- $\alpha$ -tocopheryl succinate, mixed tocopherols)	50 IU	167
Vitamin B-1 (as thiamin as thiamine HCl)	3.75 mg	250
Vitamin B-2 (riboflavin)	4.25 mg	250
Vitamin B-3 (as niacinamide, niacin)	100 mg	500
Vitamin B-6 (as pyridoxine HCl)	10 mg	500
Vitamin B-12 (as methylcobalamin, canocobalamin)	1,000 mcg	16,667
Folate (as folic acid)	800 mcg	200
Biotin	750 mg	250
Panthenic acid (as D-calcium pantothenate)	25 mg	250
Calcium (as dicalcium phosphate, carbonate, pyruvate Borogluconate, ascorbate and dicalcium pantothenate)	400 mg	40
Phosphorus (as dicalcium phosphate)	125 mg	13
Magnesium (as magnesium oxide)	125 mg	31
OptiMSM™ (methylsulfonylmethane)	364 mg	**
Alpha keto glutaric acid	300 mg	**
L-Carnipure® (L-carnitine L-tartrate)	225 mg	**
L-Tyrosine	150 mg	**
NT Factor®#	4,000 mg	**

\*Daily values are based on a 2,000 calorie per day diet

\*\*Daily values not established

# NT Factor® is a nutrient complex extracted from soy and purified using proprietary processes. It is composed only of food and food components: phosphoglycolipids (polyunsaturated phosphatidylcholine, glycolipids and other polyunsaturated phosphatidyl nutrients), *Bifido* and *Lactobacillus* bacteria (freeze-dried and microencapsulated in viable form), growth media (bacterial growth factors and food, including rice bran extract, arginine, beet root fiber, black strap molasses, glycine, magnesium sulfate, para-amino benzoate, leek, pantethine, taurine, garlic, calcium borogluconate, potassium citrate, spirulina, bromelain, natural vitamin E, calcium ascorbate,  $\alpha$ -lipoic acid, oligosaccharides, vitamin B-6, niacinamide, riboflavin, vitamin B-12, folic acid, inositol, calcium pantothenate, chromium picolinate). NT Factor® is a registered trade mark of Nutritional Therapeutics Inc., Commack, NY.

**Table 2.** Results from Piper Fatigue Scale Survey.

Category	n	Mean Age ± S.E.M.	Mean Fatigue Level ± S.E.M.		Percent Reduction
			Day 0	Day 7	
Male	31	59.2 ± 2.4	4.3 ± 0.20	2.8 ± 0.18*#	34.4
Female	36	55.6 ± 2.0	4.4 ± 0.25	2.7 ± 0.20*#	39.2
All subjects	67	57.3 ± 1.5	4.3 ± 0.16	2.8 ± 0.13*#	36.8

\*t-test  $p < 0.001$

# Wilcoxon signed-rank  $p < 0.001$

**Table 3.** Results From Subcategories of the Piper Fatigue Scale Survey.

Category	Mean Fatigue Level $\pm$ S.E.M.		Percent Reduction
	Day 0	Day 7	
Overall Fatigue	4.3 $\pm$ 0.16	2.8 $\pm$ 0.13	36.8
Behavior/Severity	4.8 $\pm$ 0.05	2.9 $\pm$ 0.03	37.8
Affective/Meaning	4.3 $\pm$ 0.03	2.8 $\pm$ 0.05	34.6
Sensory	4.2 $\pm$ 0.04	2.7 $\pm$ 0.01	33.9
Cognitive/Mood	4.1 $\pm$ 0.04	2.4 $\pm$ 0.02	40.6

## DISCUSSION

The glycerophospholipid supplement NT Factor<sup>®</sup> has been used successfully in animal and clinical lipid replacement studies.<sup>6,7,16,17</sup> In this formulation, encapsulated lipids are protected from oxidation in the gut and can be absorbed and transported into tissues without oxidative damage. NT Factor contains a variety of components, including phospholipids, glycerophospholipids and other lipids, nutrients, probiotics, vitamins, minerals and plant extracts.<sup>6</sup>

In animal studies, NT Factor<sup>®</sup> has been used to prevent hearing loss associated with aging.<sup>19</sup> Seidman et al.<sup>19</sup> found that NT Factor<sup>®</sup> prevented hearing loss associated with aging and shifted the threshold hearing from 35 - 40 dB in control aged animals to 13 - 17 dB in the treatment group ( $P < 0.005$ ). They also found that NT Factor<sup>®</sup> preserved cochlear mitochondrial function, increasing mitochondrial function by 34%. NT Factor<sup>®</sup> also prevented aging-related mitochondrial DNA deletions found in the cochlear.<sup>19</sup>

LRT has also been successfully used in clinical studies to reduce fatigue and protect cellular and mitochondrial membranes from oxidative damage.<sup>16,17</sup> For example, NT Factor<sup>®</sup> has been used in a vitamin and mineral mixture (Propax<sup>™</sup>) in cancer patients to reduce the effects of cancer therapy such as chemotherapy-induced fatigue, nausea, vomiting and other side effects associated with chemotherapy.<sup>20</sup> This double-blinded, cross-over, placebo-controlled, randomized trial on cancer patients receiving chemotherapy showed that LRT improved fatigue, nausea, diarrhea, impaired taste, constipation, insomnia and other quality of life indicators.<sup>20</sup>

NT Factor<sup>®</sup> has been used in a study with severely chronically fatigued patients to reduce their fatigue.<sup>16</sup> We found that fatigue was reduced approximately 40.5% ( $p < 0.0001$ ), from severe to moderate fatigue, after eight weeks of LRT supplementation with NT Factor.<sup>®16</sup> We also examined the effects of NT Factor<sup>®</sup> on fatigue in moderately and

mildly fatigued subjects and determined if their mitochondrial function improved with administration of NT Factor.<sup>®17</sup> Use of NT Factor<sup>®</sup> for 12 weeks resulted in a 35.5% reduction in fatigue ( $p < 0.001$ ).<sup>17</sup> In this clinical trial, there was good correspondence between reductions in fatigue and gains in mitochondrial function. After only 8 weeks of LRT with NT Factor,<sup>®</sup> mitochondrial function was significantly improved ( $p < 0.001$ ), and after 12 weeks of NT Factor<sup>®</sup> supplementation, mitochondrial function was found to be similar to that of young healthy adults.<sup>17</sup> After 12 weeks of supplement use, subjects discontinued the supplement for an additional 12 weeks, and their fatigue and mitochondrial function were again measured. After the 12-week wash-out period, fatigue and mitochondrial function were intermediate between the initial starting values and those found after eight or 12 weeks on the supplement, indicating that continued dietary LTR is probably required to show improvements in mitochondrial function and maintain lower fatigue scores.<sup>17</sup> Similar results were found with chronic fatigue syndrome and/or fibromyalgia syndrome patients, indicating that LRT plus antioxidants for 8 weeks reduced moderate to severe fatigue by 43.1%.<sup>7</sup>

In the present study, we used a new LRT preparation that contained B-complex vitamins and a similar concentration of NT Factor.<sup>®</sup> We found a 35.4% reduction in fatigue at the end of one week of LRT. Limitations in the current study did not allow us to project these findings to times beyond one week to see if even greater decreases in fatigue could be found by continuing the supplement for more than one week. Also, we do not know the effect of the addition of vitamins to the supplement base of NT Factor<sup>®</sup> and antioxidants. Thus, we cannot compare directly the results obtained in the present study to previous studies. These preliminary results, however, provide evidence that this new LRT supplement significantly reduces fatigue within one week in subjects with a variety of fatigue levels.

## DISCLOSURE

Funding for this study was provided by The Institute for Molecular Medicine, and Nutritional Therapeutics, Inc which markets the product used in this study. The authors have no financial interest in the products discussed in this contribution; however, Dr. Ellithorpe provides this product above cost to her patients.

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