Sanne Kreijkamp-Kaspers
Ekua Weba Brenu
Sonya Marshall
Don Staines
Mieke L Van Driel

Treating chronic fatigue syndrome

A study into the scientific evidence for pharmacological treatments

Background
Chronic fatigue syndrome, or myalgic encephalomyelitis (CFS), is a severe disabling condition. Patients with CFS usually trial many different medicines, both conventional and complementary. An overview of the pharmacological treatments used by CFS patients and the available evidence underpinning the use of these treatments would be of great value to both patients and their healthcare providers.

Methods
Ninety-four CFS patients recruited into an Australian study investigating immunological biomarkers filled out a questionnaire assessing the medicines they were taking. Evidence from randomised clinical trials was sought in biomedical databases.

Results
The 94 CFS patients used 474 different medicines and supplements. The most commonly used medicines were antidepressants, analgesics, sedatives, and B vitamins. We identified 20 randomised controlled trials studying these medicines in CFS patients.

Conclusion
While conventional and complementary medicines are widely used by CFS patients, the evidence for effectiveness in CFS is very limited.

Keywords: chronic fatigue syndrome; drug therapy; complementary therapies; vitamins

Chronic fatigue syndrome (CFS), also referred to as myalgic encephalomyelitis, is a disabling condition.[1,2] In addition to fatigue for more than 6 months that is not relieved by sleep and interferes with activities of daily life, patients suffer other symptoms such as cognitive impairment, muscle and joint pains and sore throat.[3] The diagnostic criteria for CFS are outlined in *Table 1*.

Table 1. Diagnostic criteria for chronic fatigue syndrome[3]

- Unexplained, persistent fatigue that is not due to ongoing exertion; is not substantially relieved by rest; is of new onset (not lifelong); and results in a significant reduction in previous levels of activity
- Four or more of the following symptoms are present for 6 months or more:
  - impaired memory or concentration
  - postexertional malaise (extreme, prolonged exhaustion and sickness following physical or mental activity)
  - unrefreshing sleep
  - muscle pain
  - multijoint pain without swelling or redness
  - headaches of a new type or severity
  - sore throat that is frequent or recurring
  - tender cervical or axillary lymph nodes

The aetiology of CFS is still poorly understood, despite extensive research into the possible causes. The most recent consensus document describes how current research indicates the presence of widespread inflammation and multisystem neuropathology as underlying pathophysiological process with dysregulation of the central nervous system, immune system and cellular energy metabolism.[4] However, an underlying cause for the observed abnormalities is still lacking. This is reflected in the multiple different treatments used by patients, both conventional and complementary and alternative medicines (CAMs).[5] The financial impact of CFS is considerable. A United States of America study calculated direct medical costs of US$2342–8675 per patient per year, while indirect costs were estimated to be on average US$20 000 per patient per year due to loss of income. The inability to work of both patient and carers adds significantly to the financial impact of this disease. This equates to a total cost of at least $18 billion per year in the USA alone.[1,6–8]

Patients with CFS often turn to their primary care physician or alternative healthcare provider for advice and support.[9,10] For example, CFS patients in the United Kingdom were more likely to have seen a complementary or alternative healthcare provider than a physiotherapist or psychologist in a 6 month timeframe,[10] while graded exercise and cognitive behavioural therapy (CBT) are recommended first line treatments.[11,12] Doctors often feel frustrated and powerless as they have very little to offer patients in terms of 'fixing' their condition. The recommended treatment modalities at present are CBT and graded exercise, which are not well accepted by patients and unlikely to lead to a full recovery in most patients.[13]

As part of a study into the immunological markers of CFS we explored which pharmacological treatments CFS patients are taking and if these treatments are supported by evidence from clinical trials.

Methods

Recruitment

Participants were recruited from Queensland and New South Wales through CFS support groups and newspaper and email advertisements into a prospective study investigating potential immunological biomarkers for CFS.[14] Patients previously diagnosed with autoimmune disorders, psychosis, epilepsy, heart disease, or who were pregnant or breastfeeding were excluded. All patients met the1994 CDC criteria for CFS.[3]

Ethics approval was obtained from the Bond University Human Research Ethics Committee.

Data collection

All patients included in the study in July 2010 filled out a questionnaire that included questions on the current use of medicines and supplements. Medicines or supplements that were not listed as 'registered medicine' with the Australian Therapeutic Goods Administration were labelled as CAM and categorised into three groups: vitamins, minerals and supplements.

Literature survey

We systematically searched for evidence from randomised controlled trials (RCTs) for each of the medicine groups used by CFS patients using MEDLINE (PubMed 1960 to June 2010) and the Cochrane Library (until June 2010). We also used bibliographies of review articles identified. We used MeSH headings and keywords including: 'chronic fatigue', 'chronic fatigue syndrome', 'myalgic encephalomyelitis', 'treatment' and 'medication' and repeated the searches for the individual medicines and medicine groups (eg. antidepressant, individual vitamins). We applied limits for study type 'clinical trial'. As we were interested in the evidence for effectiveness of each of the treatments, we searched for RCTs that provide a high level of evidence (Level 2 as graded by the National Health and Medical Research Council [www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp30.pdf]). We excluded trials that were not randomised, lacked blinding or without a control group. The methodology of RCTs minimises the risk of known and unknown biases, including the placebo effect, the influence of the characteristics of the treating doctor, patient preferences and disease severity.

Results

Medicine and supplement use

Our study population comprised 94 participants fulfilling the criteria for CFS. Their average age was 47 years (range 20–66 years) and 67 were (71%) women (*Table 2*). They used 474 different medicines and CAMs, including 220 conventional and 254 CAMs with an average of 5.0 per patient (*Table 3*).

The most commonly used conventional medicines were those acting on the central nervous system, including antidepressants (41% of patients) and sedatives (27%). Likewise, analgesics were frequently used, mainly simple analgesics (eg. paracetamol, nonsteroidal anti-inflammatory drugs [NSAIDs]), but 13% of patients used opiates (tramadol or oxycodone).

While CAMs included a wide range of medicines, 47% of patients reported the use of some form of B vitamins, 24% used magnesium and 7% were taking a co-enzyme Q10 supplement.

Literature survey

Our search strategy identified 61 studies in PubMed, of which 18 were RCTs investigating one of the treatments used by our participants. The additional two RCTs were found tracking the references of review articles. This resulted in 20 RCTs. Five RCTs involved antidepressants, the most commonly used medicine in our study population. The trials identified and their outcomes are listed in *Table 4*. Only one of these five studies reported a statistically significant improvement in symptoms in CFS patients.[15] However, this effect was only observed in patients who had received 12 weeks of CBT before starting treatment with mirtazepine. Concomitant treatment with mirtazepine and CBT did not result in an additional benefit compared to placebo. We did not find any RCTs investigating the effect of analgesics in CFS patients. Five trials studied the effect of adrenal gland hormones (eg. fludrocortisone), but benefit was only reported in two of the five studies.[16]

A recent Cochrane review[17] assessed the evidence for traditional Chinese herbs in CFS and concluded that none of the available studies was of sufficient methodological quality to be pooled in meta-analysis. While vitamins and minerals were widely used we could not find any RCTs studying CFS patients. One study with magnesium injections reported a significant improvement of symptoms.[18] The positive effects of an essential fatty acid supplement in postviral fatigue[19] found in one trial were not confirmed in a second trial.[20]

Discussion

Our study into Australian CFS patients shows that they use a wide array of medicines (prescribed and over-the-counter) and CAMs, but strong evidence for effectiveness of any of these treatments is lacking.

Other studies confirm the use of multiple medicines by CFS patients.[5,10] Patients are desperate to try anything, hoping to find some relief for their disabling symptoms. But polypharmacy often comes at a price – the risk of harm – emphasising the need for clarity about the benefits.[21] Our study raises several issues, including the limited availability of evidence and equivocal results, concerns for potential harm of polymedication, and the need for patient focused research to advance the search for effective treatments in CFS.

Availability of evidence

The paucity of RCTs evaluating efficacy of pharmacological treatments in CFS patients is

Table 2. Baseline characteristics of the study population comprising 94 chronic fatigue syndrome patients

Age	Mean	SD	Range
Age (years)	46.5	12.2	20–66
Height (cm)	168	17	147–196
Weight (kg)	71.2	14.3	45–120
	N	%	
Female	67	71.3	
Male	27	28.7	

Table 3. Conventional and complementary medicines use in a group of 94 chronic fatigue syndrome patients

Medicine (total 220 for 94 patients)	N*	Number of RCTs	Results
Antidepressants	39	5	Four no effect[22–25] One small effect only if preceded by CBT[15]
Simple analgesia (paracetamol, aspirin, NSAIDs)	35	0	
Sedative and hypnotics (benzodiazepines)	25	0	
Opioids	12	0	
Gonadal hormones (eg. hormone therapy, testosterone)	9	0	
Thyroxine	5	0	
Antiviral medicine (eg. valaciclovir)	4	1	No effect[35]
Pregabalin	3	0	
Antihistamines	3	1	No effect[36]
Adrenal hormones (eg. hydrocortisone/ fludrocortisones)	2	5	Three no effect[37-39] Two short term effect[16,28]
Other†	137		
Supplements (total 119)			
Fish oil	19	2	One no effect[20] One effect in postviral fatigue[19]
DHEA	9	0	
Co-enzyme Q10	7	0	
Melatonin	4	1	No effect[40]
Evening primrose oil	3	1	No effect[20]
Homeopathic treatment	2	1	Minor improvement[41]
Ginseng	1	1	No effect[42]
Other†	74		
Minerals (total 63)			
Magnesium	23	1	Significant effect (intramuscular injection)[18]
Zinc	13	0	
Calcium	12	0	
Iron	5	0	
Other†	10		
Vitamins (total 72)			
Vitamin B	44	1	No effect on functional status (injectable bovine liver extract)[43]
Multivitamins	18	1	No effect (polynutrient supplement)[44]
Other†	10		

* Number of times used by our study population

† Medicines and supplements used by maximum three patients with no identified trials or used for other indications (eg. statins, blood pressure medicine, asthma inhalers, contraception, eye drops)

striking and in contrast with the widely studied nonpharmacological interventions for this condition.[11,12] Most published studies identified by our literature search lack control groups, are not randomised or blinded, and thus are at a high risk of bias.

Frequently used analgesics, from simple over-the-counter to restricted prescription only narcotic analgesics have never been studied in head-to-head RCTs in CFS patients. Likewise, we found no trials studying hormonal products, such as gonadal hormones and thyroxine. The paucity of trials with vitamins and mineral or nutritional supplements is perhaps less surprising, but these products are widely used and account for large out-of-pocket expenses. However, the identified lack of evidence is not necessarily also evidence for a lack of effect, and clinical studies investigating the benefit and harm of unlimited and multiple uses of these popular products in chronic conditions such as CFS are urgently needed.

Some treatments reported in our survey have been studied in clinical trials, but the number of trials is small and the results of the available studies are equivocal. For example, we found no convincing evidence for an effect of antidepressants (used by 40% of patients in our survey). Of the five trials identified in our literature search only one study reported a small effect, but only if antidepressant treatment was preceded by CBT.[15] In all other trials no benefit of antidepressants was reported.[22–25] Interestingly, antidepressants have been shown to improve symptoms in fibromyalgia,[26] which has some overlapping symptoms with CFS.[27] Unfortunately we did not have information about the indications for the antidepressant medicine. Depression and mood disturbance is common in CFS patients and it is possible that some antidepressants are prescribed for comorbid conditions rather than CFS itself.

The RCT with intramuscular magnesium injections showed a promising result,[18] but the study was only short term (6 weeks) and it is not clear if oral magnesium supplements (taken by our surveyed patients) produce the same benefit, as oral absorption is poor and high doses might cause diarrhoea. The positive effect of adrenal hormones reported in two of the five trials should be regarded in the context of the associated risks

Table 4. Medicines taken and relevant randomised controlled trial

Study	Intervention	Number of participants	Duration of the intervention	Main outcome measures
Vercoulen[22]	Fluoxetine 20 mg	44 depressed CFS patients 52 nondepressed CFS patients	8 weeks	Subjective fatigue scale, self rated fatigue, Beck Depression Inventory, actometer, neuropsychological tests
Wearden[23]	Fluoxetine 20 mg +/- exercise	136 CFS patients	26 weeks	Fatigue questionnaire, SF-36, Hospital Anxiety and Depression Scale HADS
Natelson[24]	Phenelzine 15 mg	25 CFS patients	4 weeks	Six self rated questionnaires including Functional Status Questionnaire
Stubhaug[15]	Mirtazepine 15–45 mg +/- CBT	72 CFS patients	12–24 weeks (double crossover)	Main outcomes fatigue and global clinical impression, several secondary outcomes
Hickie[25]	Moclobemide 450–600 mg	90 CFS patients	6 weeks	Karnofsky Performance Index (investigator rated), patient rated global improvement, profile of mood states, general health questionnaire, immune responsiveness
Lerner[35]	IV valaciclovir	19 CFS patients, diagnosed <1 year	6 months	CFS energy index point score, several cardiac outcomes
Steinberg[36]	Terfenadine 60 mg bd	30 CFS patients	2 months	Self rated symptom questionnaire
Blockmans[37]	5 mg hydrocortisone and 50 µg 9-alfa-fludrocortisone	100 CFS patients	3 months, crossover	Several questionnaires including self rated fatigue, SF-36, depression questionnaire
Rowe[38]	Fludrocortisone acetate 0.1 mg	100 CFS patients with neurally mediated hypotension	9 weeks	Percentage improved at least 15 points on 100 point global impression scale
Petersen[39]	Fludrocortisone 0.1–0.2 mg	25 CFS patients	6 weeks	Self rated questionnaires, symptoms severity scales
McKenzie[16]	Hydrocortisone oral, 16 mg/m^2	70 CFS patients	12 weeks	Main: 5 or more point improvement on global wellness scale; secondary: several other scales
Cleare[28]	Hydrocortisone 5–10 mg	23 CFS patients	1 month crossover	Self reported fatigue scores
Behan[19]	Essential fatty acids	63 postviral CFS patients	3 months	Doctor with patient assessed overall condition, fatigue, myalgia, dizziness, poor concentration and depression on a 3-point scale
Warren[20]	Efol marine (fishoil + evening primrose oil)	50 CFS patients	3 months	Symptoms checklist, Beck depression inventory
Williams[40]	5 mg melatonin at night	30 CFS patients	12 weeks, crossover	Visual analogue scales, SF-36, health survey, mental fatigue inventory and HADS
Weatherly-Jones[41]	Individualised homeopathic treatment	103 CFS patients	6 months	Primary: multidimensial fatigue inventory; secondary: fatigue impact scale
Hartz[42]	Siberian ginseng	96 CFS patients	2 months	Fatigue measures
Cox[18]	IM magnesium	32 CFS patients	6 weeks	Nottingham Health Profile, proportion improved
Kaslow[43]	Bovine liver extract containing folic acid and cyanocobalamin	15 CFS patients	Single injection, crossover	Several criteria of functional status
Brouwers[44]	Polynutrient supplement	53 CFS patients	10 weeks	CIS fatigue score, number of CDC symptoms of CFS and SIP8 score

Results
No differences on any of the outcome measures, including depression
No difference for fluoxetine on fatigue or SF-36; at 13 weeks small difference for depression but not at 26 weeks
No difference on between the treatment and placebo group on any of the individual questionnaires
Only significant difference in group receiving CBT first followed by mirtazepine, not in group with start on mirtazepine followed by CBT
No significant differences for patient or investigator reported outcomes
No statistically significant differences
No significant differences
No significant differences
No significant differences
No significant differences
Greater percentage (53% vs. 29%; p=0.04) recording an improvement in wellness score, no significant differences on the other scales
Significant improvements in the hydrocortisone group
87% rated themselves as improved versus 17% taking placebo (p<0.001)
No significant differences
No significant differences
No statistically significant differences
No significant differences
80% improved versus 17% in placebo (difference 62%, 95% CI: 35–90)
No significant differences
No significant differences

with long term adrenal gland suppression, which would preclude its use in a chronic condition such as CFS.[16,28]

The frequent concomitant use of multiple drugs (prescription and over-the-counter) is of concern. Benzodiazepines and opiates, often used together, may ameliorate symptoms such as muscle pain and insomnia on the short term. But both groups of medicines can be addictive and lose effectiveness with long term use. Once started, it is often difficult to wean patients off.

The notion that 'if it's natural, it's safe' does not always hold true. Several studies have suggested that dehydroepiandrosterone (DHEA), a steroid precursor, is deficient in CFS patients,[29,30] but no trials have investigated the effectiveness of DHEA as a treatment for CFS. In Australia, DHEA is available as a natural supplement from healthfood stores, whereas in other countries such as Canada, it is available on prescription only. Dehydroepiandrosterone is not without risks, as it can cause increase in luteinising hormone and oestrogen levels as well as unfavourable changes in lipid profiles;[31,32] it is listed as a prohibited substance in the world antidoping code (www.wada-ama.org).

The high intake of medicines puts a strain, both financially and emotionally, on CFS patients and their families. Unwillingness to try 'all treatments available' might be seen as 'not wanting to get better'. The severity of symptoms fluctuates in CFS, and temporary improvements might mistakenly be attributed to the treatments used. Therefore, it is important that more evidence from randomised and blinded clinical trials becomes available. As research into effective treatments for CFS still lacks a clear direction and the list of potentially effective treatments is long, other ways of identifying targets for research are needed. A way forward could be making use of patient and prescribing clinician experiences. For example, in Horton's[33] study patients were asked which doctors had been helpful in managing their condition followed by interviews of the doctors identified aiming to identify the characteristics of the 'helpful doctor'. In another example, Frost et al[34] analysed online patient reported treatment histories and drug evaluations in order to learn about the effect of off-label use of medicines in different medical conditions.

Chronic fatigue syndrome patients and their clinicians have experiences with a large number of pharmacological treatments and often have a clear idea of what works and what doesn't work for them. Systematically analysing these reports might assist in prioritising the research agenda.

Conclusion

Our study has illustrated the wide range of seemingly unrelated medicines and CAMs taken by CFS patients. The absence of sufficient and unequivocal evidence for effectiveness to underpin use of these medicines provides testimony of the therapeutic no-man's-land surrounding CFS. Our overview of the limited evidence base for currently popular treatments for CFS may be disappointing to patients, and their doctors. However, knowledge of the evidence base allows us to make informed decisions. Patient focused input is needed to help set priorities for further clinical research that could lead to better guidance for the management of this condition.

Authors

Sanne Kreijkamp-Kaspers MD, PhD, FRACGP, MSc, is Assistant Professor, Academic General Practice, Faculty of Health Sciences & Medicine, Bond University, Gold Coast, Queensland
skreijka@bond.edu.au

Ekua Weba Brenu HBSc, GradDip, is a PhD candidate, Faculty of Health Sciences & Medicine, Bond University, Gold Coast, Queensland

Sonya Marshall PhD, BSc(Hons), is Associate Professor, Department of Biomedical Sciences, Bond University, Gold Coast, Queensland

Don Staines MBBS, MPH, FAFPHM, FAFOEM, is Public Health Medical Officer, Queensland Health – Gold Coast Public Health Unit, Gold Coast, Queensland

Mieke L Van Driel MD, MSc, PhD, is Professor of General Practice, Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland and Department of General Practice and Primary Health Care, Ghent University, Belgium.

Conflict of interest: none declared.

References

1. Assefi NP, Coy TV, Uslan D, Smith WR, Buchwald D. Financial, occupational, and personal consequences of disability in patients with chronic fatigue syndrome and fibromyalgia compared to other fatiguing conditions. J Rheumatol 2003;30:804–8.

2. Cairns R, Hotopf M. A systematic review describing the prognosis of chronic fatigue syndrome. Occup Med 2005;55:20–31.
3. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;121:953–9.
4. Carruthers BM, van de Sande MI, De Meirleir KL, et al. Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med 2011 doi: 10.1111/j.1365–2796.2011.02428.x (ePub ahead of print).
5. Boneva RS, Lin JM, Maloney EM, Jones JF, Reeves WC. Use of medications by people with chronic fatigue syndrome and healthy persons: a population-based study of fatiguing illness in Georgia. Health Qual Life Outcomes 2009;7:67.
6. Jason LA, Benton MC, Valentine L, Johnson A, Torres-Harding S. The economic impact of ME/CFS: individual and societal costs. Dyn Med 2008;7:6.
7. McCrone P, Darbishire L, Ridsdale L, Seed P. The economic cost of chronic fatigue and chronic fatigue syndrome in UK primary care. Psychol Med 2003;33:253–61.
8. Reynolds KJ, Vernon SD, Bouchery E, Reeves WC. The economic impact of chronic fatigue syndrome. Cost Eff Resour Alloc 2004;2:4.
9. Bombardier CH, Buchwald D. Chronic fatigue, chronic fatigue syndrome, and fibromyalgia. Disability and health-care use. Med Care 1996;34:924–30.
10. Sabes-Figuera R, McCrone P, Hurley M, King M, Donaldson AN, Ridsdale L. The hidden cost of chronic fatigue to patients and their families. BMC Health Serv Res 2010;10:56.
11. Price JR, Mitchell E, Tidy E, Hunot V. Cognitive behaviour therapy for chronic fatigue syndrome in adults. Cochrane Database Syst Rev 2008(3):CD001027.
12. Edmonds M, McGuire H, Price J. Exercise therapy for chronic fatigue syndrome. Cochrane Database Syst Rev 2004(3):CD003200.
13. White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet 2011;377:823–36.
14. Brenu EW, van Driel ML, Staines DR, et al. Immunological abnormalities as potential biomarkers in chronic fatigue syndrome/myalgic encephalomyelitis. J Transl Med 2011;9:81.
15. Stubhaug B, Lie SA, Ursin H, Eriksen HR. Cognitive-behavioural therapy v. mirtazapine for chronic fatigue and neurasthenia: randomised placebo-controlled trial. Br J Psychiatry 2008;192:217–23.
16. McKenzie R, O'Fallon A, Dale J, et al. Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. JAMA 1998;280:1061–6.
17. Adams D, Wu T, Yang X, Tai S, Vohra S. Traditional Chinese medicinal herbs for the treatment of idiopathic chronic fatigue and chronic fatigue syndrome. Cochrane Database Syst Rev 2009(4):CD006348.
18. Cox IM, Campbell MJ, Dowson D. Red blood cell magnesium and chronic fatigue syndrome. Lancet 1991;337:757–60.
19. Behan PO, Behan WM, Horrobin D. Effect of high doses of essential fatty acids on the postviral fatigue syndrome. Acta Neurol Scand 1990;82:209–16.
20. Warren G, McKendrick M, Peet M. 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 1999;99:112–6.
21. Salazar JA, Poon I, Nair M. Clinical consequences of polypharmacy in elderly: expect the unexpected, think the unthinkable. Expert Opin Drug Saf 2007;6:695–704.
22. Vercoulen JH, Swanink CM, Zitman FG, et al. Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. Lancet 1996;347:858–61.
23. Wearden AJ, Morriss RK, Mullis R, et al. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. Br J Psychiatry 1998;172:485–90.
24. Natelson BH, Cheu J, Pareja J, Ellis SP, Policastro T, Findley TW. Randomized, double blind, controlled placebo-phase in trial of low dose phenelzine in the chronic fatigue syndrome. Psychopharmacology 1996;124:226–30.
25. Hickie IB, Wilson AJ, Wright JM, Bennett BK, Wakefield D, Lloyd AR. A randomized, double-blind placebo-controlled trial of moclobemide in patients with chronic fatigue syndrome. J Clin Psychiatry 2000;61:643–8.
26. Hauser W, Bernardy K, Uceyler N, Sommer C. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. JAMA 2009;301:198–209.
27. Buchwald D. Fibromyalgia and chronic fatigue syndrome: similarities and differences. Rheum Dis Clin North Am 1996;22:219–43.
28. Cleare AJ, Heap E, Malhi GS, Wessely S, O'Keane V, Miell J. Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial. Lancet 1999;353:455–8.
29. Maes M, Mihaylova I, De Ruyter M. Decreased dehydroepiandrosterone sulfate but normal insulin-like growth factor in chronic fatigue syndrome (CFS): relevance for the inflammatory response in CFS. Neuro Endocrinol Lett 2005;26:487–92.
30. Kuratsune H, Yamaguti K, Sawada M, et al. Dehydroepiandrosterone sulfate deficiency in chronic fatigue syndrome. Int J Mol Med 1998;1:143–6.
31. Ballantyne CS, Phillips SM, MacDonald JR, Tarnopolsky MA, MacDougall JD. The acute effects of androstenedione supplementation in healthy young males. Can J Appl Physiol 2000;25:68–78.
32. Broeder CE, Quindry J, Brittingham K, et al. The Andro Project: physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high-intensity resistance training program. Arch Intern Med 2000;160:3093–104.
33. Horton SM, Poland F, Kale S, et al. Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in adults: a qualitative study of perspectives from professional practice. BMC Fam Pract 2010;11:89.
34. Frost J, Okun S, Vaughan T, Heywood J, Wicks P. Patient-reported outcomes as a source of evidence in off-label prescribing: analysis of data from PatientsLikeMe. J Med Internet Res 2011;13:e6.
35. Lerner AM, Zervos M, Chang CH, et al. A small, randomized, placebo-controlled trial of the use of antiviral therapy for patients with chronic fatigue syndrome. Clin Infect Dis 2001;32:1657–8.
36. Steinberg P, McNutt BE, Marshall P, et al. Double-blind placebo-controlled study of the efficacy of oral terfenadine in the treatment of chronic fatigue syndrome. J Allergy Clin Immunol 1996;97:119–26.
37. Blockmans D, Persoons P, Van Houdenhove B, Lejeune M, Bobbaers H. 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 2003;114:736–41.
38. Rowe KS. Double-blind randomized controlled trial to assess the efficacy of intravenous gammaglobulin for the management of chronic fatigue syndrome in adolescents. J Psychiatr Res 1997;31:133–47.
39. Peterson PK, Pheley A, Schroeppel J, et al. A preliminary placebo-controlled crossover trial of fludrocortisone for chronic fatigue syndrome. Arch Intern Med 1998;158:908–14.
40. Williams G, Waterhouse J, Mugarza J, Minors D, Hayden K. Therapy of circadian rhythm disorders in chronic fatigue syndrome: no symptomatic improvement with melatonin or phototherapy. Eur J Clin Invest 2002;32:831–7.
41. Weatherley-Jones E, Nicholl JP, Thomas KJ, et al. A randomised, controlled, triple-blind trial of the efficacy of homeopathic treatment for chronic fatigue syndrome. J Psychosom Res 2004;56:189–97.
42. Hartz AJ, Bentler S, Noyes R, et al. Randomized controlled trial of Siberian ginseng for chronic fatigue. Psychol Med 2004;34:51–61.
43. Kaslow JE, Rucker L, Onishi R. Liver extract-folic acid-cyanocobalamin vs placebo for chronic fatigue syndrome. Arch Intern Med 1989;149:2501–3.
44. Brouwers FM, Van Der Werf S, Bleijenberg G, Van Der Zee L, Van Der Meer JW. The effect of a polynutrient supplement on fatigue and physical activity of patients with chronic fatigue syndrome: a double-blind randomized controlled trial. QJM 2002;95:677–83.

correspondence **afp@racgp.org.au**