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IN-DEPTH REVIEW

Treatments for chronic fatigue syndrome

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Aims	To review studies evaluating the treatment of chronic fatigue and chronic fatigue syndrome, to describe predictors of response to treatment and to discuss the role of the occupational health physician.
Methods	A literature search was carried out using Medline and PsychInfo.
Results	Studies evaluating cognitive behaviour therapy, graded exercise therapy, pharmacological interventions (e.g. antidepressants and corticosteroids), immunological interventions and nutritional supplements were reviewed. The most promising results have been found with cognitive behaviour therapy and graded exercise therapy, and some predictors of outcome have been identified. Most of the other interventions were evaluated in just one or two studies and therefore evidence is insufficient to draw firm conclusions.
Conclusions	By applying the models of fatigue that form the bases for cognitive behaviour therapy and graded exercise therapy, occupational health physicians may play an important role in helping the patients with chronic fatigue syndrome to reduce their symptoms, improve their functioning and return to work.
Key words	Chronic fatigue syndrome (CFS); cognitive behaviour therapy (CBT); graded exercise therapy (GET); intervention; treatment.

Introduction

Fatigue is very common both in primary and in secondary care patients. It may be best viewed on a continuum with fatigue as a symptom at one end of the spectrum and chronic fatigue syndrome (CFS) and its associated disability at the other end. This paper describes the treatment trials of different interventions, outlines the current understandings of how acute fatigue can develop into a chronic condition and discusses the implications for occupational health physicians.

Method

A literature search was undertaken for the trials of interventions for CFS using electronic databases (Medline 1996 onwards and PsychInfo 1985 onwards) and reference lists. The search strategies were chronic fatigue or post-viral fatigue or post-viral fatigue or myalgic encephalitis or myalgic encephalomyelitis and trial or treatment or intervention.

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Results

Cognitive behaviour therapy (CBT)

Cognitive-behavioural treatments for CFS focus mainly on the factors that may be maintaining fatigue (discussed in more detail later in this article) rather than those that may have initially triggered it. CBT for this condition generally involves planned activity and rest, graded increases in activity, a sleep routine and cognitive restructuring of unhelpful beliefs and assumptions. Three of the four randomized controlled trials (RCTs) comparing CBT with a control condition found a positive effect of the treatment [1–3]. One of these studies found that some positive outcomes remained at 5-year follow-up [4]. The fourth RCT [5] and a controlled trial [6] did not find the overall beneficial effects of CBT, but the duration of the intervention in both the studies was much shorter than in the other three RCTs. The content of the CBT was also different in these two trials compared with

the other three trials; for example, the former did not attempt cognitive reappraisal and the latter encouraged limitation of activities rather than a gradual increase. Although CBT appears effective, it does not help all the patients. Predictors of the outcome are discussed below.

Predictors of response to CBT

Poor social and occupational functioning prior to becoming ill predicted poor outcome in one study of CBT [7]. Another trial identified three baseline predictors of a poor outcome: a low sense of control in relation to CFS complaints, a very passive activity pattern and a high level of focusing on bodily symptoms [2]. In the third trial [8], the poor outcome was associated with taking medical retirement or making a new claim for a disability-related benefit during treatment, although the numbers involved were small. In the same trial, patients who at follow-up continued to believe that they should avoid exercise were more likely to be unimproved at 6-month follow-up. However, the direction of causality is unclear, as it is possible that beliefs about avoidance persist as a consequence rather than a cause of unsuccessful treatment. Attributing the illness to physical causes (e.g. a virus) did not affect the outcome. This contradicts the findings from another study indicating that attributing the symptoms mainly to a physical cause predicted poorer outcome in CBT [9]. Duration of illness predicts neither the outcome [1,2,7] nor the presence of a comorbid depressive or anxiety diagnosis [1,7]. Research into predictors of response to treatment is still in the early stages and the results require replication.

Graded exercise therapy (GET)

Graded exercise therapy involves a structured activity management programme that aims for a gradual increase in aerobic activities, usually walking. Patients receive an exercise prescription adapted to their own current physical capacity. Patients are advised not to exceed the prescribed exercise duration or intensity. RCTs evaluating GET have found an overall beneficial effect on fatigue and functional work capacity compared to control groups [10–13]. One also looked at the combined effects of GET and fluoxetine but found no additional benefits of fluoxetine on fatigue or functioning [13]. This study also found higher rates of drop out for graded exercise therapy than is usually found in CBT. Graded exercise therapy appears to be associated with higher drop out rates than cognitive therapy [13,14]. Predictors of response in a trial of different 'dosages' of GET [15] found that the poor outcome was predicted by the membership of a self-help group, being in receipt of sickness benefit at the start of treatment and dysphoria. Severity of the symptoms and the duration of illness were not the predictors of response. It is important to note that GET is a carefully structured intervention; simply giving the patient the basic recommendation to exercise is unlikely to be helpful and may harm his/her confidence.

Pharmacological

Antidepressants

Two RCTs [16,17] found that antidepressants (fluoxetine and phenelzine, respectively) did not show significant benefits for mood or other outcome measures in people with CFS. Another RCT [13] involved a longer course of fluoxetine and studied people with a shorter duration of illness. This study found that people randomized to fluoxetine showed modest improvements on measures of depression but there were no significant group differences with regards to fatigue.

Corticosteroids

One RCT of 25–35 mg hydrocortisone found a greater improvement in the treated group on a self-rated scale of 'wellness' but not on the other self-rating scales [18]. Forty percent of those receiving active treatment experienced adrenal suppression. A study of a lower dose of hydrocortisone (5 or 10 mg daily) found a short-term improvement in fatigue in 28% of those taking hydrocortisone and 9% of those taking placebo, but the benefit rapidly attenuated when the treatment was discontinued [19]. RCTs of fludrocortisone have shown no beneficial effects [20,21].

Other pharmacological interventions

A small RCT found an evidence of limited benefit from an oral nicotinamide adenine dinucleotide [22] together with minor adverse side-effects. A controlled trial of selegiline reported some positive effects but found no overall benefit [23]. RCTs of moclobemide [24], sulbutiamine [25], galanthamine hydrobromide [26] and growth hormone [27] found no effects of these interventions. An RCT of acyclovir found a negative effect for one outcome and three patients withdrew due to reversible renal failure [28].

Immunological

Five RCTs assessed the effects of immunoglobin. Two of these [29,30], one of which was the largest of the RCTs [29], reported no effect of the intervention. The other three [31–33] showed limited benefits, although one study was with children where both the groups showed significant improvements [31] and another was with

a sample that was not required to meet the operational criteria for CFS [32]. Considerable adverse effects were reported with immunoglobin in up to 82% of the trial participants [30].

Interferon was evaluated in two small RCTs; one found positive effects but the methodological quality of both the studies was fairly poor [34,35]. Beneficial effects were found in an RCT of ampligen [36] and some positive effects were reported in a small controlled trial of *Staphylococcus* toxoid [37]. No beneficial effects were found in RCTs of the antihistamine terfenadine (oral) [38] or dialysable leucocyte extract [5].

Nutritional supplements

A small RCT, comparing intramuscular injections of magnesium with placebo, found beneficial effects on mood, energy levels and pain over a 6-week period. The mean pre-treatment red cell magnesium concentration in their sample was low, and restored by treatment, but subsequent studies have failed to find magnesium deficiency in people with CFS [39,40]. RCTs of Siberian ginseng [41], essential fatty acids [42] and liver extract containing folic acid and cyanocobalamin [43] did not have overall beneficial effects. A poor quality RCT of general supplements found a positive effect [44] but a controlled trial reported no effect [45].

Complementary/alternative

Some beneficial effects were found in a small RCT of massage therapy [46], but the results were based on within-group rather than between-group comparisons. A poor quality RCT of homeopathic remedies [47] and a poor quality controlled trial of osteopathy [48] also found some beneficial effects.

Prolonged rest

Although no RCTs of prolonged rest were identified, it is included here as historically it has been recommended for individuals with CFS. There is no evidence that prolonged rest is an effective treatment. Although there is no direct evidence of harmful effects of rest in people with CFS, it has been shown to perpetuate or increase fatigue in people recovering from a virus [49] and in healthy volunteers [50]. Therefore, it cannot be recommended as a treatment for CFS.

Interventions for chronic fatigue in primary care

One RCT [51] compared a self-help intervention with no intervention for primary care patients with chronic fatigue, 12% of whom also fulfilled the Oxford criteria for CFS. The self-help intervention involved a booklet based on a cognitive behaviour model and 10–15 sessions with a nurse discussing its contents. This was more effective than no treatment at improving the fatigue and psychological distress at 3-month follow-up. Another RCT in primary care [52] compared counselling with CBT for people with fatigue of at least 3 months' duration. Both the interventions led to improvements in fatigue and related symptoms and there were no significant differences between the two therapies. Factors at assessment that predicted a poor outcome at 6-month follow-up were poor social adjustment, a physical illness attribution, the patients reporting that they had never seen the GP for an emotional reason and long perceived future illness duration. Another study [14] compared CBT with graded exercise for patients with fatigue in primary care and found no significant difference in the mean decrease on a fatigue measure. However, patients offered CBT were more likely to begin the treatment and remain in treatment than those offered GET.

Discussion

The treatments that show the most promise for CFS are CBT and GET. However, further research is needed to improve the effectiveness of these treatments as many patients do not either benefit or fully recover. Trials of some of the other interventions found indications of benefit but larger and more well-controlled studies are required to replicate any positive effects. Given the promising findings with CBT and GET, recommendations for the occupational health physician are made below.

Role of the occupational health physician

Occupational health physicians may be able to play an important role in helping patients with persistent or excessive fatigue to recover, and in helping to prevent recent-onset fatigue becoming chronic. An understanding of how CFS develops can be important for guiding treatment so this will be outlined first, followed by recommendations for the management.

How does CFS develop?

No single cause of CFS has been found but various potential contributory factors have been identified. With regards to initiating factors, there is evidence that symptoms such as fatigue and myalgia can, in some cases, be triggered by an infection such as glandular fever [53], hepatitis [54] or viral meningitis [49]. However, it does not appear that chronic problems are caused by persistence of the virus that may have caused the initial symptoms and it has been suggested that the virus may act itself as a stressor rather than by any specific molecular process [55]. It has also been found that patients with chronic fatigue are more likely to have experienced severe life events or difficulties in the months

prior to onset as compared with controls [56]. Various factors influence the likelihood to which a stressor such as an infection or life event will result in long-term fatigue symptoms. These will be discussed in more detail as they can be important targets for intervention.

Coping responses to acute fatigue, such as excessive activity or excessive rest, can be important in determining whether the fatigue will persist. Sometimes, individuals with CFS report returning to extreme physical activity immediately after an acute illness, or have always tended to be overactive, perfectionist or highly achievement-oriented and have pushed themselves on through initial signs of low-level fatigue, not allowing their bodies sufficient time to recover [57]. Alternatively, individuals may have rested excessively in response to initial fatigue. Bed rest or prolonged convalescence after infections such as glandular fever is a significant predictor of greater fatigue months later [49]. One reason may be that excessive rest causes deconditioning which further exacerbates symptoms and causes greater perceived effort when the person re-attempts previous activities. A prospective study found that the measures of unfitness taken within a few weeks of the onset of Epstein–Barr virus were significantly associated with the fatigue syndrome 4 months later [53]. Furthermore, excessive day-time rest can disrupt the circadian sleep/wake cycle and cause sleeping problems at night. Disrupted sleep may in turn contribute to fatigue, muscle pain and poor concentration [58]. Patients may alternate between overdoing things when the situation requires this or when they are having a 'good day', then collapsing and resting excessively at other times [59], a pattern that does not allow them the best chance of recovery. They may also try to avoid the physical and mental activities that they believe exacerbate their symptoms. In the long term, this perpetuates intolerance of such activities and the lack of stimulation increases fatigue.

Emotional factors may also play an important role in maintaining fatigue. Psychological morbidity at the time of an acute infection and previous psychiatric history is a significant predictor of subsequent chronic fatigue and CFS [49,60]. Although stress and anxiety can cause or exacerbate somatic symptoms, including fatigue, people often fail to make the link between their physical symptoms and stress or psychological issues. As a result, they might not take appropriate action to deal with the difficult situation and the persisting stress may impede recovery. Psychological problems can also develop as secondary to the chronic fatigue and then act as maintaining factors. For example, if the individual withdraws from previous activities in an attempt to control his/her symptoms, this can result in disrupted relationships and work problems, thus adding to his/her stress levels. The withdrawal also reduces opportunities for achievement and pleasure, which in turn increases frustration and lowers mood. Depressed mood itself directly increases fatigue [61]. If the individual previously tended to strive for very high standards, it may be particularly frustrating and distressing to find himself/herself performing at a lower standard than usual and not achieving important goals [59]. The individual can lose confidence and become hopeless about the future, further lowering his/her mood. However, it has been suggested that the physical attribution made by many individuals with CFS may protect their self-esteem as they do not see their fatigue problems as resulting from any failure to cope on their part [62].

Cognitive factors can also influence the maintenance of fatigue. Catastrophic beliefs (e.g. believing that the increased activity will cause a severe relapse) are associated with a greater limitation of activities and a greater disability [63] or attributing the condition to a solely physical cause [64]. It has also been suggested that a tendency to attend to bodily sensations may enhance perceptions of symptoms and interfere with attention to other tasks [65].

Interpersonal factors such as perceived lack of social support [66] or unhelpful reactions from others may also contribute to the persistence of fatigue. For example, relatives can be overly helpful and do too much for the patient or may be very fearful about the individual exacerbating his/her symptoms, which can reinforce the patient's own worries. Sometimes relatives, health professionals or work colleagues have sceptical reactions that can increase the individual's stress and frustration levels [67,68]. More negative social interactions at baseline have been shown to predict greater fatigue 8 months later [69].

The above section outlines just some of the many factors that may act to perpetuate fatigue. Different processes are likely to be at work, to varying degrees, in different individuals.

Investigations and referrals

There is no diagnostic test for CFS. Investigations are only necessary to exclude other diagnoses. For all patients, the following investigations are recommended: full blood count, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) blood tests, urea and electrolytes, thyroid function tests, and testing urine for protein and sugar. It may also be helpful to test for Epstein–Barr virus, rheumatoid factor, antinuclear factor, cytomegalovirus (CMV), toxoplasmosis, human immunodeficiency virus (HIV), coeliac disease (endomysial antibody test) and to take a chest X-ray. Enteroviral serology, VP-1 testing and neuroimaging are not thought to be helpful. Medical referrals are only necessary in special circumstances, such as for the elderly, after foreign travel or if the person shows weight loss, any

neurological signs, has difficulty in walking, pyrexia of unknown origin or any abnormal investigations.

General advice about how to recover

For individuals in the early stages of fatigue, the advice provided may have a crucial impact on the long-term outcome. Excessive, prolonged resting in response to a virus should be discouraged once the initial high temperature has passed, although a modification of usual activities may be necessary temporarily. For individuals who have already developed more persistent fatigue, a plan of action should be formed collaboratively with the patient, emphasizing a balance between activity and rest. The patient should be shown how to pace himself/herself with breaks, and targets should be set to help gradually build up activities again. The stress response and its physiological manifestations should be presented and normalized. Some patients may benefit from psychoeducation regarding symptoms of anxiety and depression, and some may require referral to a psychologist or psychiatrist. Antidepressant medication may be considered to treat any comorbid depression, insomnia or myalgia, although research evidence to support such use in chronic fatigue patients is limited. Self-help material specific to chronic fatigue can be recommended [70]. Patients may need encouragement to help them build up pleasurable non-work activities. Overall, the physician should aim to help the patient to recognize what the problems are, acknowledge their personal strengths and weaknesses and explore potential solutions. The continuity of the relationship is important so the patient should be reviewed regularly.

It should be explained that, with each increase in activity, it is normal to experience a temporary increase in symptoms. This does not mean that they have caused harm or will relapse, and the symptoms will pass as they get fitter. They should not expect to feel better immediately; people usually find that they are initially able to do more without necessarily feeling better—that tends to come later. Similarly, it is best to prepare the patient for the fact that they will probably have setbacks. Again, it is important for them not to catastrophize but simply apply the same principles, just lowering the targets temporarily.

The physician should be aware that some patients with CFS might find it very difficult to change their behaviour. If advice and education are not sufficient, patients may benefit from referral to a health professional who is trained in CBT or GET and who has an experience of working with people with this condition.

Work issues

With regards to work, there should be liaison among the patient, his/her manager, Occupational Health and Human Resources. It is important to explore whether there are any work issues that may be contributing to the fatigue. Common examples are long or irregular working hours, failure to take breaks, a heavy workload combined with a decreased ability to cope and lack of understanding from managers or colleagues. The individual may have unhelpful thoughts and behaviours relating to work, including fear of losing his/her job, fear of making mistakes due to concentration and memory problems, fear that his/her colleagues will think they cannot cope, pushing him or herself too hard to prove that he/she can cope, being overly perfectionist, being unassertive and trying to comply with excessive work demands, and saving all his/her energy for work and 'crashing out' at evenings and weekends. The patients may also need advice about their rights at work.

For those who are not currently working and who wish to return to work at some point, an individualized return to work plan should be developed. The plan may involve a period of time where the person builds up work or work-related skills at home or in other locations (e.g. a voluntary position) first, before returning to the place of employment. The number of hours worked should be gradually increased. To do this, it may be necessary for work schedules to be reassessed. For example, rather than working two full days each week, it may be better spread the hours worked over the week. It is important to ensure that regular breaks are taken. Progress towards the targets should be regularly reviewed by their manager and by Occupational Health.

Conclusions

The treatments for CFS to have shown the most promise are CBT and GET. Limited and inconclusive evidence has been found for some of the pharmacological, immunological and dietary supplement interventions, which were sometimes associated with adverse effects. Most of these interventions have been evaluated in only one or two studies so firm conclusions cannot be drawn. There is no evidence that prolonged rest is beneficial and there is indirect evidence that it may prolong or worsen fatigue.

The occupational health physician can play an important role in helping patients to recover, creating an individualized plan that takes into account the idiosyncratic factors that appear to be maintaining fatigue in each particular case. Core elements in the programme for recovery should include the establishment of a regular pattern of activity and rest, a sleep routine, gradually increasing exercise and activities, and a plan for how the patient can access help for any contributory work, psychological, interpersonal, work or social issues.

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