British Journal of Pharmacology

REVIEW ARTICLE

Treatment and management of chronic fatigue syndrome/myalgic encephalomyelitis: all roads lead to Rome

Correspondence Jesus Castro-Marrero, Vall d'Hebron University Hospital, Collserola Research Institute, CFS/ME Unit (Lab. 145 – Floor 1), Passeig de Vall d'Hebron 119-129, E-08035 – Barcelona, Spain. E-mail: jesus.castro@vhir.org

Received 8 June 2016; **Revised** 25 November 2016; **Accepted** 14 December 2016

Jesus Castro-Marrero[1], Naia Sáez-Francàs[2], Dafna Santillo[1] and Jose Alegre[1]

[1]*CFS/ME Unit, Vall d'Hebron University Hospital, Collserola Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain, and* [2]*Psychiatry Unit, Sant Rafael Hospital (FIDMAG), Barcelona, Spain*

This review explores the current evidence on benefits and harms of therapeutic interventions in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) and makes recommendations. CFS/ME is a complex, multi-system, chronic medical condition whose pathophysiology remains unknown. No established diagnostic tests exist nor are any FDA-approved drugs available for treatment. Because of the range of symptoms of CFS/ME, treatment approaches vary widely. Studies undertaken have heterogeneous designs and are limited by sample size, length of follow-up, applicability and methodological quality. The use of rintatolimod and rituximab as well as counselling, behavioural and rehabilitation therapy programs may be of benefit for CFS/ME, but the evidence of their effectiveness is still limited. Similarly, adaptive pacing appears to offer some benefits, but the results are debatable: so is the use of nutritional supplements, which may be of value to CFS/ME patients with biochemically proven deficiencies. To summarize, the recommended treatment strategies should include proper administration of nutritional supplements in CFS/ME patients with demonstrated deficiencies and personalized pacing programs to relieve symptoms and improve performance of daily activities, but a larger randomized controlled trial (RCT) evaluation is required to confirm these preliminary observations. At present, no firm conclusions can be drawn because the few RCTs undertaken to date have been small-scale, with a high risk of bias, and have used different case definitions. Further, RCTs are now urgently needed with rigorous experimental designs and appropriate data analysis, focusing particularly on the comparison of outcomes measures according to clinical presentation, patient characteristics, case criteria and degree of disability (i.e. severely ill ME cases or bedridden).

Abbreviations

APT, adaptive pacing therapy; CBT, cognitive behavioural therapy; CDC, Centres for Disease Control and Prevention; CFS/ME, Chronic fatigue syndrome/myalgic encephalomyelitis; CoQ_{10}, Coenzyme Q_{10}; DHA, docosa; EPA, eicosapentenoic acid; FINE, Fatigue intervention by nurses evaluation trial; GET, graded exercise therapy; GLA, γ-linolenic acid; HADS, Hospital anxiety and depression scale; Max HR, maximum heart rate; ICC-ME, 2011 International Consensus criteria for ME; IOM, Institute of Medicine; NSAIDs, Non-steroidal anti-inflammatory drugs; PACE, Pacing, graded activity, and cognitive behaviour therapy; a randomized evaluation for CFS patients; PVFS, Post-viral fatigue syndrome; RCT, randomized controlled trial; SEID, systemic exertion intolerance disease; SMC, standard medical care; SSRI, selective serotonin-reuptake inhibitor; SSNRI, selective serotonin-noradrenaline reuptake inhibitor

DOI:10.1111/bph.13702

Tables of Links

TARGETS
Other protein targets[a]
CD20
Enzymes[b]
COX-2
Transporters[c]
Acyl-L-carnitine

LIGANDS	
Acetyl-L-carnitine	Imipramine
Magnesium	Mirtazapine
Acyclovir	Morphine
α-lipoic acid	GLA, γ-linolenic acid
Amitriptyline	EPA, eicosapentaenoic acid
ATP	NADH
Bupropion	Naproxen
Clomipramine	Nefazodone
Codeine	Noradrenaline
Cortisol	Nortriptyline
Desipramine	Paroxetine
DHA, docosahexaenoic acid	Pregabalin
Doxepin	Rituximab
Duloxetine	Serotonin
Fludrocortisone	Sertraline
Fluoxetine	Tramadol
Folate	Valacyclovir
Gabapentin	Valganciclovir
Ibuprofen	Vitamin C

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c]Alexander *et al.*, 2015a,b,c).

Background

The condition known as chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME), also recently renamed systemic exertion intolerance disease (SEID), is a complex, heterogeneous and extremely debilitating medical condition with no known specific cause and for which no clinically established diagnostic tests are available. Its symptoms are characterized by an extreme disabling fatigue that does not improve with rest; it persists for more than 6 months, and cannot be explained by any underlying medical condition. CFS/ME is often associated with muscle pain, sleep dysfunction, cognitive problems and post-exertional malaise; it may worsen with physical and mental activity, and exercise intolerance is a frequent complaint (Reeves *et al.*, 2007). CFS/ME is commonly found after infection by viruses, bacteria or parasites, and its pathophysiological consequences are mainly multisystemic (Bested and Marshall, 2015) Prior to developing CFS/ME, most patients are healthy, fully functional and have active social lives. Around 80% of CFS/ME patients start suddenly with a flu-like illness from which they never recover (Bested and Marshall, 2015).

At present, there are at least 20 sets of case definitions or diagnostic criteria for CFS/ME (Brurberg *et al.*, 2014). One of these sets, the 1991 Oxford criteria, includes both CFS of unknown aetiology and a subtype of CFS called post-viral fatigue syndrome (PVFS), which either follows an infection or is associated with a current infection. Important differences are that the presence of mental fatigue is necessary to satisfy the criteria and symptoms are accepted, which may suggest a psychiatric disorder (Sharpe, 1991). Among the most widely used diagnostic criteria for CFS are the 1994 Centres for Disease Control and Prevention (CDC)/Fukuda definition (Fukuda *et al.*, 1994). In 2003, a clinical case definition was developed using the term ME/CFS. These criteria became known as the 2003 clinical Canadian Consensus Criteria for diagnosis and treatment of ME/CFS (Carruthers, 2003). A revised version was subsequently presented as the 2011 International Consensus Criteria for Myalgic Encephalomyelitis (ICC-ME) for both adult and paediatric cases of ME in clinical and research settings (Carruthers *et al.*, 2011), in an attempt to provide a selective case definition for identifying patients with post-exertional neuroimmune exhaustion, a pathologically low threshold of fatigability and symptom flare after exertion.

The claim that CFS and ME are distinct clinical entities is controversial. In this comprehensive review, we will apply the term CFS/ME pragmatically. The recently proposed 2015 NIH/Institute of Medicine (IOM) definition (SEID) diagnostic criteria developed by the US IOM redefine CFS/ME for clinical applications. The IOM recommended that the name of the illness be changed from CFS/ME to SEID (Clayton, 2015). All CFS/ME (SEID) case definitions are assessed in terms of sensitivity (i.e. the ability to identify

CFS/ME patients correctly) and specificity (i.e. the ability to exclude patients who do not have CFS/ME). Subgroup analysis suggests that, depending on the case definition applied, the CFS/ME (SEID) population may represent a variety of conditions rather than a single disease entity. If patient samples include participants with different conditions, it is impossible to determine the core domains or symptoms or to apply proper treatment strategies. So, it is essential to identify patient subsets correctly in order to implement personalized treatments; failure to do so will also have detrimental consequences for research in the interpretation of epidemiological, aetiological factors and treatment (Bested and Marshall, 2015).

Currently, there are no universal or specific FDA-approved drugs for CFS/ME treatment, although some medications are used *off-label* for the illness. The therapy options available for CFS/ME focus on symptom relief (Whiting *et al.,* 2001). Treatment of CFS/ME is variable and uncertain, and the condition is primarily managed rather than cured (Rimes and Chalder, 2005). Drugs such as isoprinosine and rintatolimod have been used in experimental studies of the illness but have not been approved for marketing for any condition in the USA (Smith *et al.,* 2015). Other proposed treatments include medical approaches and complementary and alternative medicine. Even when treated, the prognosis of CFS/ME is often poor (Luyten *et al.,* 2008). Another study comparing the use of pragmatic rehabilitation and supportive listening indicated that there was no significant therapist effect on outcome measures (physical functioning or fatigue) (Goldsmith *et al.,* 2015).

In this review, we reflect on our experience in assessing and managing CFS/ME patients and review the current evidence of the treatment and management approaches for illness. Research is currently making progress, but the evidence available is limited and many questions with regard to diagnostic criteria, therapy and management approaches remain unanswered. We start with a consideration of the pharmacological interventions available in CFS/ME.

Pharmacological therapy

Very few randomized controlled trials (RCTs) have evaluated pharmacological treatments for CFS/ME. There is no pharmacological cure for the illness, but various drugs are used in order to help relieve and manage the symptoms, especially in cases in which there is a specific medical cause using highly individualized treatments. Because CFS/ME remains poorly understood, many patients have problems finding good care. The list of pharmaceuticals prescribed for CFS/ME is extensive, ranging from over-the-counter medications such as pain relievers and non-steroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, antidepressants and narcotics to antiviral and immunomodulatory drugs. The reason is that treatments are aimed both at alleviating the numerous symptoms and at correcting the secondary infections found in the majority of CFS/ME patients. Therefore, we have classified the different drugs according to the most commonly found core symptoms in CFS/ME: myalgia and muscle pain, immunological abnormalities, comorbid anxiety/depression and mood swings, sleep disturbances and cognitive dysfunction.

Mild pain relievers and NSAIDs

CFS/ME patients may benefit from NSAIDs, which are commonly used to relieve pain and reduce inflammation. In this context, the NSAIDs include ibuprofen and naproxen. They sometimes relieve frequent or severe joint and muscle pain, headaches, and fevers (Theoharides *et al.,* 2011).

Other prescription medicines include anticonvulsants, also called anti-seizure medicines. These drugs (e.g. gabapentin and pregabalin) are sometimes prescribed for pain and sleep problems. They seem to work best when used for nerve pain. Antidepressant medicine is also prescribed to ease depression and anxiety, to enhance the ability to concentrate and to improve sleep quality (Calandre *et al.,* 2015). For their part, narcotic medicines (tramadol, codeine or morphine) are sometimes prescribed for pain that is not relieved by over-the-counter drugs. Narcotics are generally reserved for the most severe cases because of the risk of addiction, and are used only for a short time (Degenhardt *et al.,* 2016).

COX-2 inhibitors

COX-2 inhibitors are NSAIDs designed to selectively inhibit the inflammation-promoting enzyme called COX-2. This drug class provides pain relief and anti-inflammatory benefits equal to those of other NSAIDs while causing less gastrointestinal distress and bleeding (Mantovani *et al.,* 2010).

Antidepressants

Because of the association between depression and CFS/ME, CFS/ME patients often take antidepressants, with varying degrees of success (Attree *et al.,* 2014) Almost all antidepressants interact with other drugs, and some of these interactions are very serious (Cleare *et al.,* 2015). CFS/ME patients are frequently prescribed antidepressants to treat secondary depression or mood swings, and tricyclic antidepressants may be prescribed in low doses to increase sleep quality and reduce pain. However, the use of antidepressants is controversial (Jackson *et al.,* 2006; Pae *et al.,* 2009) A review of pharmacological treatments for CFS/ME included five trials of antidepressants, but only one recorded significantly improved symptoms, in a cohort who had been assigned to cognitive behavioural therapy (CBT) for 12 weeks before initiating mirtazapine (Kreijkamp-Kaspers *et al.,* 2011).

Tricyclic antidepressants

Tricyclic antidepressants affect brain chemicals which are involved in managing pain. These medications may be particularly helpful for CFS/ME patients. For example, the tricyclic amitriptyline is known to relieve many symptoms, including sleeplessness and low energy levels in CFS/ME. Other tricyclics (doxepin, desipramine, nortriptyline, clomipramine and imipramine) improve sleep and relieve pain, although it can take 3 to 4 weeks for symptoms to improve. CFS/ME patients normally respond to much lower doses of tricyclics than those used to treat people with depression; in fact, many CFS/ME patients cannot tolerate the higher doses commonly used in depression therapy (Clemons *et al.,* 2011).

Other antidepressants

Other antidepressants (bupropion, nefazodone and mirtazapine) affect combinations of neurotransmitters. Some may have moderate benefits for CFS/ME patients: for example, nefazodone may improve mood, fatigue and sleep disturbances (Cleare *et al.,* 2015).

Selective serotonin-reuptake inhibitors

The widely-used antidepressants (fluoxetine, sertraline, and paroxetine) known as selective serotonin-reuptake inhibitors (SSRIs) may be helpful for CFS/ME subjects who experience significant chronic neuropathic pain, fibromyalgia, anxiety/depression and other mood disorders. Duloxetine is a new antidepressant classified as a selective serotonin–noradrenaline reuptake inhibitor (SSNRI) because it affects both neurotransmitters. SSRIs should not be taken with tricyclics, because the combination may have dangerous side effects (Theoharides *et al.,* 2011). However, neither SSRIs nor SSNRIs directly address the immune system dysregulation that underlies the disease, and there are no FDA-approved treatments that specifically do so. Any treatment used to lessen symptoms is considered 'palliative'.

Antiviral and immunomodulatory therapy

With the possible exception of the immunomodulatory drug rintatolimod, a recent systematic review did not find any pharmaceutical therapies for CFS/ME to be effective. The drugs tested were immunoglobulins, hydrocortisone, SSRIs and antiviral agents (Smith *et al.,* 2015).

Antiviral drugs

Several viruses have been tentatively identified as causative agents in subsets of CFS/ME patients, though no fully convincing evidence has been provided to date (Sanders and Korf, 2008). Treatment studies of CFS/ME subtypes may help to provide this evidence (Jason *et al.,* 2005), though the results of the antiviral drugs treatment studies conducted so far are inconclusive.

Rintatolimod

Nucleic acid (double-stranded RNA) compounds represent a potential new class of pharmaceutical products that are designed to act at the molecular level. These are inducers of interferon and are considered to be antiviral and immunomodulatory. One RCT evaluating rintatolimod found an overall beneficial effect (Whiting *et al.,* 2001). In December 2009, the US FDA rejected a New Drug Application (NDA) by the developer of the drug (Hemispherx Biopharma) to market and sell rintatolimod (as Ampligen) for the treatment of CFS/ME, on the grounds that the two RCTs submitted did not provide credible evidence of efficacy. Hemispherx Biopharma performed additional analyses and then submitted an NDA in 2012 (Strayer *et al.,* 2012). After review, the FDA refused the application, citing insufficient safety and efficacy data (http://www.fda.gov/drugs/newsevents/ucm337750.htm).

Rintatolimod (Ampligen) has undergone years of clinical trials. Ampligen (poly I: poly C12U) has a long and chequered history in CFS/ME. After the Incline Village outbreak in 1984, the FDA invited the pharmaceutical company Hemispherx to develop a drug to treat the illness. The positive results of this trial seemed to indicate that Ampligen worked by enhancing the NK-cell function and influencing the 2-5A-synthetase pathway, which plays a vital role in the defence against viral infections. Some CFS/ME patients present defects in key components in the antiviral system, the most notable being low latent 2-5A synthetase and up-regulated RNase-L activity (Suhadolnik *et al.,* 1997). Ampligen is believed to correct both these defects.

Dr Peterson along with Dr Cheney had reported the Incline village outbreak in 1984, used Ampligen in a severely ill CFS case in 1988 (Strayer *et al.,* 1994). After a year of therapy, patient function in some areas had almost returned to normal and IQ had increased by 46 points. In view of these impressive results, Dr Peterson designed another multi-centre pilot study and, along with other independent research (Suhadolnik *et al.,* 1994), this paved the way for a large-scale FDA-approved double-blind study of 92 CFS/ME patients in four US cities (Strayer *et al.,* 2012). Once more, the results were very promising: More than half of the patients administered Ampligen presented improved overall function, energy levels and cognitive performance, and many could now perform daily activities with only minimal assistance. Unfortunately, since 1996, little progress has been made in obtaining FDA approval for the drug. The FDA advised Hemispherx to conduct at least one additional clinical trial, complete various non-clinical studies and perform a number of data analyses.

Valganciclovir

Acyclovir, valacyclovir and ganciclovir are nucleotide analogue inhibitors which inhibit viral replication during DNA multiplication (for DNA- and retroviruses) or RNA multiplication (for RNA viruses) (De Clercq and Neyts, 2009). In 1988, a small RCT assessing acyclovir reported no difference in improvement compared with placebo; the conclusion was that the improvement was due either to spontaneous remission or to the placebo effect (Straus *et al.,* 1988). Three patients administered acyclovir withdrew from the trial because of reversible renal failure (Whiting *et al.,* 2001).

Interferons

Two small RCTs have evaluated the effect of interferon α versus placebo in CFS/ME (Whiting *et al.,* 2001). The first crossover RCT (30 CFS/ME subjects according to the 1994 CDC/Fukuda definition) only found treatment benefit in subgroup analysis of participants with diminished NK cell function but normal lymphocyte proliferation. In the active arm, two out of 13 participants (15%) developed neutropenia (Ridsdale *et al.,* 2001). The results of the second crossover RCT trial (20 CFS/ME patients based on the 1994 CDC/Fukuda definition) did not allow a clear interpretation of the effect of therapy (Brook *et al.,* 1993). Both studies were considered poor quality (Whiting *et al.,* 2001).

Immunoglobulins

A systematic review identified five RCTs evaluating the effect of immunoglobulin in CFS (Whiting *et al.,* 2001). Two of these trials found an overall benefit, and two presented some positive results, although in one case, only in relation to physiological effects. The largest RCT did not report any effect, and another review concluded that the potential dangers of immunotherapy for CFS/ME outweighed its possible advantages (Reid *et al.,* 2011).

Corticosteroids and hormones

Treatment with steroids such as cortisol and thyroid hormones has been also studied. Seven RCTs have been performed, four trialling hydrocortisone (McKenzie *et al.,* 1998; Cleare *et al.,* 1999; Friedman *et al.,* 1999; Cleare *et al.,* 2001), two fludrocortisone (Peterson *et al.,* 1998; Rowe *et al.,* 2001) and one with hydrocortisone plus fludrocortisone (Blockmans *et al.,* 2003). Two RCTs found an overall benefit for hydrocortisone, but this drug has not been recommended for clinical use. A 2006 systematic review found one low-quality RCT of hydrocortisone which found a significant difference between groups for fatigue, but two other RCTs found no benefit for steroid treatment (Chambers *et al.,* 2006). An RCT conducted between 1992 and 1996 in a tertiary care research institution, studied 70 CFS/ME patients who met the 1994 CDC/Fukuda definition; many had psychiatric comorbidity but, in all patients, concomitant treatment with other medications were withheld. Although hydrocortisone treatment (at a higher dose of 20–30 mg) was associated with some statistical improvement in CFS/ME symptoms, the authors concluded that a degree of adrenal suppression precludes its practical use for CFS/ME (McKenzie *et al.,* 1998).

Rituximab

Rituximab is a monoclonal antibody active against CD20, a B-cell receptor. Rituximab works by depleting B-cells, thus reducing inflammation. It was first approved by the FDA to treat non-Hodgkin's lymphoma in 1997. It is also used in the immunotherapy treatment of autoimmune disorders.

Its effect on CFS/ME was discovered by accident. Two Norwegian physicians, Dr Fluge and Prof Mella who were treating a CFS/ME patient for Hodgkin's lymphoma with rituximab, noticed that her symptoms remitted. A small pilot, open-label trial from Norway followed, using rituximab in three CFS/ME patients. All three patients experienced significant improvement; two of them responded within 6 weeks, and the third presented a delayed response after 6 months. The positive effects lasted for between 16 and 44 weeks. After relapse, the patients were administered another dose of rituximab, with the same positive results. The researchers hypothesized that B-cells might play a significant role in at least a subset of CFS/ME patients, and that CFS/ME may be amenable to therapeutic interventions aimed at modifying B-cell phenotype and function (Fluge and Mella, 2009). These positive results encouraged a larger study with a more rigorous design to test the drug's effects and, in 2009, an RCT with 30 CFS/ME patients who met the 1994 CDC/Fukuda definition was intitiated (Fluge *et al.,* 2011). As in the earlier open-label study, the responses to rituximab were significant. Sustained overall improvements were noted in 67% of CFS/ME patients (as opposed to 13% of controls). Four of the rituximab patients showed improvement past the study period. The authors concluded that the delay in the responses, starting 2–7 months after rituximab infusions in spite of rapid B-cell depletion, suggests that CFS/ME is an autoimmune condition in which the clinical response could be preceded by a gradual elimination of autoantibodies (Fluge *et al.,* 2015). These two trials have been completed and a new open-label trial is in progress (Fluge *et al.,* 2011; Fluge *et al.,* 2015). Rituximab is also undergoing a large trial in CFS/ME patients, privately funded by Invest in ME, a UK charity. Both treatments are available in the USA, but they are not FDA-approved for CFS/ME and so insurance companies do not cover the costs.

Despite the latest advances of Rituximab immunotherapy in CFS/ME, the risk of adverse effects is unclear: Reports of adverse events in other contexts such as neutropenia and infections give reason for caution (Rashidi *et al.,* 2015). The new RituxME project, a multicenter, RCT study, will recruit 152 participants at five sites in Norway. The purpose of the study is to confirm or disprove the results of the two earlier and smaller Phase II trials, which indicated improvements in symptoms in a subgroup of CFS/ME patients after rituximab infusions. The results of the RituxME study are scheduled to be published in early 2018.

Staphylococcal toxoid vaccine

Two RCTs have been carried out with staphylococcal toxoid vaccine. The first trial showed considerable benefit (Andersson *et al.,* 1998) and a large follow-up RCT for 6 months in which repeated administration of the staphylococcal toxoid vaccine Staphypan Berna (Berna Biotech, Switzerland) and testing against placebo showed overall benefit (Zachrisson *et al.,* 2004).

The results further showed that this response was related to an improvement of the clinical outcome due to treatment. However, the quality of the follow-up RCT was low and there were relatively high levels of adverse effects. A review concluded that there is insufficient evidence for treatments of this type (Chambers *et al.,* 2006).

Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) is the infusion of liquid filtrate faeces from a healthy donor into the gut of a recipient to cure a specific disease. The interest in microbiota-gut-brain axis and faecal microbiota transplantation is increasing rapidly. With the high success and safety rate in the short term reported for recurrent *Clostridium difficile* infection, FMT has emerged as a treatment for a wide range of gut disorders, but is yet to be confirmed for CFS/ME. Many questions regarding its application in CFS/ME remain unanswered including donor selection and screening, standardized application protocols, long-term safety and risk, and regulatory issues (Brussow, 2016).

In an uncontrolled study of 60 CFS/ME individuals who were given FMT and followed up 15–20 years later, 50% presented significant symptom improvement (Smits *et al.,* 2013). A study in which CFS/ME individuals received FMT therapy found that 41% achieved persistent relief of

symptoms over a period of 11–28 months (Aroniadis and Brandt, 2013). Another study reported that the response rate of 60 CFS cases after FMT was 70%. After a time lapse of 15–20 years, 12 of the patients were contacted and information about their condition was obtained. Seven of the patients reported full recovery, and five reported that they had not experienced CFS for between 1.5 and 3 years (Smits *et al.,* 2013).

Gastrointestinal disturbances are well documented in CFS/ME (Logan *et al.,* 2003; Sheedy *et al.,* 2009; Fremont *et al.,* 2013; Giloteaux *et al.,* 2016; Navaneetharaja *et al.,* 2016; Wallis *et al.,* 2016). However, the association of CFS/ME with an altered microbiota-gut-brain axis and faecal microbiota transplantation remains unclear. Despite the findings of altered diversity and stability of the gut microbiota in CFS/ME, it is not yet possible to claim that CFS/ME has a specific microbial signature, and that, as a result, an FMT trial can be conducted in these patients.

Complementary and alternative medicine

CFS/ME patients tend to use more alternative medicine treatments than people without (Jones *et al.,* 2007). Patients often leave orthodox medical care because they feel that their condition has been unjustifiably attributed to psychological causes: they are given the message that '*it is all in the mind*'. In a twin study, 91% of twins with CFS/ME and 71% without CFS/ME used at least one alternative treatment. A large proportion of the study participants stated that alternative treatments were helpful (Afari *et al.,* 2000).

Nutritional supplements

A 2006 updated systematic review concluded that supplements of essential fatty acids and magnesium showed beneficial effects in only one or two trials, and that further rigorous trials of these interventions were required (Chambers *et al.,* 2006). A 2011 review found insufficient evidence to recommend dietary supplements as a treatment for CFS/ME (Alraek *et al.,* 2011). One RCT compared a polynutrient supplement (containing several vitamins, minerals and coenzymes, taken twice daily) with a placebo for 10 weeks, but found no difference in fatigue scores (Reid *et al.,* 2011). Supplements may benefit CFS/ME patients with specific nutritional deficiencies. A biochemical test for deficiencies should be performed before treatment in order to guide treatment choices.

Acetyl-L-carnitine

The amino acid L-carnitine and its derivative acyl-L-carnitines, are required for the transport of fatty acids into the mitochondria during the breakdown of lipids for the generation of metabolic energy in muscles and in the brain (Inazu and Matsumiya, 2008). Two RCTs found benefits after supplementation with dietary L-carnitine or its esters. A 2006 systematic review reported one RCT with overall benefit, although there was no placebo control (Chambers *et al.,* 2006). In 2008, a 6 month RCT trial of acetyl-L-carnitine in 96 aged subjects with CFS/ME symptoms was reported. By the end of the treatment, significant differences between the two groups were found for both self-reported physical and mental fatigue, and the experimental group presented improvements in both the cognitive status and physical function (Malaguarnera *et al.,* 2008).

Essential fatty acids

A RCT of 63 patients who met the 1991 Oxford criteria for a subtype of CFS called PVFS, used high doses of evening primrose oil containing γ-linolenic acid (GLA) together with fish oil concentrate containing eicosapentaenoic acid (EPA) and DHA and either it, or the placebo, over 3 months. All participants were evaluated at baseline, and at 1 and 3 months. The essential fatty acid composition of their RBC membrane phospholipids was analysed at the first and last visits. This trial showed significant overall improvements in symptoms (fatigue, myalgia, dizziness, poor concentration and depression) and higher levels of essential fatty acid in RBC (all $P < 0.0001$) at the end of study (Behan *et al.,* 1990). However, a subsequent RCT attempting to replicate this study in another CFS subject cohort meeting 1991 Oxford criteria for CFS but found no significant differences in symptoms after treatment between the experimental and placebo groups or in the pretreatment RBC membrane lipids (Warren *et al.,* 1999). The discrepant results in these two studies may be due to the case selection criteria used. Also the first trial used paraffin, while the second trial used sunflower oil, which is better tolerated and less likely to adversely affect the placebo (Reid *et al.,* 2011).

Magnesium

A trial of intramuscular magnesium sulfate delivered by injection to magnesium-deficient CFS/ME patients reported positive results (Cox *et al.,* 1991). This RCT found that magnesium improved Nottingham Health Profile pain ($P = 0.022$) and emotional reaction ($P = 0.013$) domain scores compared with placebo. In this RCT, plasma and whole blood magnesium levels were normal and only the RBC magnesium content was slightly lower than the normal range (Cox *et al.,* 1991). In contrast, three subsequent case-report studies did not find magnesium deficiency in CFS/ME cohorts (Clague *et al.,* 1992; Hinds *et al.,* 1994; Swanink *et al.,* 1995). In these previous studies, blood magnesium levels were in the normal range and did not differ from healthy controls. However, none of the studies stated how the normal range was established, so it is difficult to confirm whether they were equivalent. A 2008 review concluded that there is no good evidence that intramuscular magnesium offers any benefit in CFS/ME (Reid *et al.,* 2011). Testing for magnesium deficiency in RBC would be useful in CFS/ME, with further administration of nutritional supplements if a deficiency is found. The fact that not all CFS/ME subjects have magnesium deficiency does not mean that nutritional supplementation should be dismissed.

Vitamin B_{12}

Both oral and injected vitamin B_{12} has been proposed as treatments for generalized fatigue since the 1950s. Previous studies have not suggested any benefit, either for generalized fatigue or more specifically for symptoms relief in CFS/ME (Bjorkegren, 1999; Hagglof, 2000). However, further research is needed because the studies carried out to date have been small and have used inconsistent dosing

regimens and/or non-biologically active forms of vitamin B_{12} (hydroxocobalamin) (Swanink *et al.,* 1995; Bjorkegren, 1999; Norberg, 1999; Hagglof, 2000). Recently, this question has been addressed (Regland *et al.,* 2015), drawing on 15 years' experience of treating CFS/ME patients with vitamin B_{12} (methylcobalamin, as the biologically active form). During this time, the CFS/ME patients were shown to respond best to the injected form of vitamin B_{12}.

This research group concluded (Regland *et al.,* 2015) that frequent injections of highly concentrated methylcobalamin combined with an individual daily high dose of oral folic acid may be safe and effective for fatigue and other CFS/ME symptoms. Moreover, CFS/ME patients should be tested for certain opioid and analgesic drugs and for co-existing thyroid dysfunction. Therefore, the use of methylcobalamin is recommended to find the optimal dose of vitamin B_{12} and folate for each individual.

Antioxidants

Antioxidants (including α-lipoic acid, vitamin E or C) are a group of vitamins, minerals and enzymes that help protect cells from damage by oxidative stress and also improve mitochondrial function (Nicolson, 2014). A prospective RCT recruiting 38 women CFS consecutively diagnosed with the 1994 CDC/Fukuda definition were treated with a multivitamin and mineral supplement for 2 months with follow-up. Before and after the 2 month supplementation, superoxide dismutase activity was determined and patients self-assessed their improvement in two questionnaires (FibroFatigue scale and the SF-36 subscale). There was a significant improvement in superoxide dismutase activity levels ($P = 0.005$), significant decreases in fatigue ($P = 0.0009$), sleep problems ($P = 0.008$), autonomic dysfunction symptoms ($P = 0.018$), frequency and intensity of headaches ($P = 0.0001$), and subjective feeling of infection ($P = 0.0002$). No positive effect on SF-36 quality of life was found. The conclusion was that reatment with a multivitamin and mineral supplement could be a safe and easy way to improve symptoms and quality of life in CFS/ME (Maric *et al.,* 2014).

NADH, reduced form

In 1999, an RCT crossover study of NADH 10 mg·day^{-1} for 4 weeks in 26 CFS patients reported positive results. No severe adverse effects were observed (Forsyth *et al.,* 1999), and CFS patients who received this NADH supplementation for 12 weeks obtained more effective symptoms relief than those assigned to the placebo (31% vs. 8%, $P < 0.05$). Another study comparing oral NADH supplementation with conventional therapy for 24 months in 31 CFS patients showed a higher effectiveness of NADH (in terms of reductions in mean self-reported symptom scores) compared with nutritional supplements and psychotherapy (Santaella *et al.,* 2004). A previous study by our group in 77 Spanish CFS patients showed that oral NADH (20 mg·day^{-1}) administration for 8 weeks was associated with reductions in anxiety [as assessed by Hospital Anxiety and Depression Scale (HADS)] and maximum heart rate (max HR) after an exercise challenge test (Alegre *et al.,* 2010). Earlier studies had shown that oral NADH administration had a good safety profile, with no observed adverse effects or toxicity (Forsyth *et al.,* 1999; Santaella *et al.,* 2004; Alegre *et al.,* 2010). However, a systematic review concluded that these RCTs presented several methodological problems, and a review concluded that there was still no good evidence that NADH supplementation alone was of benefit for CFS/ME (Reid *et al.,* 2011).

Coenzyme Q_{10} plus NADH and mitochondrial dysfunction

Coenzyme Q_{10} (CoQ_{10}) and NADH are common antioxidant supplements that have been used for several decades as dietary supplements for general maintenanceof health. The benefits of their administration have been extensively evaluated in several conditions (Braun *et al.,* 1991; Porter *et al.,* 1995; Malm *et al.,* 1997; Cooke *et al.,* 2008). However, several studies have shown that there is a mitochondrial dysfunction, which reduces the ATP production, as an immediate effect primary or secondary to symptoms in most CFS/ME patients (Twisk and Maes, 2009; Booth *et al.,* 2012; Castro-Marrero *et al.,* 2013; Myhill *et al.,* 2013; Castro-Marrero *et al.,* 2016).

In the UK, Myhill *et al.* highlighted the power and usefulness of the 'ATP profile' test as a diagnostic tool for differentiating between patients who have CFS/ME and other symptoms as a result of energy wastage due to stress and psychological factors and those who have insufficient energy due to cellular respiration dysfunction. The biochemical tests should be performed in CFS/ME patients before and after appropriate interventions, and possibly in other disabling fatigue conditions as well (Myhill *et al.,* 2009).

In a later study, this group noted that although mitochondrial function tests do not constitute a biochemcal diagnostic tool for CFS/ME because the symptoms of fatigue may be due to many possible causes, they are nonetheless the single most useful diagnostic and therapeutic aid in the management and treatment of CFS/ME (Myhill *et al.,* 2013). These authors also reported symptom relief and improve of quality of life in patients receiving a combination of a stone-age diet, sleep quality and hygiene, nutritional supplements and recommendations for achieving a balance between work and rest, plus additional interventions based on the deficiencies identified.

Because CoQ_{10} and NADH increase cellular ATP production via mitochondrial oxidative phosphorylation, their supplementation could help improve fatigue and other symptoms in CFS/ME (Nicolson, 2014; Castro-Marrero *et al.,* 2016). For its part, CoQ_{10} supplementation alone has been evaluated in many illnesses (such as fibromyalgia) with conflicting findings, but not yet in CFS/ME (Garrido-Maraver *et al.,* 2014). Data regarding the effects of CoQ_{10} and NADH supplementation on exercise performance and cardinal symptoms in CFS remain limited and inconsistent. Additionally, no specific assessment of cardiovascular functioning (haemodynamic parameters as cardiac output, blood volume, HR, blood pressure, stroke volume, and so on) with CoQ_{10} plus NADH supplementation during an exercise challenge test in CFS has been performed to date.

Recently our working group (Castro-Marrero *et al.,* 2016) conducted a proof-of-concept, 8 week RCT in 80 Spanish CFS/ME patients who met the 1994 CDC/Fukuda definition and were allocated to receive CoQ10 plus NADH or matching placebo. Our findings suggested that the combination of CoQ10 plus NADH was safe and potentially effective in

reducing the max HR (P = 0.022) during the exercise challenge test. There was also a trend towards a reduction in self-reported measures of fatigue (FIS 40) in the active group compared with placebo (P = 0.030). However, no effect on pain and sleep was found. Additional larger RCT trials are now needed to confirm these findings.

Relatively few pharmacological or other therapies for CFS/ME have been tested in large RCTs. Overall, a report commissioned by the AHRQ based on a systematic review for a US NIH Pathways to Prevention Workshop concluded that no available pharmacotherapy is of proven benefit in CFS/ME. Table 1 summarizes the current drug therapeutic strategies for CFS/ME.

Non-pharmacological approaches: counselling, behavioural & rehabilitation interventions

Cognitive behavioural therapy (CBT)

Experimental management approaches for CFS/ME include behavioural interventions such as CBT, a form of psychological therapy, and graded exercise therapy (GET), a form of physical activity that starts very slowly and increases gradually in intensity over time. In published reports, CBT has often been inappropriately recommended as a cure for CFS/ME patients who are able to change their belief system. However, CFS/ME is a physical illness, not a psychological one, and therefore CBT cannot cure it. Based on evidence from several RCTs, a systematic review concluded that CBT interventions showed promising results, appearing to reduce fatigue and improving physical functioning and school attendance, but did not prove effective in restoring the ability to work (Chambers *et al.,* 2006). CBT and GET have both received wide support and have demonstrated reproducible evidence for their efficacy in non-severely ill CFS outpatients (Whiting *et al.,* 2001; Van Cauwenbergh *et al.,* 2012). Earlier studies found evidence after assessing the effectiveness of all trials that have been evaluated so far for use in the treatment and management of CFS in adults and children. They substantiate their proposal that GET and CBT are beneficial for CFS patients, but in fact neither treatment has been shown to reverse the illness nor have any well-designed double-blind interventions comparing these therapies with placebo been published. All conclusions about effectiveness should be considered together with the methodological quality inadequacies of the trials. Further research into these and other therapies using standardized outcome measures is now required. A further systematic review concluded that CBT is the treatment with the most evidence to support it (Butler *et al.,* 2006).

This conclusion has subsequently been reinforced by several large-scale studies in adults and adolescents with CFS/ME (Nijhof *et al.,* 2012; Brurberg *et al.,* 2014; Janse *et al.,* 2015). However, the effect size obtained is modest, and there is limited evidence of efficacy in the most severely ill patients. CBT can be given either individually or in groups (Wiborg *et al.,* 2015). In children and adolescents with CFS/ME, internet-based consultations may be effective (Nijhof *et al.,* 2012). There is no sign of any increase in serious adverse events (Dougall *et al.,* 2014; Larun *et al.,* 2015; Smith *et al.,* 2015). While accepting that a subgroup of CFS subjects may find CBT helpful when they develop comorbid depression, anxiety and other mental health problems, we believe that CBT should not be used as a primary intervention for CFS/ME as reported in the NIH Pathways to Prevention Workshop (Green *et al.,* 2015). Patient surveys, in particular, are more in favour of pacing therapy than CBT. Pacing has consistently been shown to be the most effective, safe, acceptable and preferred form of activity management for CFS/ME and should therefore be a key component of any illness management programme (Results and in-depth analysis of the 2012 ME Association patient survey examining the acceptability, efficacy and safety of CBT, GET and pacing, as interventions used as management strategies for ME/CFS). The minimal risk of adverse effects suggests that failing to treat the most severely ill ME/CFS patients is more risky than providing this treatment. It is particularly useful for defining and setting limits, behaviours that are extremely important for these patients. One review reported that, of all therapies available to CFS/ME patients, only CBT and GET showed conclusive benefits (White *et al.,* 2011). CBT was able to relieve the symptoms of fatigue, and it appeared to be more effective than other psychological therapies. However, the patients recruited in this study fulfilled the 1991 Oxford criteria for CFS, which many today regard as outdated and unreliable.

Cognitive therapy may also be an effective treatment for adolescents with CFS/ME. Adolescents with CFS who received internet-based CBT reported improvement in fatigue, physical function and school attendance (Nijhof *et al.,* 2012). However, not all studies support cognitive therapy for CFS/ME. A 2011 systematic review of RCTs found moderate evidence of a benefit, but its effectiveness for CFS/ME outside specialist settings has been questioned and the quality of the evidence is low (Cooke *et al.,* 2008). A 2008 Cochrane review of CBT concluded that it is more effective than usual care for relieving fatigue symptoms in adults with CFS. However, the review expressed doubts about its ability to sustain a clinical response at follow-up, and did not report conclusive improvements in physical functioning, depression/anxiety or psychological distress either post-treatment or at a later date. Data on adverse effects were not systematically presented by any of the studies. The authors also concluded that while the quantity and quality of the evidence has grown in recent years, there is a surprising lack of high quality evidence on the effectiveness of CBT alone or in combination with other treatments able to guide the development of clinical management programs for CFS (Price *et al.,* 2008).

Another 2008 meta-analysis found that the effectiveness of CBT depends on the diagnostic criteria used, with studies using the 1991 Oxford criteria presenting a trend towards significantly higher effect sizes than those using the 1994 CDC/Fukuda definition. The authors also noted that CBT for CFS/ME has about the same efficacy as diverse psychological treatments for a variety of psychological disorders (Malouff *et al.,* 2008). A 2010 meta-analysis of trials that objectively measured physical activity before and after CBT showed that, although the therapy effectively reduced patients' self-reported fatigue scores, it did not improve activity levels, and changes in physical activity were not related to changes on fatigue questionnaire scores. The authors

Table 1

Overview of the included pharmacological interventions for CFS/ME

Intervention (Study ID)	Population characteristics and case definition			Outcomes reported		Quality rating	Author (year)
	Study design	Participants Duration of follow-up	Case definition	Fatigue measures	Physical functioning status		
Rintatolimod (AMP-502)	Phase II RCT. i.v. rintatolimod versus placebo	92 patients 6 months.	1988 CDC/Holmes	Exercise duration: ($P = 0.007$) Exercise work: ($P = 0.011$)	KPS: $P = 0.023$ ADL: $P = 0.034$ SCL-90R: $P = 0.05$	FAIR	(Strayer *et al.*, 1994)
Rintatolimod (AMP-516)	Phase III RCT. i.v. rintatolimod versus placebo	234 patients 10 months	1998 CDC/Holmes	ET on a treadmill with ECG testing ($P = 0.047$)	KPS, ADLs, Vitality and SF-36 scores were measured pre-and post-tto, but not compared between groups	FAIR	(Strayer *et al.*, 2012)
Rituximab (RTX; Pilot study)	Case cohort, Open-label study. Infusions of RTX versus placebo	3 patients 10 months	1994 CDC/Fukuda	NR	Improved physical health and function scores	FAIR	(Fluge and Mella, 2009)
Rituximab (KTS-1-2008)	Small RCT phase II study. Infusions of RTX versus placebo	30 patients 12 months	1994 CDC/Fukuda	Fatigue levels ($P = 0.51$)	Improved physical health and function scores	FAIR	(Fluge *et al.*, 2011)
Rituximab (KTS-2-2010)	Single-centre open-label, one armed, non-randomized Phase II study. Infusions of RTX versus placebo	29 patients 15 month treatment to 36 months	1994 CDC/Fukuda	Fatigue score (at least 6 weeks) Fatigue: 8 (6.3–10) Cognitive: 7.5 (4.7–10) Pain: 7.2 (4–9) ME/CFS overall: 8.2 (6–10)	Baseline function level: 15% (5–50) Baseline total SF-36 Physical health: 25.6 ± 6.6 Mental health: 44.6 ± 10.4	FAIR	(Fluge *et al.*, 2015)
Valganciclovir (EVOLVE)	RCT. Oral valganciclovir versus placebo	30 patients 48 weeks. 6 months tto and 6 more months. follow-up (unbinding and outcomes measured at 9 months)	1994 CDC/Fukuda	Change at 9 months for MFI-20: $P = 0.224$ and FFS: $P = 0.006$	Physical function: $P = 0.217$ Cognitive functioning: $P = 0.025$	FAIR	(Montoya *et al.*, 2013)

continues

Table 1 (Continued)

Intervention (Study ID)	Population characteristics and case definition			Outcomes reported		Quality rating	Author (year)
	Study design	Participants Duration of follow-up	Case definition	Fatigue measures	Physical functioning status		
Hydrocortisone + Fludrocortisone	Crossover RCT. Oral hydrocortisone + fludrocortisone versus placebo	80 patients 6 months	1994 CDC/Fukuda	VAS score (0–10) Fatigue degree: $P = 0.76$ AFQ score (4–28): $P = 0.69$	SF-36 physical score: $P = 0.34$ SF-36 mental score: $P = 0.02$	FAIR	(Blockmans *et al.*, 2003)
Hydrocortisone	RCT, single centre. Oral hydrocortisone versus placebo	65 patients 3 months	1988 CDC/Holmes	Mean changes POMS subscales Fatigue: $P = 0.21$ Vigour: $P = 0.45$	Mean changes Activity scale: $P = 0.32$ Global wellness score: $P < 0.001$	FAIR	(McKenzie *et al.*, 1998)
Immunoglobulins	RCT. i.v. IgG versus placebo	30 patients 6 months follow-up	1988 CDC/Holmes	NR	MOS-SF-12 (0–100 score) Physical subscale, mental health and social functions: all $P = NS$ Health perception: $P < 0.05$	FAIR	(Peterson *et al.*, 1998)
Isoprinosine (Immunovir)	RCT. Oral isoprinosine tablets versus placebo	16 patients 3 months tto to 7 months follow-up	1988 CDC/Holmes and 1994 CDC/Fukuda	NR	SCL-90R: $P = 0.25$ KPS: $P = 0.46$ ADL: data not provide	POOR	(Diaz-Mitoma *et al.*, 2003)
Acetyl-L-carnitine (ALC) versus Propionyl-L-carnitine (PLC) versus combination	Exploratory, open-label RCT. Oral ALC versus PLC versus placebo	90 patients 6 months	1994 CDC/Fukuda	MFI-20 (4–20 score) General fatigue (at 4 months): $P = 0.0003$ Physical fatigue (at 4 months): $P = 0.007$ Mental fatigue (at 4 months): $P = 0.010$ General fatigue (at 6 months): $P = 0.004$ Physical fatigue	NR	FAIR	(Vermeulen and Scholte, 2004)

continues

Table 1 (Continued)

Intervention (Study ID)	Population characteristics and case definition			Outcomes reported		Quality rating	Author (year)
	Study design	Participants Duration of follow-up	Case definition	Fatigue measures	Physical functioning status		
				(at 6 months): $P = 0.009$ Mental fatigue (at 6 months): $P = 0.015$			
Essential fatty acids	RCT Oral linoleic acid, GLA, EPA and DHA versus placebo	63 patients 3 months	1991 Oxford criteria for PVFS	Self reported fatigue (0–3) At 1 month: p=:0.09 At 3 months: $P = 0.0003$	Physical symptom: P = NS	FAIR	(Behan *et al.*, 1990)
Behan's replication study	RCT Oral Efamol marine versus placebo	50 patients 3 months	1991 Oxford	Self reported fatigue (0–3) At 1 and 3 months: all P = NS	Physical symptom: P = NS	FAIR	(Warren *et al.*, 1999)
Magnesium	RCT i.m. 50% magnesium sulfate injections versus placebo	32 patients (non magnesium deficiency) 1.5 months follow-up	1990 Australian definition	Mean change in NHPES (at 1.5 months): $P = 0.002$	Pain: $P = 0.011$ Emotional reaction: $P = 0.013$ Overall NHPES: $P = 0.001$	FAIR	(Cox *et al.*, 1991)
Vitamin B_{12}	Crossover RCT i.m. injections of hydroxocobalamin versus placebo	29 patients 1.5 months	General practitioners and hospital staff inquiry on tiredness and fatigue	Fatigue level: $P = 0.09$	Rating general well-being: $P = 0.006$ Rating happiness: $P = 0.032$	FAIR	(Ellis and Nasser, 1973)
Vitamin B_{12}	Crossover RCT. i.m. injections of a liver extract-folic acid cyanocobalamin (LEFAC) combination versus placebo	15 patients Follow-up NR	1988 CDC/Holmes	P = NS	P = NS	POOR	(Kaslow *et al.*, 1989)
Vitamin B_{12}	Case report. High dose of i.m. vitamin B_{12} injections twice weekly	2 women with CFS Follow-up NR	1998 CDC/Holmes	Self-reported energy P = NS	NR	FAIR	(Wiebe, 1996)
Vitamin B_{12} plus folic acid	Cross-sectional survey. i.m. cyanocobalamin	38 female patients Follow-up NR	1994 CDC/Fukuda and 2003	NR	FFS score (0–6): P = NS	FAIR	(Regland *et al.*, 2015)

continues

Table 1 (Continued)

Intervention (Study ID)	Population characteristics and case definition			Outcomes reported		Quality rating	Author (year)
	Study design	Participants Duration of follow-up	Case definition	Fatigue measures	Physical functioning status		
	injections plus oral folic acid		Canadian criteria (40% fulfilled 1990 FMS criteria)		PGIC score (1–7): $P < 0.0005$		
NADH (ENADA study)	Cross-over RCT. Oral NADH versus placebo	26 patients 3 months	1994 CDC/Fukuda	NR	NR	FAIR	(Forsyth *et al.*, 1999)
NADH	RCT Oral NADH or nutritional supplements versus psychotherapy	31 patients 24 months	1994 CDC/Fukuda	Symptoms score at 3 months: $P = 0.001$; at 6, 12 and 24 months: P = NS	NR	FAIR	(Santaella *et al.*, 2004)
NADH (VitaNADH)	RCT Oral NADH versus placebo	77 patients 3 months	1994 CDC/Fukuda	P = NS	Reduction in self-reported symptoms by HADS Anxiety: $P < 0.05$ Depression: P = NS	FAIR	(Alegre *et al.*, 2010)
CoQ_{10} + NADH (ReConnect)	A proof of concept RCT. Oral CoQ_{10} plus NADH versus placebo	80 patients 2 months	1994 CDC/Fukuda	Total FIS 40 score Baseline:$P = 0.32$ 1 month: $P = 0.71$ 2 months: $P = 0.03$	Self-report outcomes for pain and sleep 1 month: P = NS 2 months: P = NS	GOOD	(Castro-Marrero *et al.*, 2016)

All outcomes indicate % change from baseline.

ADL, Activities of Daily Living index (range 0–100; higher score means better health); AFQ, Abbreviated Fatigue Questionnaire (range 4–28, lower total score indicates a higher degree of subjective fatigue); AMP, ampligen study ID numbers; ET, Exercise Tolerance testing; FFS, FibroFatigue scale (range 0–6, higher score means maximal degree of the symptoms); GLA, omega-6 fatty acid made in the body from the essential omega-6 fatty acid, linoleic acid (LA); KPS, Karnofsky Performance Status (range 0–100; higher score means better health); KTS, Rituximab study ID numbers; MFI-20, Multidimensional Fatigue Inventory (range 4–20; negative changes indicate better health); MOS-SF-12, a 12-item Short Form Survey developed for the Medical Outcomes Study; NHPES, Nottingham Health Profile (range 0–100, higher score indicates greater numbers and severity of health problems); PGIC, Patients' Global Impression of Change (range 1–7, higher scores indicate worse health status); POMS, Profile Of Mood States (range 0–5, higher score means worse mood status); SCL-90R, Symptom Checklist-90 Revised (range 0–4; where 0 indicate the absence of impairment and 4 reflected extreme impairment); SF-36 PF, 36-item Short Form Survey Physical Function scales (range 0–100, higher score means less disability and better health status); tto, treatment; VAS, Visual Analogue Scale (range 0–10, higher score indicate greater pain intensity).

concluded that the effect of CBT on fatigue scores is not mediated by a change in physical activity (Wiborg *et al.,* 2010). This raises the following question: perhaps a change in activity regulation is more important in facilitating improvement in relatively active CFS patients than an increase in physical activity. Furthermore, a smaller group of CFS patients with a passive activity pattern (who show extremely low levels of physical activity) might benefit from a persistent increase in physical activity. Unfortunately, the number of patients in this group was too small to properly assess the effect of this treatment.

According to a 2014 systematic review, the lack of changes in objectively measured physical activity challenges the validity of the cognitive behavioural model of CFS/ME, because it suggests that patients still avoided post-exertional symptom exacerbations and adapted to the illness rather than recovering from it (Adamowicz *et al.,* 2014). To date, the effectiveness of CBT for the severely ill ME/CFS patients has not been assessed, and in practice, these patients may be excluded from trials because they need to attend a clinic (Chambers *et al.,* 2006).

Around 25–40% of CFS patients can be expected to have comorbid anxiety and depression. Moss-Morris's working group (Moss-Morris *et al.,* 2005) carried out a study with the following two hypotheses; GET would lead to a reduction in fatigue and disability (i) through an increase in physiological fitness and (ii) by decreasing patients' tendencies to focus on their symptoms and increasing their belief that exercise can help control their symptoms. The study included patients with and without comorbid psychopathology; all met the 1994 CDC/Fukuda definition for CFS, and those with anxiety and depression were diagnosed using the self-reported HADS. Between 50–55% of CFS patients versus 24% of controls reported that they felt much better after the 12 weeks of exercise therapy. Furthermore, around 40% of patients in this study had a probable comorbid anxiety or depression, suggesting that graded exercise could be more effective in these patients.

A study including 45 CFS/ME patients found that the effectiveness of psychodynamic counselling for treating CFS/ME was comparable with that of CBT (Chisholm *et al.,* 2001; Ridsdale *et al.,* 2001). Children have been successfully treated using antidepressants and therapy (Patel *et al.,* 2003).

Graded exercise therapy (GET)

The assessment of the effectiveness of GET and the analysis of the Cochrane database used the 1991 Oxford criteria (Larun *et al.,* 2015). It is known that depressed patients improve with activity. As defined in the 2003 Canadian Criteria, CFS/ME is a physical illness with post-exertional malaise as a core symptom of the illness. Because patients with depression were included in the 1991 Oxford criteria, the studies erroneously concluded that CFS patients were improving with GET. CFS/ME patients have demonstrated post-exertional malaise on 2 day following CPET testing. Exercise capacity varies greatly among CFS/ME patients, and some may not be able to increase their aerobic intensity (Bested and Marshall, 2015).

Nonetheless, a number of studies using both the 1991 Oxford criteria and 1994 CDC/Fukuda definition have reported the benefits of a GET programme, particularly aerobic exercise, in which patients gradually perform more intense exercise. In a Cochrane review and meta-analysis on effectiveness of GET in treating CFS/ME (Edmonds *et al.,* 2004), five studies (Fulcher and White, 1997; Powell *et al.,* 2001; Wallman *et al.,* 2004; Moss-Morris *et al.,* 2005; Wearden *et al.,* 2010) examined the effects of exercise therapy. Patients in the studies met either the 1991 Oxford criteria (Fulcher and White, 1997; Wearden *et al.,* 1998; Powell *et al.,* 2001) or the 1994 CDC/Fukuda definition (Wallman *et al.,* 2004; Moss-Morris *et al.,* 2005) for CFS. At 12 weeks, exercise therapy was slightly more beneficial for patients with depression than for controls (Fulcher and White, 1997; Wearden *et al.,* 1998; Wallman *et al.,* 2004).

Graded exercise works best for CFS/ME when combined with CBT and psychoeducation therapy, but it may not work for all CFS/ME patients. In fact, over-exercising may intensify symptoms, and some patients experience profound fatigue after even moderate exercise. Two systematic reviews cautiously conclude that some CFS/ME patients may benefit from GET, although there are limitations regarding the evidence and the generalisability of the findings (Edmonds *et al.,* 2004; Chambers *et al.,* 2006).

A 2012 systematic review concluded that despite the consistently positive outcomes of GET trials for CFS/ME, exercise therapy is not a cure and that full recovery from CFS/ME is rare (Van Cauwenbergh *et al.,* 2012). A 2004 Cochrane systematic review of five eligible studies of GET found statistically significant improvements in self-reported fatigue severity and physical functioning. This benefit was sustained after 6 months but was no longer significant compared with the control group who did not receive GET. Functional work capacity did not significantly improve. The authors stated that the evidence base and the accuracy of the results are limited, and called for higher quality studies in subgroups of CFS/ME patients and settings that measured additional outcomes such as adverse effects, quality of life and cost effectiveness over longer periods of time (Edmonds *et al.,* 2004).

A 2006 systematic review of five eligible studies of GET found an overall reduction in symptoms and an improvement in physical functioning, but GET was not shown to restore the ability to work. Withdrawals were recorded in some GET studies but were difficult to interpret due to the poor reporting of adverse effects. The protocols for many clinical studies may have biased sample selection towards inclusion of patients with less severe symptoms. In general, most of the studies cited here recruited patients who were able to attend the place where the study was being carried out, but excluded severely ill ME/CFS patients (homebound or bedbound) whose condition did not allow them to go. This is why patient selection shifts towards inclusion of patients with less severe symptoms.

The authors noted the need for research to define fully the characteristics of patients who would benefit from specific interventions, and also to develop clinically relevant objective outcome measures (Chambers *et al.,* 2006). A New Zealand study suggested that GET may result in self-reported improvement, in part by reducing the degree to which patients focus on their symptoms (Moss-Morris *et al.,* 2005). Nijs *et al.* (Vrije Universiteit Brussels, Belgium) noted that, in order to avoid detrimental effects of GET, care must be taken to avoid symptom exacerbation while tailoring the programme to

individual capabilities and the fluctuating nature of symptoms (Nijs *et al.,* 2008).

Surveys of CFS/ME patient organizations commonly reported adverse effects (Clark *et al.,* 2002; White *et al.,* 2007; Twisk and Maes, 2009) (Working Party on CFS/ME, Jan 2002. Report of the Working Party on CFS/ME to the Chief Medical Officer for England and Wales, Department of Health, UK). A survey of two Norwegian patient organizations reported also that 79% of patients with experience of graded training considered that it worsened their health status (Bjorkum *et al.,* 2009). A meta-analysis concluded that CBT and GET are equally efficacious treatments for CFS/ME, but that CBT may be more effective when patients have comorbid anxiety and/or depression (Moss-Morris *et al.,* 2005; Windgassen *et al.,* 2016). In a more recent study of a multidisciplinary intervention, which combined group CBT and GET with pharmacological treatment, at 12 months after completion, GET was slightly inferior to usual medical care alone, had not improved fatigue or health-related quality of life, and resulted in worse physical function and bodily pain scores (Nunez *et al.,* 2011). A study including 45 CFS/ME patients found that the effectiveness of psychodynamic counselling in the treatment of CFS/ME was comparable to that of CBT (Ridsdale *et al.,* 2001).

Pragmatic rehabilitation: the FINE trial

Pragmatic rehabilitation is a programme involving gradually increasing activity designed collaboratively by the patient and the therapist. In response to an earlier successful trial, a larger trial (FINE; Fatigue intervention by nurses evaluation) was conducted. In this trial, patients fulfilling 1991 Oxford CFS criteria who were allocated to pragmatic rehabilitation reported a statistically significant though clinically modest improvement in fatigue compared with patients allocated to either supportive listening or treatment as usual, but after 12 months follow-up the differences were no longer statistically significant nor was there was any significant improvement in physical functioning at any time. About 10% of the trial participants were non-ambulatory and about 30% met 1994 London criteria for ME, but separate results for these groups were not published (Wearden *et al.,* 2010). An accompanying editorial gave some possible reasons for the failure to replicate the earlier success in this trial, and called for further research. The patients in this trial had higher comorbidity and disability than patients in the earlier trial and in most other trials, and received fewer sessions than most successful trials of CBT and GET. The editorial also raised the question of whether generalists are as successful as specialists in offering behavioural interventions (Moss-Morris and Hamilton, 2010).

Adaptive pacing therapy

Adaptive Pacing Therapy (APT) is also designed to alter patients' behaviour. In contrast to CBT, however, pacing makes allowances for the characteristic fluctuations in symptom severity and delayed recovery from exercise (Nijs *et al.,* 2006). Patients receiving APT are instructed to set themselves reasonable targets for their daily activity and exercise and to avoid possible over-exertion (and aggravation of symptoms) by striking a balance between activity and rest. APT patients functioning within their individual limits then gradually raise their activity and exercise levels (i.e. GET). A single case observational study of pacing self-management comprised seven adult women CFS patients who fulfilled the 1994 CDC/Fukuda definition and received APT (Pacing Self-Management) for 5 weeks. The results suggested that 3 weeks of pacing self-management improves symptom severity and performance of daily activities, but a larger RCT is required to confirm these preliminary observations (Nijs *et al.,* 2009). A RCT conducted in 68 patients who met the 1994 CDC/Fukuda definition found that a combination of pacing and GET obtained significantly better than relaxation/flexibility therapy (Wallman *et al.,* 2004). Pacing was also the most effective, safe, acceptable and preferred form of activity management for CFS/ME and should therefore be a key component of any illness management programme according to the largest CFS/ME patient survey carried out in 2012 by the ME Association, a UK charity (www.meassociation.org.uk) with patients diagnosed according to the 2007 NICE clinical guideline (www.guidance.nice.org.uk/cg53).

A 2009 survey of 828 Norwegian CFS subjects who fulfilled the 1991 Oxford criteria for both CFS and PVFS were recruited through two local ME/CFS patient organizations (ME-association and MENiN). Pacing was evaluated as useful by 96% of the participants. Their experience indicates that CBT can be useful for some patients, but that graded training may cause deterioration of the condition in many patients. The results must, however, be interpreted with care, as the participants were not a representative sample, and we do not know the specific content of the approaches (Bjorkum *et al.,* 2009).

The PACE trial

The PACE trial (Pacing, graded activity, and cognitive behaviour therapy; a randomized evaluation) was the largest-scale 5 year trial of treatment for CFS from 2005 to 2010, funded by the UK Government at a cost of €8 million. The original PACE trial (White *et al.,* 2011) recruited a total of 641 eligible patients meeting the 1991 Oxford criteria for CFS from six secondary care clinics in the UK and were randomly assigned to one of four treatments: standard medical care (SMC) alone, SMC with CBT, SMC with GET, and SMC with APT. The aim of trial was to help the participant to return gradually to appropriate physical activities, reverse the deconditioning and thereby reduce fatigue and disability. CBT was administered on the basis of the fear avoidance theory proposed for CFS/ME, and GET on the basis of the deconditioning and exercise intolerance theories also proposed for CFS/ME. The results showed that, when combined with SMC, CBT and GET were both 'moderately' effective compared with SMC alone. APT was not found to be effective when added to SMC (White *et al.,* 2011). The performance of the CBT group did not differ significantly from that of the SMC and APT groups (Kewley, 2011). CBT and GET rehabilitation treatments achieved a greater improvement in fatigue and physical function for CFS patients than the APT or SMC-only groups when measured at the trial final outcome 1 year after randomization. However, apart from the slightly larger improvement in the GET group on the 6 min walking test, none of the study's objective measures and the long-term follow-up data (self-ratings of fatigue and physical function) showed any difference

between groups. In a 2013 paper specifically about recovery, the authors reported that 22% of patients in the CBT and GET groups had recovered following these therapies, compared with 8% in the APT group and 7% in the SMC-only group (Cella *et al.,* 2013).

A later study presented results from a step fitness test, but at 52 weeks, there were no significant differences in performance across groups on this measure (Cleare *et al.,* 2015). The trial reported that CBT and GET were safe. A subsequent paper examined the proportion of patients who recovered after the trial. 'Recovered' patients were those who obtained a specified threshold score on the self-reported fatigue and physical function scales, rated their health as much better or very much better and no longer met the authors' case definition of CFS. A follow-up study conducted 2.5 years after the commencement of the trial reported no significant differences between the various treatment groups on the primary self-report measures; that is, the treatment-specific effects evident at 52 weeks were no longer evident at 2.5 years (Sharpe *et al.,* 2015).

The PACE trial had certain limitations. Patients unable to attend hospital (i.e. many of the most severely ill patients were excluded; participants, therapists, doctors and research assessors were not masked to treatment allocation), meaning that the trial was not blinded; and finally, the primary outcomes were subjective and rated by participants, and so may be subject to biases. However, looking at the original data of the follow-up study and other PACE trials (Twisk and Maes, 2009; McCrone *et al.,* 2012), we believe that neither CBT nor GET qualify as rehabilitative therapies for all CFS or ME patients. First, the PACE trial investigated the effects of CBT and GET in chronic fatigue, as defined by the 1991 Oxford criteria – not in CFS/ME as defined by the other case criteria, let alone ME cases. The study used such a broad definition of the disease that it is likely to have included many patients who did not truly have CFS at all (Smith *et al.,* 2015). Second, the positive effect of CBT and GET on subjective measures, fatigue and physical functioning cannot be qualified as sufficient. Third, the PACE trial follow-up study (Sharpe *et al.,* 2015) concluded that outcomes with SMC alone or APT were similar to those achieved with CBT and GET at follow-up. This finding suggests that the vast majority of patients improved subjectively to the same level with SMC and APT as with CBT and GET, without the need for additional therapies (including CBT and GET).

In brief, CBT and GET are moderately effective in subjective terms in chronic fatigue. However, looking at the patients studied and the (subjective and objective) outcomes of the PACE trial, CBT and GET do not meet the requirements for rehabilitative or effective therapies for CFS, let alone for ME sufferers. The PACE trial design changed so significantly that many experts were left wondering whether there is any value in the study itself. Firstly, the physical functioning threshold in SF-36 was lowered because of poor recruitment and this increased the likelihood that many participants did not have ME/CFS at all. Secondly, the authors claimed to have performed an intention-to-treat analysis, but in fact, they excluded any subjects for whom there were no primary outcome data, and so it was not an intention-to-treat analysis.

It seems that the most we can glean from PACE is that study design is essential to good science, and the flaws in this design were enough to doom its results from the start. Table 2 shows a summary of the current counselling, pacing and behavioural strategies for CFS/ME.

Discussion

CFS/ME (SEID) is undoubtedly a challenging and emerging medical condition, but there is hope for those affected. At present, there is no cure; treatment merely aims to relieve the symptoms. In general, CFS/ME patients who are diagnosed within the first 2 years of the appearance of symptoms respond better to treatment than those diagnosed at a later date. Treatments to relieve symptoms have to be individualized for each patient. Some (though not all) investigators suggest that healthy diet and nutritional supplements are an essential component of any CFS/ME therapy approaches. Even in the absence of clinical nutritional deficiencies, the physiological demands of a chronic illness make it necessary to provide additional nutritional support – especially in light of the numerous gastrointestinal problems prevalent in the CFS/ME, which may lead to inflammation and malabsorption.

Other approaches that claim some positive effects on CFS/ME symptoms include holistic treatments, although few of these therapies have been studied in depth by experts who treat CFS/ME. Most clinicians agree that CFS/ME patients need a treatment based on a personalized multidisciplinary and integrative medicine approach. The most disruptive symptoms should be addressed first. In general, the therapy will combine psychological counselling and mild, guided exercise. CBT seems to work well with paediatric CFS/ME patients (Jason *et al.,* 2012; Nijhof *et al.,* 2012; Knight *et al.,* 2013). Prognosis is better for adolescents (aged 12–18 years) than for adults (Stulemeijer *et al.,* 2005). The participants fulfilled the 1994 CDC/Fukuda definition and a recovery rate of a 70% of adolescents was proven directly after CBT treatment. However, they often have problems at school with regard to attention and memory (Kawatani *et al.,* 2011).

Many patients can only work part-time, and some become bed-ridden. Mental impairment, especially loss of memory and the ability to concentrate, is highly disconcerting for CFS/ME (SEID) patients. Even with symptomatic treatment, some patients may find that their ability to function continues its slow decline.

An AHRQ report concluded that only counselling therapies and GET help improve fatigue and physical function in some (though not all) subsets of adults CFS/ME patients (https://www.ncbi.nlm.nih.gov/books/NBK293931).

New therapeutic strategies for CFS/ME are urgently needed since its symptoms substantially impair quality of life, both in parents and in their caregivers. Given the fluctuating nature of CFS/ME, larger multi-centre interventions should be designed with follow-up periods longer than 1–2 years, a higher presence of men and of racial and ethnic minorities, and a broader range of age and of disability (i.e. including 'home-/bed-bound' or severely ill ME cases). Studies of this kind will help to change evidence-based guidelines regarding the potential benefits and harms of treatments and management in CFS/ME and other chronic fatiguing conditions.

Table 2

Overview of the included non-pharmacological interventions for CFS/ME

INTERVENTION (Study ID)	Population characteristics and case definition			Outcomes reported		Quality rating	Author (year)
	Study design	Participants Duration of follow-up	Case definition	Fatigue measures	Physical Functioning status		
CBT	RCT CBT versus usual care for symptoms	30 patients 12 months	1991 Oxford	NR	KPS score of ≥80 At 5 months 27% At 8 months: 53% At 12 months: 73% Improvement ≥10 point on KPS At 5 months 23% At 8 months: 60% At 12 months: 73%	GOOD	(Sharpe *et al.*, 2015)
CBT	RCT CBT versus control for symptoms	69 patients 3 months	1994 CDC/Fukuda	Fatigue subscale (0–28 scoring) At 3 months: $P = 0.06$	NR	FAIR	(Lopez and Basco, 2011)
Counselling therapy	RCT Counselling versus wait list for symptoms	47 patients 12 months	1994 CDC/Fukuda	NR	NR	GOOD	(Jason *et al.*, 2005)
Self-instruction therapy	RCT Self-instruction therapy versus wait list for symptoms	169 patients 6–12 months depending on tto duration	1994 CDC/Fukuda	CIS fatigue severity scores (8–56) Second assessment: $P < 0.001$ CIS fatigue severity scores (CIS <35 and reliable change index of >1.96): $P < 0.001$	SF-36 PF scale Second assessment: $P = 0.011$ Functional impairment SIP-8 scores Second assessment: $P < 0.001$	FAIR	(Knoop *et al.*, 2008)
Stepped care therapy	RCT Stepped care versus usual care for symptoms	169 patients 6–12 months depending on treatment duration	1994 CDC/Fukuda	CIS fatigue severity scores Post-tto: $P = 0.92$ CIS fatigue severity scores (CIS <35 and reliable change index of >1.96): $P = 1.00$	SF-36 PF scale Post-tto: $P = 0.72$ Functional impairment SIP-8 scores Post-tto: $P = 0.77$	GOOD	(Tummers *et al.*, 2010)
CBT	Non-RCT CBT versus wait list for symptoms	65 patients 6 months	1994 CDC/Fukuda	CIS fatigue severity scores at 6 mo: $P = 0.099$	Functional impairment SIP-8 scores at 6 months: $P = NS$	FAIR	(Bazelmans *et al.*, 2005)

continues

Table 2 (Continued)

INTERVENTION (Study ID)	Population characteristics and case definition			Outcomes reported		Quality rating	Author (year)
	Study design	Participants Duration of follow-up	Case definition	Fatigue measures	Physical Functioning status		
					Change from baseline: $P = 0.004$		
CBT and support group	RCT CBT versus support group versus usual care for symptoms	153 patients 12 months	1994 CDC/Fukuda	CFQ-11 scale 6 months: $P = 0.19$ 12 months: $P = 0.19$ Difference between groups from baseline at 12 months CBT versus support: $P = 0.011$ CBT versus usual care: $P = 0.027$ Support versus usual care: $P =$ NR	SF-36 PF scale (all $P =$ N.S. both at 6 and 12 months) Difference between groups from baseline to 12 months CBT versus support: $P = 0.0055$ CBT versus usual care: $P = 0.0055$ Support versus usual care: $P = 0.15$	FAIR	(White *et al.*, 2011)
FINE trial	RCT Pragmatic rehabilitation versus supportive listening versus usual care for symptoms	296 patients 5 months treatment; 17.5 months follow-up	1991 Oxford	CFQ-11 scale scores Treatment effect estimate at 5 months: $P = 0.021$ Pragmatic rehab versus usual care. At 17.5 months: $P =$ N.S. CFQ-11 scale scores At 5 months: 22.78 ± 8.56 versus 26.27 ± 7.68 At 17.5 months: 23.90 ± 8.34 versus 26.02 ± 7.11 Baseline HADS depression score: $P = 0.022$ Baseline HADS total score: $P = 0.039$ EQ-5D self-care scale, those with severe problems: $P < 0.001$ CFQ-11 scale scores (pragmatic rehab. versus usual care)	SF-36 PF scale Treatment effect estimate for supportive listening versus usual care $P = 0.035$ At 17.5 months: $P =$ N.S.	GOOD	(Wearden *et al.*, 2010) (Wearden *et al.*, 2012) (Wearden and Emsley, 2013)

continues

Table 2 (Continued)

INTERVENTION (Study ID)	Population characteristics and case definition			Outcomes reported		Quality rating	Author (year)
	Study design	Participants Duration of follow-up	Case definition	Fatigue measures	Physical Functioning status		
				Age: $P = 0.044$ Illness duration: $P = 0.008$ EQ-5D mobility scale; those with severe problems: $P = 0.024$			
GET	RCT GET + fluoxetine versus GET alone versus fluoxetine alone versus control for symptoms	136 patients 6.5 months	1991 Oxford	CFQ-11 scores <4% non-cases of fatigue 3 months: P = NS 6.5 months: $P = 0.025$ Exercise improved fatigue scale scores 3 months: $P = 0.13$ 6.5 mo: $P = 0.07$	Functional work capacity 3 months: P = NR 6.5 mo: P = NR Effect of exercise on functional work capacity 3 months: $P = 0.005$ 6.5 months: $P = 0.03$	FAIR	(Wearden *et al.*, 1998)
GET	RCT Graded exercise versus standard medical care for symptoms	49 patients 3 months treatment Up to 6 months follow-up	1994 CDC/Fukuda	CFQ-11 total fatigue scores At 3 months: $P = 0.02$ CFQ-11 physical fatigue subscale scores At 3 months: $P = 0.02$ CFQ-11 mental fatigue subscale scores At 3 months: $P = 0.03$	SF-36 PF subscale score at 3 months $P = 0.49$	FAIR	(Moss-Morris *et al.*, 2005)
Orthostatic training	RCT Orthostatic training versus placebo for symptoms	38 patients 6 months treatment Up to 12 months follow up	1994 CDC/Fukuda	Improvement of ≥10 points on FIQ at 6 months: P = NR	Mean change in blood pressure drop with active stand at 6 months $P = 0.05$	FAIR	(Sutcliffe *et al.*, 2010)
CBT	RCT CBT versus COG versus ACT versus relaxation for symptoms	n° cases: NR 12 months follow-up	CFS questionnaire, psychiatric assessment for DSM-IV diagnosis,	FSS scores At 12 months: P = NR Jason, 2009 data: (comparison by	SF-36 PF scores At 12 months: $P < 0.01$ (CBT and COG over time versus ACT over time)	FAIR	(Jason *et al.*, 2009) (Hlavaty *et al.*, 2011)

continues

Table 2 (Continued)

INTERVENTION (Study ID)	Population characteristics and case definition			Outcomes reported		Quality rating	Author (year)
	Study design	Participants Duration of follow-up	Case definition	Fatigue measures	Physical Functioning status		
			and medical assessment.	energy envelope) Stayed within envelope versus outside envelope At 6 months: P = NR At 12 months: P = NS Change at 12 months from baseline: $P < 0.01$ Hlavaty, 2011 data: (comparison by homework compliance level) Minimum versus moderate versus maximum Change in score at 12 months from baseline: P = NR	% achieving clinically significant improvement: P = NS Jason, 2009 data: (comparison by energy envelope) Stayed within envelope versus outside envelope 6 months: P = NR 12 months: P = NS Change at 12 months from baseline: P = 0.03 Hlavaty, 2011 data: (comparison by homework compliance level) Minimum versus moderate versus maximum Change in score at 12 months from baseline: P = NR		
CBT plus GET	RCT CBT + GET versus usual care for symptoms	115 patients 12 months	1994 CDC/Fukuda	FIQ (0–160 score) at 12 months: P = N.S.	SF-36 PF (0–100 score) at 12 months: P = N.S.	FAIR	(Nunez *et al.*, 2011)
PACE trial	RCT CBT versus GET versus APT versus usual care for symptoms	640 patients 13 months	1991 Oxford	CFQ-11 scale scores (0–33) at 13 months Mean difference from control: P = N.S versus P = 0.0001 versus P = 0.0003 versus P = NR Mean difference from APT: NR versus P = 0.0027 versus P = 0.0059 versus NR % improved from	SF-36 PF scores (0–100) at 13 months Mean difference from control: P = NS versus P = 0.0068 versus P = 0.0005 versus NR Mean difference from APT: NR versus P = 0.0002 versus $P < 0.0001$ versus NR % improved from baseline (by ≥8 points):	GOOD	(White *et al.*, 2011) (White *et al.*, 2013) (Dougall *et al.*, 2014)

continues

Table 2 (Continued)

INTERVENTION (Study ID)	Population characteristics and case definition			Outcomes reported		Quality rating	Author (year)
	Study design	Participants Duration of follow-up	Case definition	Fatigue measures	Physical Functioning status		
				baseline (≥ 2 points): 65% versus 76% versus 80% versus 65% % within normal range (score ≤ 18): 22% versus 41% versus 33% versus 21%	49% versus 71% versus 70% versus 58% % within normal range (score ≥ 60): 35% versus 52% versus 53% versus 41%		

All outcomes indicate % change from baseline.

ACT, anaerobic activity treatment; CFQ-11, Chalder fatigue scale, an 11-item questionnaire (range 0–33, higher score means greater extent and severity of fatigue); COG, cognitive therapy; CIS, checklist of individual strength; DSM-IV, Diagnostic and Statistical Manual, fourth edition; EQ-5D, self-reported questionnaire designed to measure health status; FIQ, Fatigue Impact Questionnaire (range 0–160, higher score means greater severity of fatigue); FSS, Fatigue Severity Scale (range 9–63, higher scores means greater fatigue severity); HADS, Hospital Anxiety and Depression Scale (range 0–21 for either anxiety or depression, higher scores indicate worse symptoms); KPS, Karnofsky Performance Status (range 0–100; higher score means better health); NR, not recorded; NS, not significant; SF-36 PF, 36-item Short Form Survey Physical Function scales (range 0–100, higher score means less disability and better health status); SIP-8, Sickness Impact Profile, an 8-item questionnaire.

Concluding remarks and future directions

This review suggests that the beneficial effects of nutritional supplements are not random, but that their action is due to the removal of one of the causes of the CFS/ME. There is evidence that supplements may benefit CFS/ME patients; therefore, nutritional supplements should be recommended, at least in CFS/ME patients with a biochemically proven deficiency. Studies investigating nutritional interventions in CFS/ME remain very limited; most studies have had small sample sizes, and lacked long term follow-up (>6 months). Despite the relative consistency in case definition, the studies differed with regard to inclusion and exclusion criteria and reporting participants' sociodemographic characteristics and clinical features (e.g. sex, race, BMI, illness duration, type and frequency of symptoms, and so on). This heterogeneity in study design makes the application of the findings to the clinical setting more difficult. Therefore, longer-term RCTs in homogeneous populations that use more specific case criteria are now warranted.

In agreement with several previous studies, pacing was consistently shown to be the most helpful treatment, CBT was useful for some patients but not all for all; graded training may cause the condition to worsen. However, the results must be interpreted with care, as the participants are not a representative sample.

In summary, nutritional supplementation is recommended in CFS/ME patients with biochemically proven deficiencies. CFS/ME treatment should also be optimized by the use of individualized pacing strategies, customization of CBT and other types of counselling and behavioural therapies so as to help relieve the symptoms. GET should be carefully modulated by an individual pacing strategy using strict case definitions to avoid the push-crash cycle. Further additional larger interventions should now incorporate personalized integrative medicine approaches for identifying CFS/ME patients most likely to respond to each type of treatment. Researchers and the medical community also need to develop new initiatives and additional forms of individualized treatment and management in CFS/ME in order to achieve significant improvements in quality of life, especially in those severely ill ME cases and bed-ridden patients.

Acknowledgments

The authors are grateful to Michael Maudsley, Dr Juan B. Gomez (Headache Research Group, Vall d'Hebron University Hospital, Barcelona, Spain) and Prof Derek Pheby (Buckinghamshire New University, Uxbridge, UK) for reviewing the manuscript and for providing critical comments and feedback on a draft of this manuscript.

Conflict of interest

The authors declare no conflicts of interest.

References

Adamowicz JL, Caikauskaite I, Friedberg F (2014). Defining recovery in chronic fatigue syndrome: a critical review. Qual Life Res 23: 2407–2416.

Afari N, Eisenberg DM, Herrell R, Goldberg J, Kleyman E, Ashton S *et al.* (2000). Use of alternative treatments by chronic fatigue syndrome discordant twins. Integr Med 2: 97–103.

Alegre J, Roses JM, Javierre C, Ruiz-Baques A, Segundo MJ, de Sevilla TF (2010). Nicotinamide adenine dinucleotide (NADH) in patients with chronic fatigue syndrome. Rev Clin Esp 210: 284–288.

Alexander SPH, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E *et al.* (2015a). The Concise Guide to PHARMACOLOGY 2015/16: Overview. Br J Pharmacol 172: 5734–5143.

Alexander SPH, Fabbro D, Kelly E, Marrion N, Peters JA, Benson HE *et al.* (2015b). The Concise Guide to PHARMACOLOGY 2015/16: Enzymes. Br J Pharmacol 172: 6024–6109.

Alexander SPH, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E *et al.* (2015c). The Concise Guide to PHARMACOLOGY 2015/16: Transporters. Br J Pharmacol 172: 6110–6202.

Alraek T, Lee MS, Choi TY, Cao H, Liu J (2011). Complementary and alternative medicine for patients with chronic fatigue syndrome: a systematic review. BMC Complement Altern Med 11: 87.

Andersson M, Bagby JR, Dyrehag L, Gottfries C (1998). Effects of staphylococcus toxoid vaccine on pain and fatigue in patients with fibromyalgia/chronic fatigue syndrome. Eur J Pain 2: 133–142.

Aroniadis OC, Brandt LJ (2013). Fecal microbiota transplantation: past, present and future. Curr Opin Gastroenterol 29: 79–84.

Attree EA, Arroll MA, Dancey CP, Griffith C, Bansal AS (2014). Psychosocial factors involved in memory and cognitive failures in people with myalgic encephalomyelitis/chronic fatigue syndrome. Psychol Res Behav Manag 7: 67–76.

Bazelmans E, Prins JB, Lulofs R, van der Meer JW, Bleijenberg G (2005). Cognitive behaviour group therapy for chronic fatigue syndrome: a non-randomised waiting list controlled study. Psychother Psychosom 74: 218–224.

Behan PO, Behan WM, Horrobin D (1990). Effect of high doses of essential fatty acids on the postviral fatigue syndrome. Acta Neurol Scand 82: 209–216.

Bested AC, Marshall LM (2015). Review of myalgic encephalomyelitis/chronic fatigue syndrome: an evidence-based approach to diagnosis and management by clinicians. Rev Environ Health 30: 223–249.

Bjorkegren K (1999). Vitamin B12, chronic fatigue and injection treatment. Lakartidningen 96: 5610.

Bjorkum T, Wang CE, Waterloo K (2009). Patients' experience with treatment of chronic fatigue syndrome. Tidsskr Nor Laegeforen 129: 1214–1216.

Blockmans D, Persoons P, Van Houdenhove B, Lejeune M, Bobbaers H (2003). Combination therapy with hydrocortisone and fludrocortisone does not improve symptoms in chronic fatigue syndrome: a randomized, placebo-controlled, double-blind, crossover study. Am J Med 114: 736–741.

Booth NE, Myhill S, McLaren-Howard J (2012). Mitochondrial dysfunction and the pathophysiology of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Int J Clin Exp Med 5: 208–220.

Braun B, Clarkson PM, Freedson PS, Kohl RL (1991). Effects of coenzyme Q10 supplementation on exercise performance, VO2max, and lipid peroxidation in trained cyclists. Int J Sport Nutr 1: 353–365.

Brook MG, Bannister BA, Weir WR (1993). Interferon-alpha therapy for patients with chronic fatigue syndrome. J Infect Dis 168: 791–792.

Brurberg KG, Fonhus MS, Larun L, Flottorp S, Malterud K (2014). Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review. BMJ Open 4: e003973.

Brussow H (2016). Biome engineering-2020. J Microbial Biotechnol 9: 553–563.

Butler AC, Chapman JE, Forman EM, Beck AT (2006). The empirical status of cognitive-behavioral therapy: a review of meta-analyses. Clin Psychol Rev 26: 17–31.

Calandre EP, Rico-Villademoros F, Slim M (2015). An update on pharmacotherapy for the treatment of fibromyalgia. Expert Opin Pharmacother 16: 1347–1368.

Carruthers BM (2003). Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols (Canadian case definition). J Chronic Fatigue Syndrome 11: 7–115.

Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T*et al.* (2011). Myalgic encephalomyelitis: international consensus criteria. J Intern Med 270: 327–338.

Castro-Marrero J, Cordero MD, Saez-Francas N, Jimenez-Gutierrez C, Aguilar-Montilla FJ, Aliste L *et al.* (2013). Could mitochondrial dysfunction be a differentiating marker between chronic fatigue syndrome and fibromyalgia? Antioxid Redox Signal 19: 1855–1860.

Castro-Marrero J, Saez-Francas N, Segundo MJ, Calvo N, Faro M, Aliste L *et al.* (2016). Effect of coenzyme Q10 plus nicotinamide adenine dinucleotide supplementation on maximum heart rate after exercise testing in chronic fatigue syndrome – A randomized, controlled, double-blind trial. Clin Nutr 35: 826–834.

Cella M, White PD, Sharpe M, Chalder T (2013). Cognitions, behaviours and co-morbid psychiatric diagnoses in patients with chronic fatigue syndrome. Psychol Med 43: 375–380.

Chambers D, Bagnall AM, Hempel S, Forbes C (2006). Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis: an updated systematic review. J R Soc Med 99: 506–520.

Chisholm D, Godfrey E, Ridsdale L, Chalder T, King M, Seed P *et al.* (2001). Chronic fatigue in general practice: economic evaluation of counselling versus cognitive behaviour therapy. Br J Gen Pract 51: 15–18.

Clague JE, Edwards RH, Jackson MJ (1992). Intravenous magnesium loading in chronic fatigue syndrome. Lancet 340: 124–125.

Clark C, Buchwald D, MacIntyre A, Sharpe M, Wessely S (2002). Chronic fatigue syndrome: a step towards agreement. Lancet 359: 97–98.

Clayton EW (2015). Beyond myalgic encephalomyelitis/chronic fatigue syndrome: an IOM report on redefining an illness. JAMA 313: 1101–1102.

Cleare AJ, Heap E, Malhi GS, Wessely S, O'Keane V, Miell J (1999). Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial. Lancet 353: 455–458.

Cleare AJ, O'Keane V, Miell J (2001). Plasma leptin in chronic fatigue syndrome and a placebo-controlled study of the effects of low-dose

hydrocortisone on leptin secretion. Clin Endocrinol (Oxf) 55: 113–119.

Cleare AJ, Reid S, Chalder T, Hotopf M, Wessely S (2015). Chronic fatigue syndrome. BMJ Clin Evid 28; pii: 1101.

Clemons A, Vasiadi M, Kempuraj D, Kourelis T, Vandoros G, Theoharides TC (2011). Amitriptyline and prochlorperazine inhibit proinflammatory mediator release from human mast cells: possible relevance to chronic fatigue syndrome. J Clin Psychopharmacol 31: 385–387.

Cooke M, Iosia M, Buford T, Shelmadine B, Hudson G, Kerksick C *et al.* (2008). Effects of acute and 14-day coenzyme Q10 supplementation on exercise performance in both trained and untrained individuals. J Int Soc Sports Nutr 5: 8.

Cox IM, Campbell MJ, Dowson D (1991). Red blood cell magnesium and chronic fatigue syndrome. Lancet 337: 757–760.

De Clercq E, Neyts J (2009). Antiviral agents acting as DNA or RNA chain terminators. Handb Exp Pharmacol : 53–84.

Degenhardt L, Gisev N, Cama E, Nielsen S, Larance B, Bruno R (2016). The extent and correlates of community-based pharmaceutical opioid utilisation in Australia. Pharmacoepidemiol Drug Saf 25: 521–538.

Diaz-Mitoma FTE, Kumar A, Lim W, Larocque L, Hyde BM (2003). Clinical improvement in chronic fatigue syndrome is associated with enhanced natural killer cell-mediated cytotoxicity: the results of a pilot study with Isoprinosine®. J Chronic Fatigue Syndr 11: 71–95.

Dougall D, Johnson A, Goldsmith K, Sharpe M, Angus B, Chalder T *et al.* (2014). Adverse events and deterioration reported by participants in the PACE trial of therapies for chronic fatigue syndrome. J Psychosom Res 77: 20–26.

Edmonds M, McGuire H, Price J (2004). Exercise therapy for chronic fatigue syndrome. Cochrane Database Syst Rev: CD003200.

Ellis FR, Nasser S (1973). A pilot study of vitamin B12 in the treatment of tiredness. Br J Nutr 30: 277–283.

Fluge O, Bruland O, Risa K, Storstein A, Kristoffersen EK, Sapkota D *et al.* (2011). Benefit from B-lymphocyte depletion using the anti-CD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. PLoS One 6: e26358.

Fluge O, Mella O (2009). Clinical impact of B-cell depletion with the anti-CD20 antibody rituximab in chronic fatigue syndrome: a preliminary case series. BMC Neurol 9: 28.

Fluge O, Risa K, Lunde S, Alme K, Rekeland IG, Sapkota D *et al.* (2015). B-lymphocyte depletion in myalgic encephalopathy/ chronic fatigue syndrome. An open-label phase II study with rituximab maintenance treatment. PLoS One 10: e0129898.

Forsyth LM, Preuss HG, MacDowell AL, Chiazze L Jr, Birkmayer GD, Bellanti JA (1999). Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. Ann Allergy Asthma Immunol 82: 185–191.

Fremont M, Coomans D, Massart S, De Meirleir K (2013). High-throughput 16S rRNA gene sequencing reveals alterations of intestinal microbiota in myalgic encephalomyelitis/chronic fatigue syndrome patients. Anaerobe 22: 50–56.

Friedman TC, Adesanya A, Poland RE (1999). Low-dose hydrocortisone for chronic fatigue syndrome. JAMA 281: 1888–1889.

Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A (1994). The chronic fatigue syndrome: a comprehensive approach to its definition and study. International chronic fatigue syndrome study group. Ann Intern Med 121: 953–959.

Fulcher KY, White PD (1997). Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. BMJ 314: 1647–1652.

Garrido-Maraver J, Cordero MD, Oropesa-Avila M, Vega AF, de la Mata M, Pavon AD *et al.* (2014). Clinical applications of coenzyme Q10. Front Biosci (Landmark Ed) 19: 619–633.

Giloteaux L, Goodrich JK, Walters WA, Levine SM, Ley RE, Hanson MR (2016). Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome. Microbiome 4: 30.

Goldsmith LP, Dunn G, Bentall RP, Lewis SW, Wearden AJ (2015). Therapist effects and the impact of early therapeutic alliance on symptomatic outcome in chronic fatigue syndrome. PLoS One 10: e0144623.

Green CR, Cowan P, Elk R, O'Neil KM, Rasmussen AL (2015). National institutes of health pathways to prevention workshop: advancing the research on myalgic encephalomyelitis/chronic fatigue syndrome. Ann Intern Med 162: 860–865.

Hagglof M (2000). Vitamin B12 and chronic fatigue. Lakartidningen 97: 501.

Hinds G, Bell NP, McMaster D, McCluskey DR (1994). Normal red cell magnesium concentrations and magnesium loading tests in patients with chronic fatigue syndrome. Ann Clin Biochem 31 (Pt 5): 459–461.

Hlavaty LE, Brown MM, Jason LA (2011). The effect of homework compliance on treatment outcomes for participants with myalgic encephalomyelitis/chronic fatigue syndrome. Rehabil Psychol 56: 212–218.

Inazu M, Matsumiya T (2008). Physiological functions of carnitine and carnitine transporters in the central nervous system. Nihon Shinkei Seishin Yakurigaku Zasshi 28: 113–120.

Jackson JL, O'Malley PG, Kroenke K (2006). Antidepressants and cognitive-behavioral therapy for symptom syndromes. CNS Spectr 11: 212–222.

Janse A, Worm-Smeitink M, Bussel-Lagarde J, Bleijenberg G, Nikolaus S, Knoop H (2015). Testing the efficacy of web-based cognitive behavioural therapy for adult patients with chronic fatigue syndrome (CBIT): study protocol for a randomized controlled trial. BMC Neurol 15: 137.

Jason L, Benton M, Torres-Harding S, Muldowney K (2009). The impact of energy modulation on physical functioning and fatigue severity among patients with ME/CFS. Patient Educ Couns 77: 237–241.

Jason LA, Barker K, Brown A (2012). Pediatric myalgic encephalomyelitis/chronic fatigue syndrome. Rev Health Care 3: 257–270.

Jason LA, Corradi K, Torres-Harding S, Taylor RR, King C (2005). Chronic fatigue syndrome: the need for subtypes. Neuropsychol Rev 15: 29–58.

Jones JF, Maloney EM, Boneva RS, Jones AB, Reeves WC (2007). Complementary and alternative medical therapy utilization by people with chronic fatiguing illnesses in the United States. BMC Complement Altern Med 7: 12.

Kaslow JE, Rucker L, Onishi R (1989). Liver extract-folic acid-cyanocobalamin vs placebo for chronic fatigue syndrome. Arch Intern Med 149: 2501–2503.

Kawatani J, Mizuno K, Shiraishi S, Takao M, Joudoi T, Fukuda S *et al.* (2011). Cognitive dysfunction and mental fatigue in childhood

chronic fatigue syndrome – a 6-month follow-up study. Brain Dev 33: 832–841.

Kewley AJ (2011). The PACE trial in chronic fatigue syndrome. Lancet 377: 1832 .author reply 1834-1835

Knight SJ, Scheinberg A, Harvey AR (2013). Interventions in pediatric chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review. J Adolesc Health 53: 154–165.

Knoop H, van der Meer JW, Bleijenberg G (2008). Guided self-instructions for people with chronic fatigue syndrome: randomised controlled trial. Br J Psychiatry 193: 340–341.

Kreijkamp-Kaspers S, Brenu EW, Marshall S, Staines D, Van Driel ML (2011). Treating chronic fatigue syndrome – a study into the scientific evidence for pharmacological treatments. Aust Fam Physician 40: 907–912.

Larun L, Brurberg KG, Odgaard-Jensen J, Price JR (2015). Exercise therapy for chronic fatigue syndrome. Cochrane Database Syst Rev 2: CD003200.

Logan AC, Venket Rao A, Irani D (2003). Chronic fatigue syndrome: lactic acid bacteria may be of therapeutic value. Med Hypotheses 60: 915–923.

Lopez MA, Basco MR (2011). Feasibility of dissemination of cognitive behavioral therapy to Texas community mental health centers. J Behav Health Serv Res 38: 91–104.

Luyten P, Van Houdenhove B, Pae CU, Kempke S, Van Wambeke P (2008). Treatment of chronic fatigue syndrome: findings, principles and strategies. Psychiatry Investig 5: 209–212.

Malaguarnera M, Gargante MP, Cristaldi E, Colonna V, Messano M, Koverech A *et al*. (2008). Acetyl L-carnitine (ALC) treatment in elderly patients with fatigue. Arch Gerontol Geriatr 46: 181–190.

Malm C, Svensson M, Ekblom B, Sjodin B (1997). Effects of ubiquinone-10 supplementation and high intensity training on physical performance in humans. Acta Physiol Scand 161: 379–384.

Malouff JM, Thorsteinsson EB, Rooke SE, Bhullar N, Schutte NS (2008). Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: a meta-analysis. Clin Psychol Rev 28: 736–745.

Mantovani G, Maccio A, Madeddu C, Serpe R, Antoni G, Massa E *et al*. (2010). Phase II nonrandomized study of the efficacy and safety of COX-2 inhibitor celecoxib on patients with cancer cachexia. J Mol Med (Berl) 88: 85–92.

Maric D, Brkic S, Tomic S, Novakov Mikic A, Cebovic T, Turkulov V (2014). Multivitamin mineral supplementation in patients with chronic fatigue syndrome. Med Sci Monit 20: 47–53.

McCrone P, Sharpe M, Chalder T, Knapp M, Johnson AL, Goldsmith KA *et al*. (2012). Adaptive pacing, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fatigue syndrome: a cost-effectiveness analysis. PLoS One 7: e40808.

McKenzie R, O'Fallon A, Dale J, Demitrack M, Sharma G, Deloria M *et al*. (1998). Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. JAMA 280: 1061–1066.

Montoya JG, Kogelnik AM, Bhangoo M, Lunn MR, Flamand L, Merrihew LE *et al*. (2013). Randomized clinical trial to evaluate the efficacy and safety of valganciclovir in a subset of patients with chronic fatigue syndrome. J Med Virol 85: 2101–2109.

Moss-Morris R, Hamilton W (2010). Pragmatic rehabilitation for chronic fatigue syndrome. BMJ 340: c1799.

Moss-Morris R, Sharon C, Tobin R, Baldi JC (2005). A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. J Health Psychol 10: 245–259.

Myhill S, Booth NE, McLaren-Howard J (2009). Chronic fatigue syndrome and mitochondrial dysfunction. Int J Clin Exp Med 2: 1–16.

Myhill S, Booth NE, McLaren-Howard J (2013). Targeting mitochondrial dysfunction in the treatment of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) – a clinical audit. Int J Clin Exp Med 6: 1–15.

Navaneetharaja N, Griffiths V, Wileman T, Carding SR (2016). A role for the intestinal microbiota and virome in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)? J Clin Med 5; pii: E55.

Nicolson GL (2014). Mitochondrial dysfunction and chronic disease: treatment with natural supplements. Altern Ther Health Med 20: 18–25.

Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM (2012). Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. Lancet 379: 1412–1418.

Nijs J, Meeus M, De Meirleir K (2006). Chronic musculoskeletal pain in chronic fatigue syndrome: recent developments and therapeutic implications. Man Ther 11: 187–191.

Nijs J, Paul L, Wallman K (2008). Chronic fatigue syndrome: an approach combining self-management with graded exercise to avoid exacerbations. J Rehabil Med 40: 241–247.

Nijs J, van Eupen I, Vandecauter J, Augustinus E, Bleyen G, Moorkens G *et al*. (2009). Can pacing self-management alter physical behavior and symptom severity in chronic fatigue syndrome? A case series. J Rehabil Res Dev 46: 985–996.

Norberg B (1999). Turn of tide for oral vitamin B12 treatment. J Intern Med 246: 237–238.

Nunez M, Fernandez-Sola J, Nunez E, Fernandez-Huerta JM, Godas-Sieso T, Gomez-Gil E (2011). Health-related quality of life in patients with chronic fatigue syndrome: group cognitive behavioural therapy and graded exercise versus usual treatment. A randomised controlled trial with 1 year of follow-up. Clin Rheumatol 30: 381–389.

Pae CU, Marks DM, Patkar AA, Masand PS, Luyten P, Serretti A (2009). Pharmacological treatment of chronic fatigue syndrome: focusing on the role of antidepressants. Expert Opin Pharmacother 10: 1561–1570.

Patel MX, Smith DG, Chalder T, Wessely S (2003). Chronic fatigue syndrome in children: a cross sectional survey. Arch Dis Child 88: 894–898.

Peterson PK, Pheley A, Schroeppel J, Schenck C, Marshall P, Kind A *et al*. (1998). A preliminary placebo-controlled crossover trial of fludrocortisone for chronic fatigue syndrome. Arch Intern Med 158: 908–914.

Porter DA, Costill DL, Zachwieja JJ, Krzeminski K, Fink WJ, Wagner E *et al*. (1995). The effect of oral coenzyme Q10 on the exercise tolerance of middle-aged, untrained men. Int J Sports Med 16: 421–427.

Powell P, Bentall RP, Nye FJ, Edwards RH (2001). Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. BMJ 322: 387–390.

Price JR, Mitchell E, Tidy E, Hunot V (2008). Cognitive behaviour therapy for chronic fatigue syndrome in adults. Cochrane Database Syst Rev: CD001027.

Rashidi A, Oak E, Bartlett NL (2015). Maintenance rituximab every 2 months is more toxic than every 3 months in patients with non-Hodgkin lymphoma. Blood 125: 3354–3355.

Reeves WC, Jones JF, Maloney E, Heim C, Hoaglin DC, Boneva RS *et al.* (2007). Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. Popul Health Metr 5: 5.

Regland B, Forsmark S, Halaouate L, Matousek M, Peilot B, Zachrisson O *et al.* (2015). Response to vitamin B12 and folic acid in myalgic encephalomyelitis and fibromyalgia. PLoS One 10: e0124648.

Reid S, Chalder T, Cleare A, Hotopf M, Wessely S (2011). Chronic fatigue syndrome. BMJ Clin Evid pii: 1101.

Ridsdale L, Godfrey E, Chalder T, Seed P, King M, Wallace P *et al.* (2001). Chronic fatigue in general practice: is counselling as good as cognitive behaviour therapy? A UK randomised trial. Br J Gen Pract 51: 19–24.

Rimes KA, Chalder T (2005). Treatments for chronic fatigue syndrome. Occup Med (Lond) 55: 32–39.

Rowe PC, Calkins H, DeBusk K, McKenzie R, Anand R, Sharma G *et al.* (2001). Fludrocortisone acetate to treat neurally mediated hypotension in chronic fatigue syndrome: a randomized controlled trial. JAMA 285: 52–59.

Sanders P, Korf J (2008). Neuroaetiology of chronic fatigue syndrome: an overview. World J Biol Psychiatry 9: 165–171.

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

Sharpe M (1991). Psychiatric management of PVFS. Br Med Bull 47: 989–1005.

Sharpe M, Goldsmith KA, Johnson AL, Chalder T, Walker J, White PD (2015). Rehabilitative treatments for chronic fatigue syndrome: long-term follow-up from the PACE trial. Lancet Psychiatry 2: 1067–1074.

Sheedy JR, Wettenhall RE, Scanlon D, Gooley PR, Lewis DP, McGregor N *et al.* (2009). Increased d-lactic Acid intestinal bacteria in patients with chronic fatigue syndrome. In Vivo 23: 621–628.

Smith ME, Haney E, McDonagh M, Pappas M, Daeges M, Wasson N *et al.* (2015). Treatment of myalgic encephalomyelitis/chronic fatigue syndrome: a systematic review for a national institutes of health pathways to prevention workshop. Ann Intern Med 162: 841–850.

Smits LP, Bouter KE, de Vos WM, Borody TJ, Nieuwdorp M (2013). Therapeutic potential of fecal microbiota transplantation. Gastroenterology 145: 946–953.

Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SPH *et al.* (2016). The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 44 (Database Issue): D1054–D1068.

Straus SE, Dale JK, Tobi M, Lawley T, Preble O, Blaese RM *et al.* (1988). Acyclovir treatment of the chronic fatigue syndrome. Lack of efficacy in a placebo-controlled trial. N Engl J Med 319: 1692–1698.

Strayer DR, Carter WA, Brodsky I, Cheney P, Peterson D, Salvato P *et al.* (1994). A controlled clinical trial with a specifically configured RNA drug, poly(I).poly(C12U), in chronic fatigue syndrome. Clin Infect Dis 18 (Suppl 1): S88–S95.

Strayer DR, Carter WA, Stouch BC, Stevens SR, Bateman L, Cimoch PJ *et al.* (2012). A double-blind, placebo-controlled, randomized, clinical trial of the TLR-3 agonist rintatolimod in severe cases of chronic fatigue syndrome. PLoS One 7: e31334.

Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G (2005). Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ 330: 14.

Suhadolnik RJ, Peterson DL, O'Brien K, Cheney PR, Herst CV, Reichenbach NL *et al.* (1997). Biochemical evidence for a novel low molecular weight 2-5A-dependent RNase L in chronic fatigue syndrome. J Interferon Cytokine Res 17: 377–385.

Suhadolnik RJ, Reichenbach NL, Hitzges P, Adelson ME, Peterson DL, Cheney P *et al.* (1994). Changes in the 2-5A synthetase/RNase L antiviral pathway in a controlled clinical trial with poly(I)-poly(C12U) in chronic fatigue syndrome. In Vivo 8: 599–604.

Sutcliffe K, Gray J, Tan MP, Pairman J, Wilton K, Parry SW*et al.* (2010). Home orthostatic training in chronic fatigue syndrome--a randomized, placebo-controlled feasibility study. Eur J Clin Invest 40: 18–24.

Swanink CM, Vercoulen JH, Bleijenberg G, Fennis JF, Galama JM, van der Meer JW (1995). Chronic fatigue syndrome: a clinical and laboratory study with a well matched control group. J Intern Med 237: 499–506.

Theoharides TC, Asadi S, Weng Z, Zhang B (2011). Serotonin-selective reuptake inhibitors and nonsteroidal anti-inflammatory drugs – important considerations of adverse interactions especially for the treatment of myalgic encephalomyelitis/chronic fatigue syndrome. J Clin Psychopharmacol 31: 403–405.

Tummers M, Knoop H, Bleijenberg G (2010). Effectiveness of stepped care for chronic fatigue syndrome: a randomized noninferiority trial. J Consult Clin Psychol 78: 724–731.

Twisk FN, Maes M (2009). A review on cognitive behavorial therapy (CBT) and graded exercise therapy (GET) in myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS): CBT/GET is not only ineffective and not evidence-based, but also potentially harmful for many patients with ME/CFS. Neuro Endocrinol Lett 30: 284–299.

Van Cauwenbergh D, De Kooning M, Ickmans K, Nijs J (2012). How to exercise people with chronic fatigue syndrome: evidence-based practice guidelines. Eur J Clin Invest 42: 1136–1144.

Vermeulen RC, Scholte HR (2004). Exploratory open label, randomized study of acetyl- and propionylcarnitine in chronic fatigue syndrome. Psychosom Med 66: 276–282.

Wallis A, Butt H, Ball M, Lewis DP, Bruck D (2016). Support for the microgenderome invites enquiry into sex differences. Gut Microbes 6: 19171.

Wallman KE, Morton AR, Goodman C, Grove R, Guilfoyle AM (2004). Randomised controlled trial of graded exercise in chronic fatigue syndrome. Med J Aust 180: 444–448.

Warren G, McKendrick M, Peet M (1999). The role of essential fatty acids in chronic fatigue syndrome. A case-controlled study of red-cell membrane essential fatty acids (EFA) and a placebo-controlled treatment study with high dose of EFA. Acta Neurol Scand 99: 112–116.

Wearden AJ, Dowrick C, Chew-Graham C, Bentall RP, Morriss RK, Peters S *et al.* (2010). Nurse led, home based self help treatment for patients in primary care with chronic fatigue syndrome: randomised controlled trial. BMJ 340: c1777.

Wearden AJ, Dunn G, Dowrick C, Morriss RK (2012). Depressive symptoms and pragmatic rehabilitation for chronic fatigue syndrome. Br J Psychiatry 201: 227–232.

Wearden AJ, Emsley R (2013). Mediators of the effects on fatigue of pragmatic rehabilitation for chronic fatigue syndrome. J Consult Clin Psychol 81: 831–838.

Wearden AJ, Morriss RK, Mullis R, Strickland PL, Pearson DJ, Appleby L *et al.* (1998). Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. Br J Psychiatry 172: 485–490.

White PD, Goldsmith K, Johnson AL, Chalder T, Sharpe M (2013). Recovery from chronic fatigue syndrome after treatments given in the PACE trial. Psychol Med 43: 2227–2235.

White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC *et al.* (2011). Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet 377: 823–836.

White PD, Sharpe MC, Chalder T, DeCesare JC, Walwyn R (2007). Protocol for the PACE trial: a randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy. BMC Neurol 7: 6.

Whiting P, Bagnall AM, Sowden AJ, Cornell JE, Mulrow CD, Ramirez G (2001). Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. JAMA 286: 1360–1368.

Wiborg JF, Knoop H, Stulemeijer M, Prins JB, Bleijenberg G (2010). How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. Psychol Med 40: 1281–1287.

Wiborg JF, van Bussel J, van Dijk A, Bleijenberg G, Knoop H (2015). Randomised controlled trial of cognitive behaviour therapy delivered in groups of patients with chronic fatigue syndrome. Psychother Psychosom 84: 368–376.

Wiebe E (1996). N of 1 trials. Managing patients with chronic fatigue syndrome: two case reports. Can Fam Physician 42: 2214–2217.

Windgassen S, Goldsmith K, Moss-Morris R, Chalder T (2016). Establishing how psychological therapies work: the importance of mediation analysis. J Ment Health 25: 93–99.

Zachrisson O, Colque-Navarro P, Gottfries CG, Regland B, Mollby R (2004). Immune modulation with a staphylococcal preparation in fibromyalgia/chronic fatigue syndrome: relation between antibody levels and clinical improvement. Eur J Clin Microbiol Infect Dis 23: 98–105.