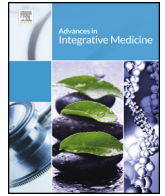




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Mitochondrial modifying nutrients in treating chronic fatigue syndrome: A 16-week open-label pilot study

Ranjit Menon^{a,*}, Lachlan Cribb^a, Jenifer Murphy^a, Melanie M. Ashton^{a,b,c,d},
Georgina Oliver^a, Nathan Dowling^a, Alyna Turner^b, Olivia Dean^{b,e}, Michael Berk^{b,c,d},
Chee H. Ng^a, Jerome Sarris^{a,f}

^a Professorial Unit, The Melbourne Clinic, Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia

^b Deakin University, School of Medicine, IMPACT Strategic Research Centre, Barwon Health, Geelong, Victoria, Australia

^c Department of Psychiatry, Orygen, the National Centre of Excellence in Youth Mental Health, University of Melbourne, Melbourne, Victoria, Australia

^d Florey Institute for Neuroscience and Mental Health, University of Melbourne, Melbourne, Victoria, Australia

^e University of Melbourne, Department of Psychiatry, Level 1 North, Main Block, Royal Melbourne Hospital, Parkville, Australia

^f NICM, School of Health and Science, Western Sydney University, Campbelltown, New South Wales, Australia

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ABSTRACT

Introduction: Recent evidence suggests that mitochondrial dysfunction may play a role in the pathophysiology of chronic fatigue syndrome (CFS). We undertook a pilot investigation of a combination of nutraceutical nutrient compounds which are involved in mitochondrial function and energy generation, to assess their efficacy in improving symptoms of CFS. An open-label design was employed as CFS is largely treatment-resistant with limited placebo-response.

Methods: A 16-week open-label trial of a nutraceutical combination (primary nutrients: Coenzyme Q10, Alpha lipoic acid, Acetyl-L-carnitine, N-acetyl cysteine, B Vitamins, in addition to co-factors) was undertaken in ten patients with CFS. Fatigue symptoms, mood and general health were assessed at each 4-week time point over 16 weeks. Of the ten patients (7 female, 3 male) with a mean age of 36.3, eight completed the trial.

Results: Linear mixed model analysis demonstrated a significant improvement in fatigue symptoms across treatment period on the Chalder Fatigue Scale ($p < 0.001$). Specific improvements were found in tiredness, weakness, feeling sleepy or drowsy, as well as in sleep, and clinician-reported symptom-improvement. No benefit was observed in mood or other functional domains. No serious adverse events were noted.

Conclusion: These preliminary findings suggest that a combination nutraceutical compound of mitochondrial agents may improve CFS symptoms. Further investigation is warranted in a larger double-blind RCT.

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1. Introduction

Chronic fatigue syndrome (CFS) is a prolonged multisystem illness, characterised by poor stamina and delayed post-exertional fatigue, that adversely affects one's functioning across numerous physical and mental domains [1]. A diagnosis of CFS is generally made only after other alternate medical and psychiatric causes of chronic fatigue have been excluded. However, uncertainty

regarding lack of specific laboratory tests or markers, clear aetiology of illness, and overlap with other neuropsychiatric disorders (e.g. depression), remain barriers to effective diagnosis, treatment, and management [2]. While debate exists regarding appropriate treatment strategies, if left untreated, prognosis for recovery is generally poor [3].

It is estimated that between 2 in 1000 and 2 in 100 adults in the United States of America have CFS [4]. Current treatments for CFS include pharmacological (e.g. fluoxetine, rintatolimod and galantamine), psychological (e.g. cognitive behaviour therapy (CBT), adaptive pacing therapy), and lifestyle interventions (e.g. graded exercise) [5]. These treatments target the symptoms of CFS such as muscle pain, sleep disturbance, affective symptoms and

* Corresponding author at: The Melbourne Clinic, Department of Psychiatry, The University of Melbourne, 130 church st, Richmond, Melbourne, Australia.

E-mail address: Ranjit.Menon@unimelb.edu.au (R. Menon).

fatigue [6]. A large systematic review of interventions for CFS (n = 44 studies) found mixed results for the effectiveness of most interventions [6]. The authors concluded that this is most likely due to heterogeneous study methodologies and patient populations. However, despite the methodological pitfalls, CBT and graded exercise therapy emerged as the most promising interventions for CFS currently. Although CBT and graded exercise therapy are considered to be effective treatments for CFS, the availability and access to skilled clinicians who deliver these interventions is limited, and many sufferers balk at seeing this as a psychological problem needing a psychological approach, and many struggle with the idea of treating a disorder marked by fatigue with exercise that triggers fatigue. The attrition rates are thus high with approximately 20–40% discontinuing treatment [7]. For many who remain in treatment, they continue to experience significant social, occupational, and functional impairment. Thus new treatment approaches are urgently needed.

While fatigue remains a common complaint across numerous disorders, it is posited that CFS is related to metabolic dysfunction, oxidative and nitrosative stress [8], mitochondrial dysfunction and impaired biogenesis [11], and is in turn related to oxidative stress and systemic inflammation. Mitochondria are structures within cells primarily responsible for energy generation, and are particularly active in oxygen-rich and highly energy dependent tissues, such as the brain. Impaired energy metabolism triggers pro-apoptotic signalling (programmed cell death), oxidative damage (damage caused by free radicals), excitotoxicity (cell death due to excess cell stimulation) and impedes mitochondrial DNA repair [9]. These processes can interact and potentiate one another, which in turn results in a continuation of mitochondrial damage and subsequent energy depletion. Reduced energy levels threaten cellular homeostasis and integrity, particularly in highly metabolically active organs in the body such as the brain. Additionally, because of the high levels of oxygen metabolism in brain tissue, neural mitochondria are also highly susceptible to oxidative stress [10]. Mitochondrial dysfunction leads to further oxidative stress, which in turn causes further damage to the mitochondrion. This phenomenon of mitochondrial dysfunction has been observed in CFS, with Myhill, Booth & McLaren-Howard demonstrating a very strong correlation between dysfunctional adenosine triphosphate (ATP) metabolism and CFS [1]. As such, interventions that improve mitochondrial function, by sustaining ATP levels, have face value as being likely to improve neuronal dysfunction, and offer neuroprotection which may significantly impede the progression of neurological damage.

While research into the neurobiology and neuroimmunology of CFS has gained increasing attention of late, new therapeutic interventions remain sparse. Early research suggests that patients suffering from CFS may improve with the supplementation of mitochondrial nutrients and antioxidants [11]. Among many mitochondrial-enhancing agents to consider as potential treatments for CFS, only a selected few can be chosen for reasons of practicality. These include antioxidants (Co-enzyme Q10 [Co Q10], idebenone, N-acetylcysteine (NAC), vitamin C, vitamin E and menadione), agents that specifically improve lactic acidosis (dichloroacetate and dimethylglycine), agents that correct secondary biochemical deficiencies (carnitine, creatine), respiratory chain co-factors (nicotinamide, thiamine, riboflavin, pantothenic acid, pyridoxine and Co-Q10), and hormones (growth hormone and corticosteroids). This supplementation may assist in restoring mitochondrial energy production, protecting cellular structures and enzymes from oxidative damage, and decreasing fatigue. Given that CFS is largely a heterogeneous illness associated with a complex and multifactorial aetiology, it is plausible that adjunctive use of a combination of metabolic therapies may have positive effects on mitochondrial dysfunction and CFS symptoms.

2. Methods

2.1. Overview

This open-label study aimed to examine the efficacy of a novel and practical adjunctive intervention of a combination of nutraceutical agents acting on mitochondrial targets. No placebo was employed due to CFS being considered a stable chronic disorder that can be regarded as 'treatment-resistant', and with a relatively low placebo-response [12]. The original study intervention was planned to be 20-weeks, however, due to an unexpected product change from the company producing the nutraceuticals and subsequent discontinuation of the study, it was capped at 16-weeks. Thus we present the data from a 16-week open-label observational pilot study. Participants received the intervention daily, adjunctive to treatment as usual, with assessment visits at baseline, W4, W8, W12, W16. The primary outcome measure was the Chalder Fatigue Scale (CFQ). It was hypothesised that the combination therapy would improve symptoms of fatigue (assessed on the CFQ), in addition to depression, as assessed on the Montgomery-Asberg Depression Rating Scale (MADRS), and social functioning via the Health Survey and Work and Social Adjustment Scale (WSAS). All elements of this investigation aligned as closely as possible with CONSORT clinical trial criteria. Due to the open label nature of this investigation however, some CONSORT elements were not relevant and were thus not presented.

2.2. Inclusion criteria

- Males and females aged 18–65 years.
- Diagnosed with chronic fatigue syndrome by an independent physician (a letter or referral will be preferred to confirm diagnosis).
- Fulfil criteria for CFS as per the US Centres for Disease Control and Prevention (CDC), which requires persistent, unexplained fatigue for at least 6 months, concurrent with at least four of the following:
 - Impaired memory/concentration.
 - Sore throat, new headaches.
 - Unrefreshing sleep, muscle pain.
 - Multi-joint pain.
 - Tender lymph nodes.
 - Post-exertional malaise.
- Have capacity to consent to the study and comply with study procedures.
- Be using effective contraception if female, sexually active and of childbearing age.
- If currently receiving treatment, stable treatment was required for at least four weeks prior to enrolment.

2.3. Exclusion criteria

- Individuals with known or suspected active and unstable systemic medical disorder.
- Individuals who have a major depressive episode in the two years preceding the diagnosis of CFS.
- Acute suicidality as indicated by a score of 5 or 6 on Item 10 of the MADRS (or at the discretion of Principal Investigator).
- Individuals with current diagnosis of a psychotic disorder, bipolar disorder, substance abuse/dependence, eating disorder, significant personality disorder.
- Recent gastrointestinal ulcers or renal stones.
- Individuals who are pregnant or lactating.
- Individuals with a diagnosis of epilepsy.

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