Scientific Research Publishing

International Journal of Clinical Medicine, 2018, 9, 600-619
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Reduction of Pain, Fatigue, Gastrointestinal and Other Symptoms and Improvement in Quality of Life Indicators in Fibromyalgia Patients with Membrane Lipid Replacement Glycerolphospholipids and Controlled-Release Caffeine

Garth L. Nicolson[1*], Robert Settineri[2], Gonzalo Ferreira[3], Paul Breeding[4]

[1]Department of Molecular Pathology, The Institute for Molecular Medicine, Huntington Beach, CA, USA
[2]Sierra Research, Irvine, CA, USA
[3]Department of Biophysics, Facultad de Medicina, Universidad de la Republica, Ion Channels Laboratory, Montevideo, Uruguay
[4]Health First, Pearland, TX, USA
Email: *gnicolson@immed.org

How to cite this paper: Nicolson, G.L., Settineri, R., Ferreira, G. and Breeding, P. (2018) Reduction of Pain, Fatigue, Gastrointestinal and Other Symptoms and Improvement in Quality of Life Indicators in Fibromyalgia Patients with Membrane Lipid Replacement Glycerolphospholipids and Controlled-Release Caffeine. *International Journal of Clinical Medicine*, **9**, 600-619.
https://doi.org/10.4236/ijcm.2018.97051

Received: June 25, 2018
Accepted: July 23, 2018
Published: July 26, 2018

Abstract

Objectives: A preliminary, open label study was initiated to determine if oral wafers containing a combination of membrane glycerolphospholipids and controlled-release caffeine could reduce self-reported pain, fatigue, and gastrointestinal symptoms and improve quality of life (QOL) indicators in fibromyalgia patients. **Methods:** Pain, fatigue and other symptoms were determined using validated, patient survey forms completed over an 8-day test period and compared to baseline values. Participants included 21 patients (15 females and 6 males) of average age of 48.5 ± 9.8 years with a diagnosis of fibromyalgia. These patients consumed four daily chewable wafers containing glycerolphospholipids (4.8 g) and one controlled-released caffeine (184 mg) wafer that maintained caffeine levels at approximately one cup of coffee for over 8 h. **Results:** Participants in the study responded to the combination test supplement within days. By the end of the study there were significant overall improvements (36.1%, $p < 0.001$), reductions in pain (27.2%, $p < 0.001$), fatigue (37.8%, $p < 0.001$), gastrointestinal symptoms (54.7%, $p < 0.001$) and improved ability to complete tasks and participate in activities (quality of life indicators) (39.1%, $p < 0.001$). Regression analysis of the data using a generalized mixed-effects model and calculating R^2 values indicated that reductions

in pain, fatigue and gastrointestinal symptoms and improvements in quality of life indicators were consistent, and occurred with a low degree of variance. Males responded slightly better to the combination supplement than females but for most parameters these differences were not significant. **Conclusions:** The combination membrane lipid replacement glycerolphospholipid supplement with controlled-release caffeine was safe and effective and significantly reduced pain, fatigue and gastrointestinal symptoms as well as improved QOL indicators in fibromyalgia patients.

Keywords

Pain, Fatigue, Gastrointestinal Symptoms, Quality of Life, Phospholipids, Caffeine

1. Introduction

Fibromyalgia is characterized by chronic, widespread pain, abnormal processing of pain and increased sensitivity to external stimuli, along with fatigue, gastrointestinal symptoms and changes in memory, mood and sleep [1] [2] [3]. In 2010 the American College of Rheumatology established diagnostic criteria for the diagnosis of fibromyalgia based on a pain index and symptom severity scale [2]. Using this diagnostic criteria it has been estimated that between 0.1% - 3.3% of the populations in western countries and 2.0% of the population of the United States have fibromyalgia, with higher incidence rates in females compared to males [4].

In the last few years natural supplements have been used to reduce symptoms in patients with fibromyalgia, chronic fatigue and other chronic illnesses [5]; however, few if any of these natural supplements were considered effective [6]. Some symptoms, such as fatigue and pain, also occur naturally during aging, and they are important secondary conditions in many chronic diseases [7].

Pain and fatigue are related functionally to cellular energy systems found primarily in mitochondria and specifically in the electron transport chain of the mitochondrial inner membrane [8] [9]. Damage to mitochondrial membranes occurs in various diseases, mainly by oxidation of phospholipid components, and this can result in ion leakage across inner mitochondrial membranes and reductions in the ability of mitochondria to produce high-energy molecules [10] [11]. During aging and most chronic diseases the production of oxidative free radicals, such as Reactive Oxygen and Nitrogen species (ROS/RNS) and other molecules, can cause oxidative stress and cellular damage [10] [11] [12]. ROS/RNS damage often occurs to cellular membranes, and in particular, to the glycerolphospholipids of mitochondrial membranes [11] [12] [13] [14].

Membrane Lipid Replacement (MLR) therapy plus antioxidants has been used to replace damaged glycerolphospholipids in various clinical disorders and in aged individuals [8] [14] [15]. MLR results in the replacement of damaged cellu-

lar lipids with undamaged, unoxidized lipids to ensure proper function of cellular and organelle membranes. Combined with antioxidants, MLR supplements have proven to be effective in reducing ROS/RNS-associated changes in cellular activities and functions and for reducing symptom severity and providing host support in various clinical conditions [8] [14] [15] [16]. In fibromyalgia patients, the MLR supplement NTFactor Lipids® has been used to reduce fatigue [8] [16]. In a preliminary case report pain, fatigue and gastrointestinal symptoms were reduced in a small number of fibromyalgia patients (P.A. Breeding and G.L. Nicolson, in preparation)

In fibromyalgia patients another natural approach to reducing the severity of symptoms has been to use low-dose caffeine (equivalent to one or less than one cup of coffee or about 40 - 50 mg of caffeine) to moderate doses (equivalent to 1.5 - 2.5 cups of coffee) of caffeine to reduce pain and fatigue [17]. In the study of Scott *et al.* [17] caffeine consumption had a modest but significant effect on chronic pain reduction compared to an absence of caffeine consumption, but among non-opioid users this effect was not significant [17]. Caffeine is one of the most widely consumed natural food supplements in the world, and it is present in numerous foods and beverages. Caffeine is generally considered safe at doses up to 400 mg per day for adults [18] [19].

Here we tested the results of a combination natural supplement that contained a formulation of MLR glycophospholipids (NTFactor Lipids®) plus a low dose of controlled-released caffeine in chewable wafers in an open-label study format that used self-reported results on pain, fatigue, gastrointestinal symptoms and quality of life (QOL) indicators in a small group of fibromyalgia patinets.

2. Materials and Methods

2.1. Materials and Methods

An open label, Institutional Review Board approved, clinical trial was initiated to study the effects of an all-natural glycerolphospholipid chewable wafer supplement (Patented Energy™ with NTFactor Lipids®) and a chewable wafer containing NTFactor Lipids® and 184 mg controlled-release caffeine (Brite-Alert™) on fibromyalgia signs and symptoms. The supplement products provided a total of 4.8 g per day of NTFactor Lipids® and 184 mg controlled-release caffeine per day (released over 8 - 9 h). The supplement products were provided by Nutritional Therapeutics, Inc. (Hauppuage, NY). The dose of caffeine in the Brite-Alert™ wafer maintains the caffeine blood level equivalent to approximately one cup of coffee over an 8 - 9 h period. NTFactor Lipids® is a patented, proprietary lipid complex containing an exogenous source of polyunsaturated phosphatidylcholine, phosphatidyglycerol, phosphatidylserine, phosphatidylinositol, and other membrane phospholipids [8]. The participants took the daily dose for 8 days: one Brite-Alert™ wafer plus one Patented Energy™ wafer in the morning and two Patented Energy™ wafers in the afternoon.

To monitor patients we constructed a Combined Fibromyalgia Symptom

Survey Form (**Supplementary Figure 1**) that was based on established, validated, published symptom survey forms for pain, fatigue, gastrointestinal symptoms and QOL indicators [20] [21] [22] [23] [24]. Each question in the survey form was answered numerically based on a linear scale from 0 to 10. One question (Q38, based on time of day when subject is most symptomatic) was deleted from the analysis due to its non-numerical response. So that the general scale remained the same in the overall survey form, from lowest (0) to highest (10) severity of symptoms, the QOL portion of the survey form used this same format, which causes improvements in QOL to be shown by lower, not higher, scores.

2.2. Subjects

Participants (male and female) were recruited online using fibromyalgia support sites on social media (Facebook). The minimum sample size necessary to determine a significant difference ($p < 0.05$) in the results was estimated to be 20 subjects. Thus 30 patients with a confirmed diagnosis of fibromyalgia [1] [2] were recruited and sent an Informed Consent document and a Protocol document that explained the trial and the requirements of subjects in the trial. Qualifying participants who signed the Informed Consent document and agreed to the trial protocol were sent an eight day supply of the test supplements and the necessary copies of the Combined Fibromyalgia Symptom Survey Form and a Protocol Form.

2.3. Study Design

Male and Female subjects of age 18 - 65 years with a confirmed diagnosis of fibromyalgia [2] and who signed an Informed Consent document and agreed to participate in the study were sent the test supplements. Each participant was instructed to take the test supplements in the morning and afternoon and complete the symptom survey form early in the evening on day 0 (the evening before starting the test supplements), day 1 (evening on the first day after taking the supplements), day 2 (evening on the second day after taking the supplements), day 4 (evening on the fourth day), day 6 (evening on the sixth day) and day 8 (evening on the eighth day). After the 8-day trial, the completed survey forms were returned by mail in a self-addressed mailer to the Lead Investigator. Participants were also advised not to change any of their daily medications, diet or routine during the study.

2.4. Statistics

Data were analyzed by analysis of variance (ANOVA), with significance defined as $p < 0.05$. Further data analysis was performed with regression analysis, with significance defined as $p < 0.05$. This was established using a generalized mixed-effects model and calculating R^2 as Marginal R^2 and Conditional R^2 values [25]. All of the statistical analyses were done indpendently by the Statistical Unit at Cornell University.

3. Results

3.1. Subjects in the Study

Of the 30 participants recruited to this open-label pilot study, 21 subjects (15 females and 6 males) were fully compliant and completed the study. The main reason for subjects not completing the study was non-compliance with trial instructions. Either subjects did not sign the Informed Consent document, or they did not take all of the study supplements, or they failed to send back all of the fully completed symptom survey forms. Most of the subjects that withdrew from the study did so without taking the test supplements. However, one participant left the trial because of severe headaches, which had occurred intermittently before the trial; one participant left because of symptoms unrelated to the trial, and one left due to cardiovascular complaints that had also occurred before the trial. In all of these cases the subjects reported that their symptoms that caused them to leave the study had occurred intermittently before starting the study.

The mean age of participants completing the study was 48.5 ± 9.8 years (16 females, 48.7 ± 10.2 years and 6 males, 48.0 ± 5.6 years, respectively). There was no significant difference in mean age between males and females or between participants completing the study and those that did not complete the study.

3.2. Effects of MLR Supplements on Fibromyalgia Symptoms and QOL

We examined the daily effects of the test supplements on self-reported symptom severity and QOL scores during the 8-day trial and found significant improvements in the individual scores on specific questions (**Supplementary Table 1**). For example, the overall mean scores (**Figure 1(A)**) for the 46 questions evaluated in the trial significantly improved during the trial (significantly lower total scores). In the case of QOL, the scale was inverted to show improvements by lower scores (**Supplementary Figure 1**). Patients positively responded to the test supplements, as shown by significant improvements in total overall scores over the 8-day study period (**Figure 1(A)**, 36.1%, $p < 0.001$).

In addition, when the scores in the subparts of the combined symptom survey form were examined for reductions in pain (**Figure 1(B)**, 27.2%, $p < 0.001$), fatigue (**Figure 1(C)**, 37.8%, $p < 0.001$), and gastrointestinal symptoms (**Figure 1(D)**, 54.7%, $p < 0.001$) as well as improvements in QOL indicators (**Figure 1(E)**, 39.1%, $p < 0.001$), by day 8 there were significant differences (ANOVA) from the baseline values obtained before starting the MLR supplements. These significant differences were also obtained on each day monitored during the trial compared to baseline values on all symptoms and indicators.

3.3. Analysis of Data Based on Gender

We examined the trial data to see if there were any differences between the responses to the test supplements between females and males. Both females and males responded to the test supplements, but there were some differences

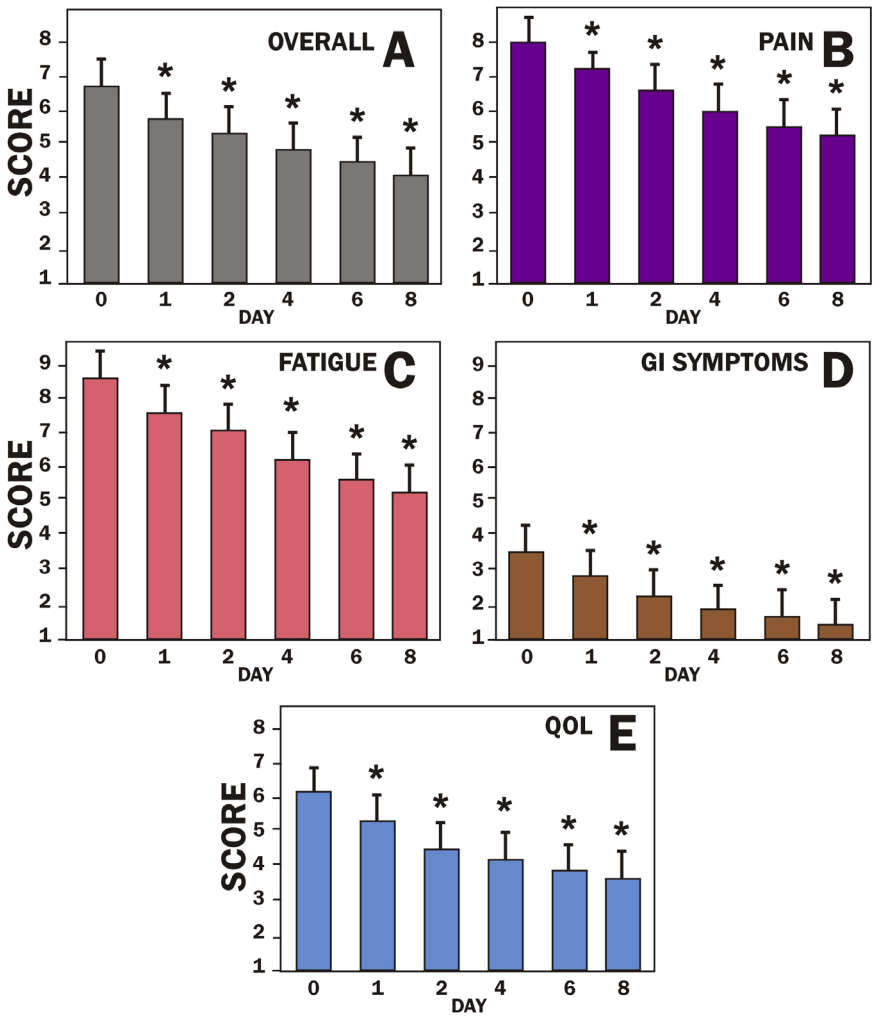

Figure 1. Combined and sub-parts of the symptom survey form scores by day for the study. Bars indicate mean ± SEM for overall scores (A), and for pain (B) fatigue (C), gastrointestinal symptoms (D), and QOL indicators (E). Note that the QOL indicator scores are shown in reciprocal format with improvements showing lower scores.

between males and females in responses overall (**Figure 2(A)**). When we examined the subparts of the symptom survey, we found some differences in responses between males and females with respect to pain (**Figure 2(B)**), fatigue (**Figure 2(C)**), gastrointestinal symptoms (**Figure 2(D)**) and QOL indicators (**Figure 2(E)**). Similar to the combined scores, females and males showed significant differences between test and baseline scores in all subcategories examined ($p < 0.001$); however the differences found between the scores of females and males did not reach significance in most analyses.

3.4. Model Analysis of the Data

We used the procedures of Nakagawa and Schielzeth [25] to calculate R^2 values for a generalized mixed-effects model. Calculations for fixed effects (gender) (Marginal R^2 values) or random effects (subjects) (Conditional R^2 values) for the

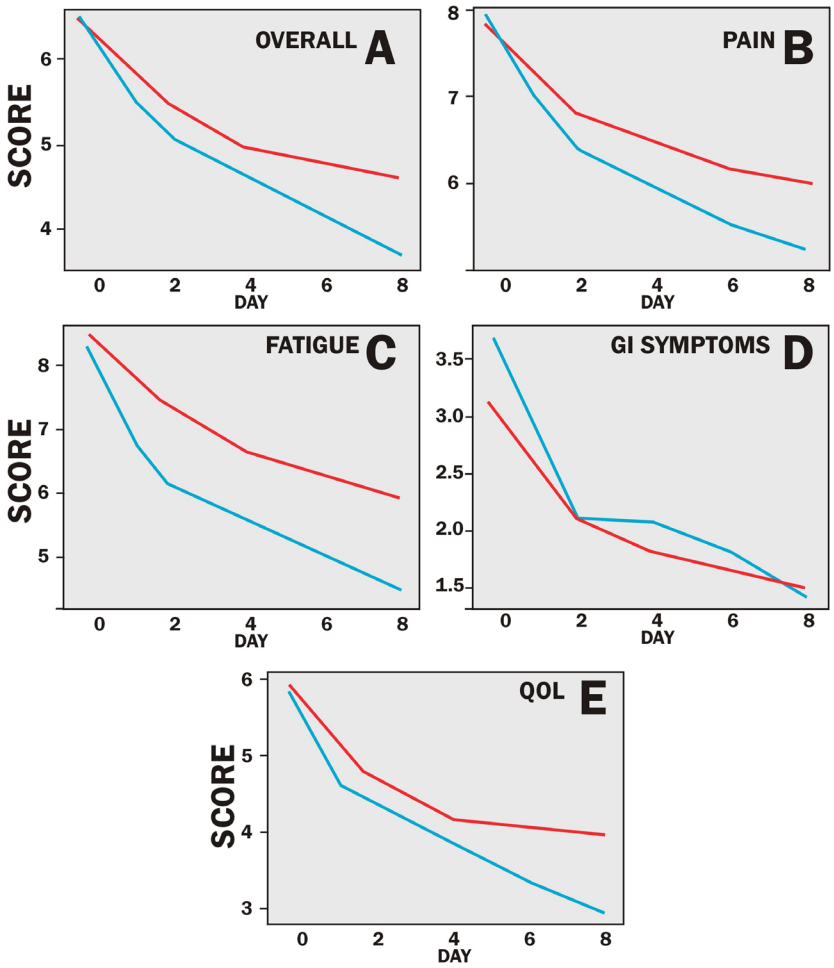

Figure 2. Collective symptom survey form scores by day and gender for the study. Plots indicate overall scores (A), and for pain (B) fatigue (C), gastrointestinal symptoms (D), and QOL indicators (E). Plots are shown for males (blue) and females (red). Note that the QOL indicator scores (E) are shown in reciprocal format with improvements showing lower scores.

various parameters yielded R^2 values for the model with day as the variable, including the baseline values at day 0. The various R^2 values were: Marginal R^2 = 0.2846, Conditional R^2 = 0.94996 (overall score); Marginal R^2 = 0.3923, Conditional R^2 = 0.9111 (fatigue score); Marginal R^2 = 0.2494, Conditional R^2 = 0.9266 (pain score); Marginal R^2 = 0.1023, Conditional R^2 = 0.9340 (gastrointestinal symptom score); Marginal R^2 = 0.1099, Conditional R^2 = 0.9691 (quality of life score). The Marginal and Conditional R^2 values indicate a low degree of variance and good consistency for the trial, even though the number of subjects in the study was limited. The Conditional R^2 scores in the generalized, mixed-effects model suggested that increasing the number of participants (subjects) in the study would be unlikely to change the results.

4. Discussion

Oral supplements that contain membrane glycerolphospholipids have been used

successfully in several clinical MLR studies [8] [14] [15] [16] [26] [27]. Here we used the MLR supplement NTFactor Lipids® with fructooligosaccahrides and antioxidants to protect the phospholipids from disruption, degradation and oxidation in the gut [14] [15]. These membrane glycerolphospholipids can be absorbed and transported into tissues and cells without excessive oxidative damage [8] [14] [15]. Once inside cells, the undamaged, replacement membrane phospholipids can exchange with damaged membrane phospholipids, resulting in removal of the latter molecules from cells. They also provide important lipid precursors for specific molecules, such as cardiolipin in the inner mitochondrial membrane. An important addition to the supplements we used was the incorporation of fructooligosaccharides and antioxidants in the MLR glycerolphospholipid mixture to avert oxidation and other types of damage to the phospholipids. This is important for maintaining potency during storage before they can be ingested and while they are ingested and dispersed into small lipid globules that are absorbed by the gut epithelium and transferred to the lymph and blood circulations for transport to various tissues and cells [8] [14] [15].

In animal studies a similar MLR supplement was used to prevent age-associated hearing loss [28]. Hearing loss is normally associated with aging, but addition of MLR glycerolphospholipids to animal chow shifted the threshold hearing from 35 - 40 dB in control aged laboratory rats to 13 - 17 dB in the treatment group ($p < 0.005$). Seidman *et al.* also found that cochlear mitochondrial function was preserved, and aging-related mitochondrial DNA deletions found in the cochlear were significantly reduced in the animals receiving the glycerolphospholipid supplement in their chow [28].

Most clinical studies using oral MLR supplements have been designed to reduce fatigue and protect cellular and mitochondrial membranes from oxidative damage [8] [14] [15] [16]. In some studies NTFactor® has been used in a vitamin and mineral mixture (Propax™) for cancer patients to reduce the adverse effects of cancer therapy, such as chemotherapy-induced fatigue, nausea, vomiting and other side effects [29] [30]. In a double-blind, placebo-controlled, randomized cross-over trial on cancer patients receiving chemotherapy MLR improved fatigue scores, nausea, diarrhea, impaired taste, constipation, insomnia and improved QOL indicators [29].

In several clinical studies MLR glycerolphospholipids have been shown to significantly reduce fatigue [8] [14] [15] [16] [27] [31] [32] [33]. For example, using aged subjects with chronic fatigue in a cross-over format, fatigue scores were significantly reduced from severe to moderate after eight weeks of MLR supplementation with NTFactor®. Mitochondrial function also improved with administration of the MLR glycerolphospholipids [32]. After 12 weeks there was a 35.5% reduction in fatigue ($p < 0.001$), and there was good correspondence between reductions in fatigue and gains in mitochondrial function ($p < 0.001$). By 12 weeks of supplementation mitochondrial function was found to be similar to that of young, healthy adults [32]. However, when subjects were placed on pla-

cebo without their knowledge for an additional 12 weeks, their fatigue and mitochondrial function were intermediate between the initial starting values and those found after eight or 12 weeks on the MLR supplement [32]. Here fibromyalgia patients showed significant reductions in fatigue similar to those found in previous studies with fibromyalgia patients [27].

In addition to fatigue, in the present study we also examined subjects for reductions in widespread pain and gastrointestinal symptoms, common complaints of fibromyalgia patients, as well as changes in QOL indicators. We found significant reductions in pain ($p < 0.001$) and gastrointestinal symptoms ($p < 0.001$) as well as improvements in QOL indicators ($p < 0.001$). The changes in fatigue, pain, gastrointestinal symptoms and QOL indicators were found to be significant on each day of the study ($p < 0.001$). Although there were differences between the responses of males and females in the study, consistent with previously studies, these differences were generally not statistically significant.

Using a mixed-effects statistical model and calculating Marginal and Conditional R^2 values indicated that the data were consistent and occurred with a low degree of variance. Although the number of subjects and time of the study were quite limited, the statistical analysis suggested that increasing the number of participants or the time of the study would be unlikely to change the conclusions. In fact, the results suggested that further reductions in overall scores, pain, fatigue, gastrointestinal symptoms and improvements in QOL were likely to occur with further time on the combination supplement.

Recently a case study with fibromyalgia patients using the MLR glycerolphospholipids (Patented Energy™ wafers) without added controlled-release caffeine demonstrated that individual fibromyalgia patients evaluated in a clinic setting by specialists also showed reductions in pain, fatigue and gastrointestinal symptoms in the same time-frame as the current study (Breeding, P.A. and Nicolson, G.L. in preparation). This indicated that the effects seen here were not due to caffeine alone.

The formulation used in this clinical study contained controlled-release caffeine that delivered a modest dose of caffeine over eight hours. Caffeine in low to moderate doses has been used previously to reduce pain and other symptoms in patients with various diagnoses. Thirty clinical studies involving more than 10,000 patients have been conducted with combinations of drugs and caffeine to assess the value of caffeine as an added adjuvant [34]. For example, the pooled data on use of caffeine to increase the effectiveness of various analgesics compared to the analgesics alone have shown that caffeine can increase the overall relative potency by an estimated factor of 1.41 [34]. Vaeroy *et al.* [35] found that fibromyalgia patients benefited when a low dose of caffeine was added to a combination mixture of carisoprodol and paracetamol (acetaminophen) to reduce pain and other symptoms. When caffeine was in the mixture, the combination was more effective ($p = 0.015$) [35]. Here we did not compare caffeine alone to NTFactor Lipids alone or to the combination of NTFactor Lipids plus con-

trolled-release caffeine, because the caffeine supplement that was under test (Brite Alert™) already contains NTFactor Lipids.

Although the etiology of fibromyalgia remains unclear, some of the possible causes are related to altered pain processing, resulting in malfunction at multiple levels. Some examples include aberrant ion channels, changes in intracellular Ca^{2+} and mitochondrial defects in neuroendocrine and skeletal muscle cell signal processing [36] [37] [38] [39]. Glycerolphospholipids and caffeine might act at these levels, and caffeine is known to be an important modulator of Ca^{2+} release in muscles and neuroendocrine cells [40] [41]. A recent study from our group supports the notion that NTFactor Lipids may act not just by replacement of damaged membrane glycerolphospholipids, but also by modulating and restoring the function of ion channels, intracellular Ca^{2+} and mitochondrial function [42]. The clinical trial results here are consistent with what has been described for the fibromyalgia syndrome etiology and the mechanism of action of NTFactor Lipids® and caffeine.

5. Conclusion

We tested the hypothesis that NTFactor Lipids® plus controlled-release, low-dose caffeine could reduce pain, fatigue, and gastrointestinal symptoms while improving QOL scores in fibromyalgia patients. Within days we found significant self-reported improvements in patients taking the combined supplement. The supplement was safe and effective and significantly reduced pain, fatigue and gastrointestinal symptoms and enhanced QOL scores during the 8-day period of the study. Although the number of patients in the study was limited, the statistical analysis suggested that increased numbers of participants would be unlikely to change the conclusions.

Acknowledgements

The authors would like to thank Allergy Research Group, Inc., Nutritional Therapeutics, Inc. and the Institute for Molecular Medicine for clinical trial financial support and for providing study materials.

Disclosures

Garth L. Nicolson and Robert Settineri are part-time consultants to Allergy Research Group, Inc. and Nutritional Therapeutics, Inc. Gonzalo Ferreira and Paul Breeding have no conflicts to disclose.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Wolf, F., Clauw, D.J. and Fitzcharles, M.A. (2010) The American College of Rheumatology Preliminary Diagnostic Creiteria for Fibromyalgia and Measurement of

Symptom Severity. *Arthritis Care and Research*, **62**, 600-610.
https://onlinelibrary.wiley.com/doi/full/10.1002/acr.20140
https://doi.org/10.1002/acr.20140

[2] Wolf, F., Clauw, D.J., Fitzcharles, M.A., Goldenberg, D.L., Häuser, W., Katz, R.S., Mease, P., Russell, A.S., Russell, I.J. and Winfield, J.B. (2011) Fibromyalgia Creiteria and Severity Scales for Clinical and Epidemiological Studies: A Modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *Journal of Rheumatology*, **38**, 1113-1122. http://www.jrheum.org/content/38/6/1113
https://doi.org/10.3899/jrheum.100594

[3] Breeding, P.C., Russell, N.C. and Nicolson, G.L. (2012) An Integrative Model of Chronically Activated Immune-Hormonal Pathways Important in the Generation of Fibromyalgia. *British Journal of Medical Practitioners*, **5**, a524-a534.
http://www.bjmp.org/content/integrative-model-chronically-activated-immune-hormonal-pathways-important-generation-fibrom

[4] Gran, J.T. (2003) The Epidemiology of Chronic Generalized Musculoskeletal Pain. *Best Practice and Research in Clinical Rheumatology*, **17**, 547-561.
https://www.bprclinrheum.com/article/S1521-6942(03)00042-1/fulltext
https://doi.org/10.1016/S1521-6942(03)00042-1

[5] Chambers, D., Bagnall, A.-M., Hempel, S. and Forbes, C. (2006) Interventions for the Treatment, Management and Rehabilitation of Patients with Chronic Fatigue Syndrome/Myalgic Encepthalomyelitis: An Updated Systematic Review. *Journal of the Royal Society of Medicine*, **99**, 506-520.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1592057/

[6] Reid, S., Chalder, T., Cleare, A., Hotopf, M. and Wessley, S. (2011) Chronic Fatigue Syndrome. *BMJ Clinical Evidence*, **2011**, 1101.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3275316/

[7] Kroenke, K., Wood, D.R., Mangelsdorff, A.D., Meier, N.J. and Powell, J.B. (1988) Chronic Fatigue in Primary Care: Prevalence, Patient Characteristics, and Outcome. *Journal of the American Medical Association*, **260**, 929-934.
https://jamanetwork.com/journals/jama/article-abstract/373491?redirect=true
https://doi.org/10.1001/jama.1988.03410070057028

[8] Nicolson, G.L. (2016) Membrane Lipid Replacement: Clinical Studies Using a Natural Medicine Approach to Restoring Membrane Function and Improving Health. *International Journal of Clinical Medicine*, **7**, 133-143.
http://www.scirp.org/Journal/PaperInformation.aspx?PaperID=63602
https://doi.org/10.4236/ijcm.2016.72015

[9] Brand, M.D. and Nicholis, D.G. (2011) Assessing Mitochondrial Dysfunction in Cells. *Biochemical Journal*, **435**, 297-312.
http://www.biochemj.org/content/ppbiochemj/435/2/297.full.pdf
https://doi.org/10.1042/BJ20110162

[10] Halliwell, B. (1996) Oxidative Stress, Nutrition and Health, Experimental Strategies for Optimization of Nutritional Antoxidant Intake in Humans. *Free Radical Research*, **25**, 57-74.
https://www.tandfonline.com/doi/abs/10.3109/10715769609145656
https://doi.org/10.3109/10715769609145656

[11] Duchen, M.R. and Szabadkai, G. (2010) Roles of Mitochondria in Human Disease. *Essays in Biochemistry*, **47**, 115-137.
https://www.ncbi.nlm.nih.gov/pubmed/20533904
https://doi.org/10.1042/bse0470115

[12] Montero, J., Mari, M., Colell, A., Morales, A., Basanez, G., Garcia-Ruiz, C. and Fer-

nandez-Checa, J.C. (2010) Cholesterol and Peroxidized Cardiolipin in Mitochondrial Membrane Properties, Permeabilization and Death. *Biochimica et Biophysica Acta*, **797**, 1217-1224.
https://www.sciencedirect.com/science/article/pii/S0005272810000563
https://doi.org/10.1016/j.bbabio.2010.02.010

[13] Adibhatla, R.M. and Hatcher, J.F. (2010) Lipid Oxidation and Peroxidation in CNS Health and Disease: From Molecular Mechanisms to Therapeutic Opportunities. *Antioxidants and Redox Signaling*, **12**, 125-169.
https://doi.org/10.1089/ars.2009.2668

[14] Nicolson, G.L. and Ash, M.E. (2014) Lipid Replacement Therapy: A Natural Medicine Approach to Replacing Damaged Phospholipids in Cellular Membranes and Organelles and Restoring Function. *Biochimica et Biophysica Acta*, **1838**, 1657-1679. http://www.sciencedirect.com/science/journal/00052736/1838/6
https://doi.org/10.1016/j.bbamem.2013.11.010

[15] Nicolson, G.L. and Ash, M.E. (2017) Membrane Lipid Replacement for Chronic Illnesses, Aging and Cancer Using Oral Glycerolphospholipid Formulations with Fructooligosaccharides to Restore Phospholipid Function in Cellular Membranes, Organelles, Cells and Tissues. *Biochimica et Biophysica Acta*, **1859**, 1704-1724.
https://doi.org/10.1016/j.bbamem.2017.04.013

[16] Nicolson, G.L., Rosenblatt, S., Ferreira de Mattos, G., Settineri, R., Breeding, P.C., Ellithorpe, R.R. and Ash, M.E. (2016) Clinical Uses of Membrane Lipid Replacement Supplements in Restoring Membrane Function and Reducing Fatigue in Chronic Diseases and Cancer. *Discoveries*, **4**, e54.
http://www.discoveriesjournals.org/discoveries/D.2016.01.PA-Dr Nicolson.pdf

[17] Scott, J.R., Hassett, A.L., Brummett, C.M., Clauw, D.J. and Harte, S.E. (2017) Caffeine as an Opioid Analgesic Adjuvant in Fibromyalgia. *Journal of Pain Research*, **10**, 1801-1809.
https://www.dovepress.com/caffeine-as-an-opioid-analgesic-adjuvant-in-fibromyalgia-peer-reviewed-article-JPR

[18] McLellan, T.M., Caldwell, J.A. and Lieberman, H.R. (2016) A Review of Caffeine's Effects on Cognitive, Physician and Occupational Performance. *Neuroscience and Biobehavioral Reviews*, **71**, 294-312. https://doi.org/10.1016/j.neubiorev.2016.09.001

[19] Doepker, C., Lieberman, H.R., Smith, A.P., Peck, J.D., El-Sohemy, A. and Welsh, B.T. (2016) Caffeine: Friend or Foe? *Annual Review of Food Science and Technology*, **7**, 117-137.
https://www.annualreviews.org/doi/abs/10.1146/annurev-food-041715-033243
https://doi.org/10.1146/annurev-food-041715-033243

[20] Kerns, R.D., Turk, D.C. and Rudy, T.E. (1985) The West Haven-Yale Multidimensional Pain Inventory (WHYMPI). *Pain*, **23**, 345-356.
https://www.researchgate.net/publication/222437274_The_West_Haven-Yale_multidimensional_pain_inventory_WHYMPI
https://doi.org/10.1016/0304-3959(85)90004-1

[21] Hann, D.M., Denniston, M.M. and Baker, F. (2000) Measurement of Fatigue in Cancer Patients: Further Validation of the Fatigue Symptom Inventory. *Quality of Life Research*, **9**, 847-854. https://doi.org/10.1023/A:1008900413113

[22] Van Zanten, S.J.V., Talley, N.J., Bytzer, P., Klein, K.B., Whorwell, P.J. and Zinmeister, A.R. (1999) Design of Treatment Trials for Functional Gastrointestinal Disorders. *Gut*, **45**, 69-77.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1766689/
https://doi.org/10.1136/gut.45.2008.ii69

[23] Bennett, R., Friend, R., Jones, K.D., Ward, R., Han, B.K. and Ross, R.L. (2009) The

Revised Fibromyalgia Impact Questionnaire (FIQR): Validation and Psychometric Properties. *Arthritis Research and Therapy*, **11**, R120.
https://doi.org/10.1186/ar2783

[24] Adam, B., Liebregts, T., Saadat-Gilani, K., Vinson, B. and Holtmann, G. (2005) Validation of the Gastrointestinal Symptom Score for the Assessment of Symptoms in Patients with Functional Dyspepsia. *Alimentary Pharmacology and Therapy*, **22**, 357-363.
https://www.researchgate.net/publication/7662529_Validation_of_the_gastrointestinal_symptom_score_GIS_in_patients_with_functional_dyspepsia
https://doi.org/10.1111/j.1365-2036.2005.02572.x

[25] Nakagawal, S. and Schielzeth, H. (2013) A General and Simple Method for Obtaining R2 from Generalized Linear Mixed-Effects Models. *Methods in Ecology and Evolution*, **4**, 133-142.
https://besjournals.onlinelibrary.wiley.com/doi/epdf/10.1111/j.2041-210x.2012.00261.x
https://doi.org/10.1111/j.2041-210x.2012.00261.x

[26] Ellithorpe, R.A., Settineri, R., Jacques, B. and Nicolson, G.L. (2012) Lipid Replacement Therapy Functional Food with NTFactor® for Reducing Weight, Girth, Body Mass, Appetite, Cravings for Foods and Fatigue while Improving Blood Lipid Profiles. *Functional Foods in Health and Disease*, **2**, 11-24.
http://www.functionalfoodscenter.net/files/49450833.pdf

[27] Nicolson, G.L. and Ellithrope, R.R. (2006) Lipid Replacement and Antioxidant Nutritional Therapy for Restoring Mitochondrial Function and Reducing Fatigue in Chronic Fatigue Syndrome and Other Fatiguing Illnesses. *Journal of Chronic Fatigue Syndrome*, **13**, 57-68.
http://www.immed.org/publications/Nicolson_ElllithorpeJCFS_copy.pdf
https://doi.org/10.1300/J092v13n01_06

[28] Seidman, M., Khan, M.J., Tang, W.X. and Quirk, W.S. (2002) Influence of Lecithin on Mitochondrial DNA and Age-Related Hearing Loss. *Otolaryngology—Head and Neck Surgery*, **127**, 138-144.
http://journals.sagepub.com/doi/full/10.1067/mhn.2002.127627
https://doi.org/10.1067/mhn.2002.127627

[29] Colodny, L., Lynch, K., Farber, C., Papish, S., Phillips, K., Sanchez, M., Cooper, K., Pickus, O., Palmer, D., Percy, T.B., Faroqui, M. and Block, J.B. (2000) Results of a Study to Evaluate the Use of Propax to Reduce Adverse Effects of Chemotherapy. *Journal of the American Nutraceutical Association*, **3**, 17-25.

[30] Nicolson, G.L. (2010) Lipid Replacement Therapy: A Nutraceutical Approach for Reducing Cancer-Associated Fatigue and the Adverse Effects of Cancer Therapy while Restoring Mitochondrial Function. *Cancer and Metastasis Reviews*, **29**, 543-552. https://doi.org/10.1007/s10555-010-9245-0

[31] Ellithorpe, R.R., Settineri, R. and Nicolson, G.L. (2003) Reduction of Fatigue by Use of a Dietary Supplement Containing Glycophospholipids. *Journal of the American Nutraceutical Association*, **6**, 23-28.
http://www.immed.org/illness/treatment_considerations.html

[32] Agadjanyan, M., Vasilevko, V., Ghochikyan, A., Berns, Kesslak, P., Settineri, R. and Nicolson, G.L. (2003) Nutritional Supplement (NTFactor) Restores Mitochondrial Function and Reduces Moderately Severe Fatigue in Aged Subjects. *Journal of Chronic Fatigue Syndrome*, **11**(3), 23-36.
http://www.immed.org/treatmentconsiderations/06.16.12/AgadjanyanNicolsonJCFS.pdf
https://doi.org/10.1300/J092v11n03_03

[33] Ellithorpe, R., Settineri, R., Mitchell, C., Jacques, B., Ellithorpe, T. and Nicolson,

G.L. (2011) Lipid Replacement Therapy Drink Containing a Glycophospholipid Formulation Rapidly and Significantly Reduces Fatigue While Improving Energy and Mental Clarity. *Functional Foods in Health and Disease*, **1**, 245-254. http://www.functionalfoodscenter.net/files/49450874.pdf

[34] Laska, E.M., Sunshine, A., Mueller, F., *et al.* (1984) Caffeine as an Analgesic Adjuvant. *Journal of the American Medical Association*, **251**, 1711-1718. https://jamanetwork.com/journals/jama/article-abstract/392180?redirect=true https://doi.org/10.1001/jama.1984.03340370043028

[35] Vaerøy, H., Abrahamsen, A., Forre, Ø. and Kåss, E. (1989) Treatment of Fibromyalgia (Fibrositis Syndrome): A Parallel Double Blind Trial with Carisoprodol, Paracetamol and Caffeine (Somadril Comp) versus Placebo. *Clinical Rheumatology*, **8**, 245-250. https://link.springer.com/article/10.1007/BF02030081 https://doi.org/10.1007/BF02030081

[36] Jahan, F., Nanji, K., Qidwai, W. and Qasim, R. (2012) Fibromyalgia Syndrome: An Overview of Pathophysiology, Diagnosis and Management. *Oman Medical Journal*, **27**, 192-195. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3394355/ https://doi.org/10.5001/omj.2012.44

[37] Bellato, E., Marina, E., Castoldi, F., Barbasetti, N., Mattei, L., Bonasina, D.E. and Blonna, D. (2012) Fibromyalgia Syndrome: Etiology, Pathogenesis, Diagnosis, and Treatment. *Pain Research and Treatment*, **2012**, Article ID: 426130. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3503476/ https://doi.org/10.1155/2012/426130

[38] Lund-Olesen, L.H. and Lund-Olesen, K. (1994) The Etiology and Possible Treatment of Chronic Fatigue Syndrome/Fibromyalgia. *Medical Hypotheses*, **43**, 55-58. https://www.ncbi.nlm.nih.gov/pubmed/7968720 https://doi.org/10.1016/0306-9877(94)90049-3

[39] Green, H.J., Ranney, D., Burnett, M., Galvin, P., *et al.* (2014) Excitation-Contraction Coupling Properties in Women with Work-Related Myalgia: A Preliminary Study. *Canadian Journal of Physiology and Pharmacology*, **92**, 498-506. http://www.nrcresearchpress.com/doi/pdf/10.1139/cjpp-2014-0029 https://doi.org/10.1139/cjpp-2014-0029

[40] Stephenson, D.G. (2008) Caffeine—A Valuable Tool in Excitation-Contraction Coupling Research. *Journal of Physiology*, **586**, 695-696. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2375628/ https://doi.org/10.1113/jphysiol.2007.148270

[41] Tsai, T.D. and Barish, M.E. (1995) Imaging of Caffeine-Inducible Release of Intracellular Calcium in Cultured Embryonic Mouse Telencephalic Neurons. *Developmental Neurobiology*, **27**, 252-265. https://doi.org/10.1002/neu.480270211 https://onlinelibrary.wiley.com/doi/pdf/10.1002/neu.480270211

[42] Ferreira, G., Costa, C., Bassaizteguy, V., Santos, M., Cardozo, R., Montes, J., Settineri, R. and Nicolson, G.L. (2018) Incubation of Human Sperm with Micelles Made from Glycerophospholipid Mixtures Increases Sperm Motility and Resistance to Oxidative Stress. *PLoS ONE*, **13**, e0197897. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0197897 https://doi.org/10.1371/journal.pone.0197897

Supplementary

Name _____ Day (circle): 0 1 2 3 8

IMM COMBINED SYMPTOM SURVEY FORM—FIBROMYALGIA

1.Rate the **level** of your pain at the present moment.

0 1 2 3 4 5 6 7 8 9 10

No pain **Very intense pain**

2.In general, how much does your pain problem interfere with your day-to-day **activities**?

0 1 2 3 4 5 6 7 8 9 10

No interference **Extreme interference**

3.Since the time you developed a pain problem, how much has your pain changed your **ability to work**?

0 1 2 3 4 5 6 7 8 9 10

No change **Extreme change**

___ Check here, if you have retired for reasons other than your pain problem.

4. How much has your pain changed the amount of satisfaction or enjoyment you get from participating in **social and recreational activities**?

0 1 2 3 4 5 6 7 8 9 10

No change **Extreme change**

5. How **supportive or helpful is your spouse** (significant other) to you in relation to your pain?

0 1 2 3 4 5 6 7 8 9 10

Not at all supportive **Extremely supportive**

6. Rate your overall **mood** during the past week.

0 1 2 3 4 5 6 7 8 9 10

Extremely low mood **Extremely high mood**

7. On the average, how **severe** has your pain been during the last week?

0 1 2 3 4 5 6 7 8 9 10

Not at all severe **Extremely severe**

8. How much has your pain changed your **ability to participate** in recreational and other social activities?

0 1 2 3 4 5 6 7 8 9 10

No change **Extreme change**

9. How much has your pain changed the amount of **satisfaction** you get from family-related activities?

0 1 2 3 4 5 6 7 8 9 10

No change **Extremechange**

10. How **worried** is your spouse (significant other) about you in relation to your pain problem?

0 1 2 3 4 5 6 7 8 9 10

Not at all worried **Extremely worried**

11. During the past week, how much **control** do you feel that you have had over your life?

0 1 2 3 4 5 6 7 8 9 10

Not at all in control **Extremely in control**

12. How much **suffering** do you experience because of your pain?

0 1 2 3 4 5 6 7 8 9 10

No suffering **Extreme suffering**

13. How much has your pain changed your **marriage and other family relationships**?

0 1 2 3 4 5 6 7 8 9 10

No change **Extreme change**

14. How much has your pain changed the **amount of satisfaction or enjoyment** you get from **work**?

0 1 2 3 4 5 6 7 8 9 10

No change **Extreme change**

__ Check here, if you are not presently working.

15. Do you have an urgent feeling of need to vomit but it does not occur or have **nausea**?

0 1 2 3 4 5 6 7 8 9 10

None **Very severe**

16. Do you have **vomiting** of mucus and stomach contents or strong unproductive retching?

0 1 2 3 4 5 6 7 8 9 10

None **Very severe**

17. Do you feel **bloated** or congestion of food without prior food intake?

0 1 2 3 4 5 6 7 8 9 10

None **Very severe**

18. Do you have **abdominal cramps or stomach pain** without specific localization?

0 1 2 3 4 5 6 7 8 9 10

None **Very severe**

19. Do you feel that your stomach is **overfilled** soon after starting to rest or not able to finish your meal?

0 1 2 3 4 5 6 7 8 9 10

None **Very severe**

20. Do you have **belching** with acid taste, heartburn, burning sensation in the esophagus or food pipe?

0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

21. Do you experience **discomfort** or sickness combined with the need to **vomit**?
0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

22. Do you have loss of **appetite**?
0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

23. Do you have an unpleasant feeling or **pain behind the sternum** or breastbone?
0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

24. Do you have **pain localized in the upper abdomen** below the sternum or breastbone?
0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

25. Rate your **levelof fatigue** on the day you felt **mostfatigued** during the last week.
0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

26. Rate your **level of fatigue** on the day you felt **least** fatigued during the last week.
0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

27. Rate your **level of fatigue** on the **average** during the last week.
0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

28. Rate your level of **fatigueright now**.
0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

29. Rate how much in the last week fatigue interfered with your **general level of activity**.
0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

30. Rate how much in the last week fatigue interfered with your **ability to bathe and dress.**
0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

31. Rate how much in the last week fatigue interfered with your **normal work activity** (includes both work outside the house and housework or work around the home)

0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

32. Rate how much in the last week fatigue interfered with your **ability to concentrate**.
0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

33. Rate how much in the last week fatigue interfered with your**relations with other people.**
0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

34. Rate how much in the last week fatigue interfered with your**enjoyment of life.**
0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

35. Rate how much in the last week fatigue interfered with **yourmood.**
0 1 2 3 4 5 6 7 8 9 10
None **Very severe**

36. Indicate in the last 8 days**how many days** you felt fatigued for any part of the day.
0 1 2 3 4 5 6 7 8
None **Days**

37. Rate **how much of the day**, on the average, you felt fatigued in the last week.
0 1 2 3 4 5 6 7 8 9 10
None **Entire Day**

38. Indicate which of the following best describes the **daily pattern** of your fatigue in the last week.

0	1	2	3	4
None	Worse in morning	Worse in afternoon	Worse in evening	No consistent daily pattern

39. Do you have any difficulty combing your hair?
0 1 2 3 4 5 6 7 8 9 10
None **Very severe difficulty**

40. Can you walk continuously for 20 minutes?
0 1 2 3 4 5 6 7 8 9 10
None **Very severe difficulty**

41. Can you prepare a homemade meal?
0 1 2 3 4 5 6 7 8 9 10

None **Very severe difficulty**

42. Are you able to vacuum, scrub or sweep floors?
0 1 2 3 4 5 6 7 8 9 10
None **Very severe difficulty**

43. Can you lift and carry a bag full of groceries?
0 1 2 3 4 5 6 7 8 9 10
None **Very severe difficulty**

44. Can you climb one flight of stairs?
0 1 2 3 4 5 6 7 8 9 10
None **Very severe difficulty**

45. Can you change bed sheets?
0 1 2 3 4 5 6 7 8 9 10
None **Very severe difficulty**

46. Can you sit in a chair for 45 minutes?
0 1 2 3 4 5 6 7 8 9 10
None **Very severe difficulty**

47. Can you go shopping for groceries?
0 1 2 3 4 5 6 7 8 9 10
None **Very severe difficulty**

Supplementary Figure 1. The signs/symptoms survey form used for this study. Participants were directed to fill out the form in the evening on the indicated days of the study and return the form to the Institute for Molecular Medicine.

Supplementary Table 1. Mean scores and SEM by day for each variable (each question in the symptom survey form).

	Overall		Baseline		Day 1		Day 2		Day 4		Day 6		Day 8	
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Q1	5.43	2.35	7.62	1.56	6.14	2.01	5.48	2.29	4.81	2.20	4.38	2.29	4.14	1.98
Q2	6.56	2.38	8.10	1.97	7.14	2.20	6.67	2.46	6.10	2.26	5.86	2.43	5.52	2.20
Q3	8.67	1.79	9.43	1.57	9.24	1.61	8.76	1.79	8.52	1.75	8.19	1.78	7.86	1.90
Q4	7.66	2.02	9.19	1.36	8.24	1.79	7.76	1.89	7.14	2.08	7.14	1.88	6.48	2.02
Q5	6.58	2.89	7.19	2.62	7.14	2.65	6.48	2.89	6.43	2.98	6.14	3.20	6.10	3.13
Q6	4.67	1.94	5.95	1.96	5.48	2.02	4.81	2.04	4.19	1.57	3.81	1.57	3.76	1.48
Q7	6.31	1.90	8.05	1.53	7.05	1.66	6.33	1.80	5.95	1.60	5.24	1.61	5.24	1.64
Q8	7.42	2.19	9.00	1.55	8.19	2.04	7.62	2.13	7.00	1.92	6.48	1.86	6.24	2.43
Q9	7.37	2.13	8.71	1.85	8.19	1.86	7.48	2.18	6.95	2.04	6.62	2.06	6.24	1.89
Q10	4.69	2.69	5.86	2.24	5.29	2.57	4.62	2.69	4.38	2.69	4.00	2.85	4.00	2.85
Q11	4.99	2.02	5.76	2.28	5.62	2.22	5.05	2.13	4.81	1.72	4.38	1.72	4.33	1.74

Continued

Q12	6.66	1.93	8.00	1.64	7.52	1.89	6.71	1.82	6.48	1.72	5.76	1.73	5.48	1.63
Q13	7.37	2.35	8.05	2.04	7.38	2.48	7.38	2.38	7.29	2.41	7.05	2.50	7.05	2.40
Q14	8.17	2.01	8.90	1.76	8.71	1.87	8.52	1.91	7.86	2.13	7.57	2.09	7.43	2.01
Q15	2.36	3.40	3.38	3.40	2.52	3.57	2.24	3.35	2.05	3.53	2.05	3.40	1.90	3.36
Q16	0.56	1.26	0.90	1.45	0.76	1.34	0.48	0.87	0.33	0.73	0.33	0.73	0.57	1.96
Q17	2.62	2.93	3.90	2.83	3.14	2.85	2.57	3.12	2.29	2.92	2.05	2.87	1.76	2.81
Q18	2.71	2.70	4.33	2.48	3.33	2.76	2.57	2.66	2.10	2.59	2.05	2.62	1.90	2.57
Q19	2.70	2.91	4.19	2.80	3.95	2.80	2.81	3.03	2.00	2.76	1.76	2.59	1.48	2.62
Q20	2.15	2.84	3.14	3.28	2.71	3.02	2.14	2.83	1.76	2.62	1.62	2.62	1.52	2.56
Q21	1.40	2.79	1.95	3.11	1.52	2.80	1.33	2.92	1.24	2.76	1.19	2.75	1.14	2.67
Q22	3.02	2.89	4.24	2.72	3.62	2.96	2.81	2.96	2.71	2.87	2.52	2.82	2.24	2.83
Q23	2.29	2.57	3.52	3.14	3.00	2.86	2.48	2.56	2.14	2.43	1.48	1.91	1.14	1.71
Q24	2.32	2.56	3.57	2.99	2.90	2.70	2.19	2.14	2.19	2.60	1.67	2.33	1.38	2.16
Q25	7.54	1.92	9.19	0.93	8.57	1.29	7.62	1.80	7.29	1.55	6.57	1.80	6.00	2.00
Q26	5.14	1.87	6.52	1.72	5.52	1.86	5.52	1.75	4.76	1.48	4.57	1.69	3.95	1.77
Q27	6.30	2.08	8.05	1.60	7.29	1.42	6.71	1.55	5.95	1.63	5.29	1.87	4.52	2.20
Q28	5.88	2.71	8.62	1.32	7.10	2.12	5.95	2.31	4.86	2.61	4.62	2.25	4.14	2.65
Q29	6.49	2.17	8.62	1.36	7.48	1.99	6.57	1.96	5.90	1.76	5.48	1.75	4.90	1.92
Q30	4.52	2.86	6.48	2.94	5.48	3.11	4.95	2.46	3.90	2.61	3.38	2.31	2.90	2.19
Q31	6.96	2.29	8.71	1.59	8.00	1.95	7.33	2.18	6.48	1.89	5.86	2.13	5.38	2.22
Q32	6.40	2.17	8.38	1.56	7.38	2.13	6.38	1.94	5.81	1.91	5.57	1.83	4.86	1.71
Q33	6.67	2.33	8.29	1.76	7.38	2.38	7.10	2.17	6.00	2.35	5.71	2.17	5.52	1.97
Q34	7.07	2.40	8.67	1.88	7.90	2.19	7.62	2.13	6.48	2.60	6.05	2.11	5.71	2.17
Q35	6.96	2.31	8.95	1.43	8.14	2.20	7.52	2.29	6.33	1.71	5.52	1.83	5.29	1.85
Q36	8.98	1.78	9.58	1.33	9.40	1.51	9.29	1.88	8.87	1.89	8.51	1.96	8.21	1.84
Q37	7.83	1.91	9.33	1.15	8.71	2.00	8.14	1.85	7.33	1.71	6.90	1.58	6.57	1.60
Q39	2.94	3.06	3.81	3.43	3.38	3.34	3.19	3.36	2.62	2.96	2.43	2.68	2.24	2.55
Q40	4.84	3.48	6.19	3.60	5.57	3.67	5.19	3.79	4.33	3.26	4.19	3.22	3.57	2.98
Q41	4.60	2.75	5.81	3.16	5.00	2.90	4.71	2.67	4.29	2.39	3.95	2.65	3.86	2.52
Q42	5.38	2.52	7.29	2.24	6.24	2.32	5.33	2.54	4.76	2.30	4.43	2.31	4.24	2.19
Q43	4.65	2.64	6.14	2.08	5.19	2.66	4.67	2.67	4.33	2.65	3.86	2.63	3.71	2.57
Q44	4.45	2.81	6.00	2.49	5.05	3.04	4.14	2.80	4.00	2.72	3.95	2.71	3.57	2.64
Q45	4.47	2.36	5.57	2.29	5.05	2.58	4.71	2.26	4.00	2.26	3.86	2.20	3.62	2.16
Q46	4.86	3.00	6.14	2.85	5.43	3.28	4.90	3.02	4.52	2.87	4.19	2.94	3.95	2.77
Q47	4.78	2.63	6.43	2.48	5.24	2.77	4.90	2.70	4.38	2.40	4.00	2.39	3.71	2.33