ISSN: 0975-833X

*Available online at http://www.journalcra.com*

**INTERNATIONAL JOURNAL OF CURRENT RESEARCH**

*International Journal of Current Research*
*Vol. 14, Issue, 01, pp.20271-20275, January, 2022*

*DOI: https://doi.org/10.24941/ijcr.42839.01.2022*

**RESEARCH ARTICLE**

# MANAGEMENT OF FATIGUE – A NARRATIVE REVIEW OF PROPOSED INTERVENTIONS AND THEIR EFFECTIVENESS

**Tingshan Yan[1], Manisha Oberoi[2], Ayman Askari[2], Hana Morrissey[3,*] and Patrick Ball[3]**

[1]Medical student, Keele University, School of Medicine, UK
[2]Lead Medical Science Liaison, Althea MMJ UK Ltd, UK
[2]Consultant Rheumatologist, The Robert Jones and Agnes Hunt Orthopaedic Hospital, NHS Foundation Trust, SY10 7AG United Kingdom
[3,*]Professor of Pharmacy, The University of Wolverhampton, Faculty of Science and Engineering, School of Pharmacy, Wulfruna Street, WV1 1LY United Kingdom
[3]Reader in Clinical Pharmacy, The University of Wolverhampton, Faculty of Science and Engineering, School of Pharmacy, Wulfruna Street, WV1 1LY United Kingdom.

**ARTICLE INFO**

*Article History:*
Received 07th October, 2021
Received in revised form
16th November, 2021
Accepted 14th December, 2021
Published online 28th January, 2022

*Keywords:*
Chronic Fatigue Syndrome, Traditional Medicine, Cognitive Behavioural Therapy, Structured Exercise, Fatigue Management.

***Corresponding author:***
***Hana Morrissey***

**ABSTRACT**

**Introduction:** Fatigue is a significant and frequently encountered health complaint that may accompany many medical conditions, communicable and non-communicable. Long-Covid is increasingly presenting to general practice and specialist neurology and rheumatology clinics which in most cases involves elements of CFS causing sudden increase in the patients seeking solutions for chronic fatigue. **Results:** There are many supplements offered commercially for the treatment of fatigue. Some are categorised as complementary or traditional medicines and are not licensed or controlled as medicinal products. Of those licensed as medicines, many are not licenced for the treatment of fatigue, so are prescribed 'off-label.' Patients have reported variable experiences with the different supplements and medications discussed. This paper attempts to document the available evidence for their efficacy in the treatment of fatigue. **Conclusion**: In almost all cases, only some patients derive any benefit and the benefits found are marginal culture RCT comparative studies using standardised products from those listed in this review are required to be able to make a definitive conclusion.



***Citation: Tingshan Yan, Manisha Oberoi, Ayman Askari, Hana Morrissey and Patrick Ball.*** *"*Management of Fatigue – A narrative review of proposed interventions and their effectiveness..*", 2022. International Journal of Current Research, 14, (01), 20271-20275.*

# INTRODUCTION

Fatigue is a significant and frequently encountered health complaint that may accompany many medical conditions, communicable and non-communicable. The prevalence of fatigue in the general population is said to range between 0.2-0.4% worldwide depending on the target study group and the different scoring systems used to assess fatigue (Galland-Decker, 2019). When fatigue cannot be explained by association with any other physical or mental health conditions it is usually referred to as Chronic Fatigue Syndrome (CFS), which is also known as Myalgic Encephalomyelitis.

CFS is defined as a condition with cellular energy dysfunction, dysregulation of the central nervous system (CNS) and the immune system, with negative impact on the cardiovascular system (Leonard, 2010). Leonard *et al*. concluded it was closer to 0.4% than 0.2% (Leonard, 2010). In the UK Nacul *et al*. studied 143,000 people between 18 and 64 years of age across 3 UK primary care service regions; London, East Anglia and East Yorkshire (Nacul, 2011). They concluded that applying the Canadian definition of CFS (Carruthers, 2033), the UK incidence was around 0.11%, but applying the CDC criteria[5] it was closer to 0.19% (Nacul *et al*., 2011). Nacul *et al*. concluded that taking the two prevalence estimate average, the

yearly incidence of CFS in the UK can be estimated as an average of 0.15%, meaning that at any one time the UK has between 150,000 and 250,000 people affected[3]. CFS may manifest an array of symptoms; fatigue and tiredness is often described as profound, with mental and physical exhaustion that increases with minimal effort, and does not improve with rest (NICE, 2007; NICE, 2021). Detailed guidelines for the Investigation and Diagnosis in the UK were recently updated and are available from the National Institute for Health and Care Excellence (NICE) (NICE, 2007; NICE, 2021). There are several scales used to assess fatigue in research and practice. The Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale (Webster, 2003) remains the most widely validated and adopted scoring scale. The optimised version of FACIT for fatigue is FACIT-F (FACIT, 2021) in which patients' self-report fatigue level and its effect on their daily activities and function. It was originally designed in 1990s as a subset of the Functional Assessment Cancer Therapy-General (FACT-G) scoring system for cancer therapy (Webster, 2003), and has now been extended to evaluate fatigue in a range of illness. The FACIT-F score, now in its 4$^{th}$ version and consists of 13 items. It uses a 5-point Likert type scale (0-4) and allows the patient to evaluate their fatigue symptoms over a recall period of 7 days. It can be performed either by self-report (e.g., paper or computer) or used in an interview (e.g., telephone or face to face). It has been translated into more than 45 languages. Over 150 published studies have proved its reliability and validity in clinical research settings (Webster, 2003; FACIT, 2021). Recently, with the emergence of Covid-19, there is an observed rise in this pattern of symptoms. The use of lockdown by governments may be a factor in this increase, but long-Covid is increasingly recognised in primary care and specialist neurology and rheumatology clinics which in most cases involve elements similar to CFS. Evidence-based treatment options are limited, and opinions conflicting (Venkatesan, 2021). This article reviews treatment approaches that have been explored, and the evidence for their effectiveness. Those affected by long-Covid and CFS in general are frequently dissatisfied with the current management and often desperate for alternatives.

**Available treatments:** The National Institute for Health and Care Excellence (NICE) recommends personalised treatment to patients with different symptoms (NICE, 2007; NICE, 2021). For patients with mild or moderate CFS, cognitive behavioural therapy (CBT) is usually offered, to help gain more control over their symptoms, and better understand how behaviours can affect their illness progression and challenge feelings that prevent symptom improvement. Alongside CBT, graded exercise therapy (GET) and structured exercise programmes, are also commonly offered. This exercise programme can be personalised to adapt to the patient's current physical performance levels and to gradually increase the amount of physical activity the patient can carry out[6 7]. The long-term, debilitating nature of this condition coupled with the slow response to established treatments prompts many patients to seek alternative or adjunct treatments to accelerate recovery.

**The evidence for supplements:** There are many supplements offered commercially for the treatment of fatigue. Most are categorised as complementary or traditional medicines and are not licensed or controlled as medicinal products. Those that are licensed as medicines, are not licenced for the treatment of fatigue indication and prescribed 'off-label. 'Patients have reported variable experiences with the different supplements and medications discussed in this paper. Their results in the treatment of fatigue are reported below.

**Ginseng:** As part of traditional medicine, ginseng has long been used in Asian countries such as China and South Korea to combat fatigue, stress, and minor aliment illnesses. The two major species of ginsengs available commercially are the Korean (*panax ginseng*) and American ginseng (*panax quinquefolius*). Approximately 40 different ginsenosides components of the ginseng extract have been identified. Animal studies have demonstrated effects on cognitive performance enhancement, glucose metabolism, and antitumor activities[11].Although there is no clear biological mechanism known for fatigue reduction, theories including the stimulation of hypothalamic-pituitary-adrenal cortex axis and the enhancement of mitochondrial metabolism in the muscles have been proposed. One meta-analysis looking at 12 randomised controlled trials (RCTs) (n=630 participants) found that there was a statistically significant efficacy of ginseng supplements on fatigue reduction (SMD = 0.34; 95% CI = 0.16 to 0.52), however no positive effect was found on physical performance enhancement (SMD = −0.01; 95% CI = −0.29 to 0.27) (Bach, 2016). Another systemic review of 10 studies to evaluate the effects of both American and Korean ginseng as treatments of fatigue. Four studies (2000 mg for a period between 8 weeks to 6 months) found that American ginseng demonstrated self-reported fatigue reduction in the intervention group compared to the control group however, doses lower than did not show statistically significant improvement (11). In the same review 5 out of 6 studies reported on the use of Asian ginseng found significant differences in fatigue measures in the intervention group compared to control group (Arring, 2017).

**D-ribose:** D-ribose, also known as ribose or beta-D-ribofuranose, is a natural pentose carbohydrate. Previously, different theories were proposed on its effects on the synthesis of mitochondrial energy in heart and skeletal muscles. One pilot study (n=41, of participants diagnosed with fatigue), D-ribose was administration at a dose of 5g, 3-times per day for a total of 280g, patients self-reported improvement in energy, sleep, mental clarity, wellbeing, and reduction of pain intensity (Teitelbaum, 2006).

**L-carnitine and Amantadine:** L-carnitine is a naturally occurring amino acid found in nearly all cells of the body. It assists in the transport of long chain fatty acids into mitochondria to produce cellular energy. One unblinded cross-over clinical trial (n=30) showed that after an 8-week treatment with L-carnitine supplementation and an antiviral drug, amantadine, with a 2-week washout period in between, patients reported statistically significant clinical improvement [14]. However, there was no improvement of fatigue associated with the use of amantadine alone. Moreover, the poorly tolerated side effects of amantadine caused half of the participants to drop out during the period they were prescribed the medication. Another randomised controlled clinical trial (n=66) in aged patients (>85 years of age) diagnosed with fatigue after slight physical activity showed that after receiving 2g levocarnitine once daily for 6 months, the levocarnitine treated group had a decrease of 4.10 points on the physical fatigue component of the Wessely and Powell scale, and a decrease of 2.70 on the mental fatigue. Their fatigue severity score decreased by 22.60.

This was a statistically significant difference from the placebo group (Malaguarnera, 2007). Similar positive treatment outcome was also demonstrated in another open label, randomised control study (n=90 CFS patients) using different forms of L-carnitidines[16].Patients were divided into 3 groups and were given 2g/day acetylcarnitine, 2g/day propionlcarnitine or a combination of both compounds for 24 weeks. Results showed that 59% patients in the acetylcarnitine group and 63% patients in the propionylcarnitine group had marked clinical improvement. Less clinical improvement was demonstrated in the combined treatment group. Patients in the acetylcarnitine group exhibited improvement in mental fatigue, whereas those in the propionylcarnitine group showed improvement in general fatigue. Interestingly, 2 weeks after treatment cessation, 52% patients in the acetylcarnitine group, 50% patients in the propionylcarnitine group and 37% patients in the combined group had worsened fatigue.

**Vitamin B12 and folate:** The majority of patients with CFS were found to have hypomethylation of their CD4 T cells[17], as well as the DNA within genes linked to CD4 T cell regulation (de Vega, 2014). As vitamin B12 and folate play vital roles in methylation of various cell process, several studies have looked at the use of vitamin B12 for the treatment of CFS. In a study published in 2015, researchers investigated 38 patients with CFS who were on long term vitamin B12 injections ranging from 6 months up to 20 years. Patients were divided into "Good" and "Mild" responders based on their scores on the self-reported rating scale, the fibro fatigue scale (FFS) and the patients' global impression of change (PGIC) questionnaire. A dose-response relationship with B12 and folic acid was found, where the "good" responders had significant improvement in their social life and the effect was shown to be long lasting (Regland *et al*., 2015). Another study published in 2019, using10.000 mcg of hydroxocobalamin as nasal drops twice weekly in 51 patients over a period of 3 months showed that 34 patients had a positive response to the treatment. Their median vitamin B12 level improved from 328 (244–429) pmol/l before treatment to 973 (476–1,476) pmol/l after treatment. Most importantly, their evaluation of symptoms on the checklist individual strength fatigue (CISF) scale and the functioning score of the Rand validity index (RVI) both showed statistically significant improvements (van Campen, 2019).

**Dextroamphetamine and Methylphenidate:** Dextroamphetamine and methylphenidate are medications licenced for prescription to patients with attention deficit hyperactivity disorder (ADHD). However, some studies have found that these medications may also provide symptom relief in patients with CFS. A small placebo-controlled trial was conducted over a 6-week period where 10 patients with CFS were randomly allocated to the dexamphetamine treatment group and 10 to the placebo group (Olson, 2003). Patients' symptoms were evaluated on the fatigue severity scale (FSS). The result showed that 9 out of 10 patients in the intervention group had statistically significant change in the mean fatigue score. However, no significant changes were reflected from the Short-Form Health Survey and physical functioning among the patients (Olson, 2003). Similarly, a 4-weekdouble-blinded randomised placebo-controlled crossover study on the use of 2 x 10mg/day methylphenidate on CFS patients found that methylphenidate relieved fatigue significantly and improved concentration in CFS patients compared to placebo but the improvements in fatigue were deemed clinically significant in only 17% of patients (Blockmans, 2006).

**Co-enzyme Q10 (CoQ10) and nicotinamide adenine dinucleotide hydride (NADH):** Biologically, CoQ10 is naturally produced in the human body and plays an important role in mitochondrial ATP production. Its antioxidant effect also protects mitochondria from oxidative stress. Emerging evidence has shown that the use of CoQ10 supplements can help restore mitochondrial function and reduce unexplained fatigue (Bentler, 2005). Fukuda *et al*. used the reduced form of CoQ10, in both an open-label study and a randomised controlled trial. Patients with CFS were asked to rate their clinical improvements on a subjective questionnaire. The open-label study involving 20 patients showed improvement in patient's depressive symptoms, improved performance on the arithmetic task and increased sleep hours. Unfortunately, no significant change was demonstrated on the Chalder fatigue Questionnaire (CFQ) scores before and after the CoQ10supplement (Fukuda, 2016). Interestingly, an 8-week randomised double-blind placebo-controlled trial conducted of73 patients with CFS demonstrated that patients treated with a combination of oralCoQ10 (200mg/day) and NADH (20mg/day) showed a significant improvement of fatigue as reflected by the reduction in their fatigue impact scale scores designed as a symptoms assessment questionnaire in the study[25]. The sole use of NADH (10mg/day) was also studied in a placebo-controlled cross over study in 26 CFS patients over a 12-week period. The results showed 8 out of the 26 patients responded favourably to NADH as compared to 2 of 26 to placebo (Forsyth, 1999). When comparing the effect of NADH to other nutritional supplements and psychotherapy on 31 patients for 24 months, the 12 patients who were assigned to the NADH treatment showed statistically significant reduction of the mean symptoms score compared to patient treated with nutritional or psychotherapy groups (Santaella, 2004). The overall conclusion appears to be that use of CoQ10 and NADH in combination should be further explored in larger studies (Castro-Marrero, 2005).

**Citalopram:** Citalopram, a commonly used selective serotonin reuptake inhibitor antidepressant has also been trailed for treatment of CFS. In a 2003 trial, conducted on 31 patients with idiopathic chronic fatigue, they received placebo for 1 week then citalopram 20-40mg/day for 2 months. Based on the RVI, fatigue for patients was significantly reduced when switched from placebo to citalopram. The result was particularly beneficial in patients who had suffered from fatigue for less than 5 years and had taken citalopram for 2 months (Hartz, 2006). Another open-label study also looking at 16 patients who suffered from both CFS and major depressive disorder found that, after treating the patients with s-citalopram 10mg to 20mg daily for 12 weeks, patients demonstrated a significant reduction in the mean total CFQ scores, as well as a significant reduction in the total Fatigue Impact Scores (Amsterdam, 2008). In contrast to the effect of citalopram, a meta-analysis reviewing 18 RCTs on the effects of antidepressants to fatigue in fibromyalgia syndrome showed that other agents such as fluoxetine, paroxetine and duloxetine showed no clinical efficacy on fatigue. Moclobemide, a monoamine oxidase inhibitor also failed to improve fatigue symptoms (Häuser, 2009).

**Magnesium:** A previous study in 1991 found that 20 CFS patients all had reduced red cell magnesium concentrations

(Cox, 1991). It has been hypothesised that magnesium deficiency could be linked to cellular oxidative stress and result in multi-system illnesses such as CFS. A randomised controlled trial allocated 15 CFS patients to the intramuscular magnesium injection group and 17 CFS patients to placebo group[31]. Twelve of the 15 patients self-reported improved energy levels, better emotional state, and less pain after receiving an intramuscular injection of magnesium sulphate every week for 6 weeks. The results were statistically significant for energy, pain and emotional reactions components of the Nottingham Health Profile score, but not for the sleep, social isolation or physical mobility components. The use of intramuscular administration seems to have been surprisingly well tolerated by patients, although the authors did speculate whether oral administration should be investigated.

**Cannabinoids:** No studies of cannabinoids as an intervention in ME/CFS were identified, but improvement in sleep pattern is essential in patients who have CFS associated with sleep dysregulation. Two studies of cannabis use in fibromyalgia reported some improvement in fatigue as a symptom (Mitchell, 2016)

**Rintatolimod:** Rintatolimod is a high molecular weight biologic agent in the form of a mis-matched RNA double stranded polymer. It acts through stimulation of the Toll-Like receptor 3 (TLR3). The Toll Like Receptors are activated by surface components on invading microbes and stimulate a pathway leading to the release of inflammatory cytokines and uprated expression of immune cells. TLR3 activation specifically stimulates the TIR-domain containing adapter-inducing interferon β (TRIF) pathway. In patients with CFS, in Phase 2 and 3 placebo controlled, randomised, double blind, multi-centre trials, IV administration twice weekly for up to 40 weeks, around 30-40% of patients showed improvement[32]. It is not yet licensed for use in the UK, but clinical trials are in progress.

# CONCLUSION

CFS/ME is a challenging condition. As outlined in the NICE guidelines CBT and graded physical therapy remain the gold standard, but availability of specialist services across the UK is patchy. Faced with a debilitating condition with only gradual improvement, it is unsurprising that patients remain keen to try experimental therapies. Of these, the rintatolimod has some of the strongest evidence to date, but still only 30-40% of patients demonstrated improvement. None of the therapies evaluated to date has sufficient supporting evidence to become part of a guideline, as most products are not standardised between studies to be able to compare or collate their findings. If these therapies are used, it should be on a case by case basis, under specialist supervision where possible and the outcome should be closely monitored and reported. Clearly a great deal more research is required Using larger patient cohorts, longer follow up and perhaps combinations of the agents that have demonstrated some benefit.

# REFERENCES


Galland-Decker C, Marques-Vidal P, Vollenweider P. Prevalence and factors associated with fatigue in the Lausanne middle-aged population: a population-based, cross-sectional survey. *BMJ Open* 2019;9(8):e027070. doi: 10.1136/bmjopen-2018-027070

Leonard AJ, Meredyth E, Nicole P, Molly B, Abigail B, Jessica H, *et al*. The Development of a Revised Canadian Myalgic Encephalomyelitis Chronic Fatigue Syndrome Case Definition. *American Journal of Biochemistry and Biotechnology* 2010;6(2) doi: 10.3844/ajbbsp.2010.120.135

Nacul LC, Lacerda EM, Pheby D, Campion P, Molokhia M, Fayyaz S, *et al*. Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care. *BMC Medicine* 2011;9(1):91. doi: 10.1186/1741-7015-9-91

Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner AM, *et al*. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Journal of Chronic Fatigue Syndrome* 2003;11(1):7-115. doi: 10.1300/J092v11n01_02

CDC. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Symptoms and Diagnosis of ME/CFS Atlanta: Centers For Disease Control; 2018 (Available from: https://www.cdc.gov/me-cfs/symptoms-diagnosis/index.html accessed 18/12/2021.

NICE. Clinical Guideline CG 53 Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management London, England: National Institute for Health and Care Excellence; 2007 (Available from: https://www.nice.org.uk/guidance/cg53#choosing-and-planning-treatment accessed 12/12/2021.

NICE. NICE Guideline NG206 Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management London, England: National Institute for Health and Care Excellence; 2021 (Available from: https://www.nice.org.uk/guidance/ng206 accessed 12/12/2021.

Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health Qual Life Outcomes* 2003;1:79-79. doi: 10.1186/1477-7525-1-79

FACIT.org. FACIT Fatigue Functional Assessment of Chronic Illness Therapy - Fatigue Scale New York, USA: Facit.org; 2021 (Available from: https://www.facit.org/ measures/ FACIT-Fatigue accessed 12/12/2021.

Venkatesan P. NICE guideline on long COVID. *The Lancet Respiratory Medicine* 2021;9(2):129. doi: https://doi.org/10.1016/S2213-2600(21)00031-X

Bach HV, Kim J, Myung SK, Cho YA. Efficacy of Ginseng Supplements on Fatigue and Physical Performance: a Meta-analysis. *J Korean Med Sci* 2016;31(12):1879-86. doi: 10.3346/jkms.2016.31.12.1879

Arring NM, Millstine D, Marks LA, Nail LM. Ginseng as a Treatment for Fatigue: A Systematic Review. *J Altern Complement Med* 2018;24(7):624-33. doi: 10.1089/acm.2017.0361 (published Online First: 20180406)

Teitelbaum JE, Johnson C, St Cyr J. The use of D-ribose in chronic fatigue syndrome and fibromyalgia: a pilot study. *J Altern Complement Med* 2006;12(9):857-62. doi: 10.1089/acm.2006.12.857

Plioplys AV, Plioplys S. Amantadine and L-Carnitine Treatment of Chronic Fatigue Syndrome. *Neuropsychobiology* 1997;35(1):16-23. doi: 10.1159/000119325

Malaguarnera M, Cammalleri L, Gargante MP, Vacante M, Colonna V, Motta M. L-Carnitine treatment reduces

severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial. *Am J Clin Nutr* 2007;86(6):1738-44. doi: 10.1093/ajcn/86.5.1738

Vermeulen RC, Scholte HR. Exploratory open label, randomized study of acetyl- and propionylcarnitine in chronic fatigue syndrome. *Psychosom Med* 2004;66(2):276-82. doi: 10.1097/01.psy.0000116249.60477.e9

Brenu E. Methylation Profile of CD4+ T Cells in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. *Journal of Clinical & Cellular Immunology* 2014;05 doi: 10.4172/2155-9899.1000228

de Vega WC, Vernon SD, McGowan PO. DNA methylation modifications associated with chronic fatigue syndrome. *PLoS ONE* 2014;9(8):e104757. doi: 10.1371/journal.pone.0104757 (published Online First: 20140811)

Regland B, Forsmark S, Halaouate L, Matousek M, Peilot B, Zachrisson O, *et al*. Response to vitamin B12 and folic acid in myalgic encephalomyelitis and fibromyalgia. *PLoS ONE* 2015;10(4):e0124648-e48. doi: 10.1371/journal.pone.0124648

van Campen CLM, Riepma K, Visser FC. Open Trial of Vitamin B12 Nasal Drops in Adults With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Comparison of Responders and Non-Responders. *Front Pharmacol* 2019;10:1102. doi: 10.3389/fphar.2019.01102 (published Online First: 20190920)

Olson LG, Ambrogetti A, Sutherland DC. A pilot randomized controlled trial of dexamphetamine in patients with chronic fatigue syndrome. *Psychosomatics* 2003;44(1):38-43. doi: 10.1176/appi.psy.44.1.38

Blockmans D, Persoons P, Van Houdenhove B, Bobbaers H. Does methylphenidate reduce the symptoms of chronic fatigue syndrome? *Am J Med* 2006;119(2):167.e23-30. doi: 10.1016/j.amjmed.2005.07.047

Bentler SE, Hartz AJ, Kuhn EM. Prospective observational study of treatments for unexplained chronic fatigue. *J Clin Psychiatry* 2005;66(5):625-32. doi: 10.4088/jcp.v66n0513

Fukuda S, Nojima J, Kajimoto O, Yamaguti K, Nakatomi Y, Kuratsune H, *et al*. Ubiquinol-10 supplementation improves autonomic nervous function and cognitive function in chronic fatigue syndrome. *Biofactors* 2016;42(4):431-40. doi: 10.1002/biof.1293 (published Online First: 20160429)

Castro-Marrero J, Cordero MD, Segundo MJ, Sáez-Francàs N, Calvo N, Román-Malo L, *et al*. Does oral coenzyme Q10 plus NADH supplementation improve fatigue and biochemical parameters in chronic fatigue syndrome? *Antioxid Redox Signal* 2015;22(8):679-85. doi: 10.1089/ars.2014.6181 (published Online First: 20141218)

Forsyth LM, Preuss HG, MacDowell AL, Chiazze L, Jr., Birkmayer GD, Bellanti JA. Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. *Ann Allergy Asthma Immunol* 1999;82(2):185-91. doi: 10.1016/s1081-1206(10)62595-1

Santaella ML, Font I, Disdier OM. Comparison of oral nicotinamide adenine dinucleotide (NADH) versus conventional therapy for chronic fatigue syndrome. *P R Health Sci J* 2004;23(2):89-93.

Hartz AJ, Bentler SE, Brake KA, Kelly MW. The effectiveness of citalopram for idiopathic chronic fatigue. *J Clin Psychiatry* 2003;64(8):927-35. doi: 10.4088/jcp.v64n0811

Amsterdam JD, Shults J, Rutherford N. Open-label study of s-citalopram therapy of chronic fatigue syndrome and co-morbid major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32(1):100-6. doi: 10.1016/j.pnpbp.2007.07.019 (published Online First: 20070803)

Häuser W, Bernardy K, Uçeyler N, Sommer C. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *JAMA* 2009;301(2):198-209. doi: 10.1001/jama.2008.944

Cox IM, Campbell MJ, Dowson D. Red blood cell magnesium and chronic fatigue syndrome. *The Lancet* 1991;337(8744):757-60. doi: https://doi.org/10.1016/0140-6736(91)91371-Z

Mitchell WM. Efficacy of rintatolimod in the treatment of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). *Expert Review of Clinical Pharmacology* 2016;9(6):755-70. doi: 10.1586/17512433.2016.1172960

*******