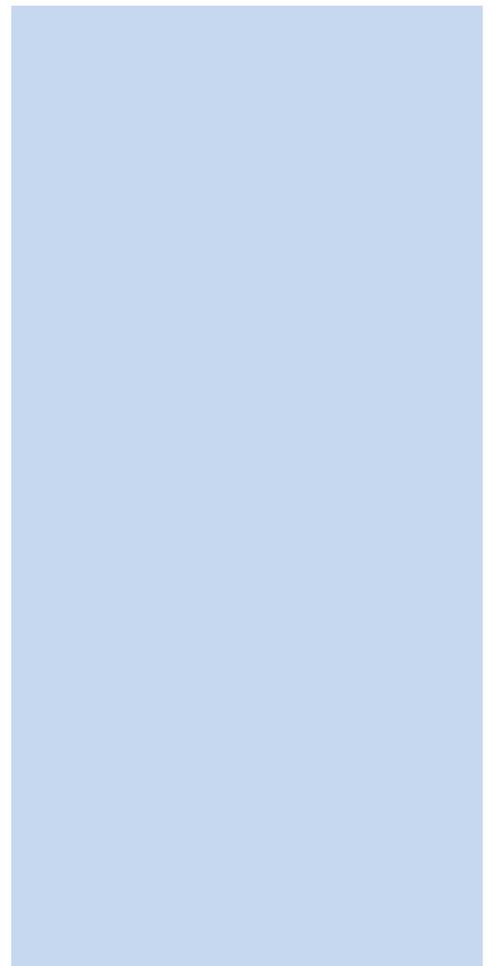
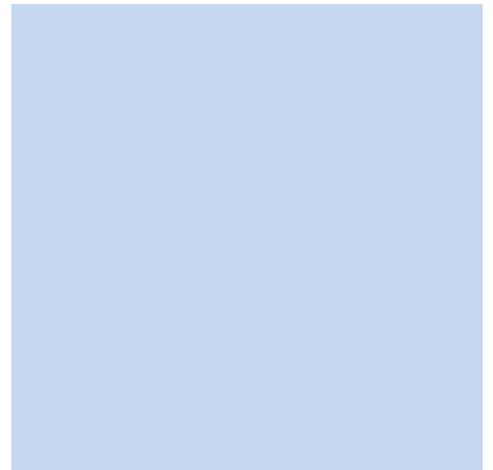




Occupational Aspects of the Management of Chronic Fatigue Syndrome: a National Guideline





Occupational Aspects of the Management of Chronic Fatigue Syndrome: a National Guideline

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Executive summary

Chronic fatigue syndrome (CFS) is a medically unexplained illness characterised by severe, disabling fatigue and other symptoms. Although there is a large body of research into CFS and its treatment, few studies have looked at the employment outcomes of individuals with CFS. This review summarises current evidence and is intended to assist occupational health professionals, managers and other interested parties in providing advice on fitness for work in employees with CFS.

Three key questions were used as the basis for a systematic evidence review:

1. What treatments are effective in enabling individuals with CFS to return to or remain at work?
2. What are the predictive factors for a successful return to work in individuals who are currently absent from work?
3. What is the risk of relapse and what are the risk factors for relapse, in terms of non-attendance or poor functioning at work?

Key findings of the review:

- Cognitive behavioural therapy and graded exercise therapy have been shown to be effective in restoring the ability to work in those who are currently absent from work.
- Concurrent depression in individuals with CFS is associated with poorer work outcomes. Therefore, co-morbid psychiatric conditions such as depression should be treated, if present. Other factors which predict poor work outcomes include a greater number of physical symptoms and signs, and older age at presentation.
- There is some evidence that individuals treated with cognitive behavioural therapy have a lower risk of relapse than a control group five-years after treatment.
- There is a lack of published primary research on the best way to manage return to work in individuals with CFS.
- Employers and occupational health professionals should be aware that most individuals with CFS are likely to fall under the remit of the Disability Discrimination Act 1995.

Guideline Development Group

Guideline leader

Dr Karen Pratt

Specialist Registrar in Occupational
Medicine, BUPA Wellness, London

Director of NHS Plus evidence-based guideline project

Dr Ira Madan

Consultant Occupational Physician,
Guy's and St Thomas' NHS
(Foundation) Trust, London

External assessors

Professor Michael Sharpe

Professor of Psychological Medicine
and Symptoms Research, School of
Molecular and Clinical Medicine,
University of Edinburgh

Professor Peter White

Professor of Psychological Medicine,
Wolfson Institute of Preventative
Medicine
(School of Medicine and Dentistry),
Queen Mary's University of London

Guideline Development Group members

Dr William Bruce-Jones

General Adult and Liaison
Psychiatrist, Avon and Wiltshire
Mental Health Partnership NHS
Trust

Nikie Catchpool

Occupational Advanced Practitioner
Therapist,
Bath and Wiltshire CFS/ME Service,
Royal National Hospital for
Rheumatic Diseases
NHS Foundation Trust, Bath

Professor Trudie Chalder

Professor of Cognitive Behavioural
Psychotherapy,
Institute of Psychiatry, at the
Maudsley, King's College, London

Chris Clark	Chief Executive, Action for ME (until March 2006), AfME, 3rd Floor, Canningford House, 38 Victoria Street, Bristol BS1 6BY
Sharon Hynes	Head of Human Resources and Training, BUPA Wellness, London
Dr Meirion Llewelyn	Consultant Physician, Infectious Diseases/General Medicine, Royal Gwent Hospital, Newport, Gwent
Dr Jon Poole	Consultant Occupational Physician, Dudley NHS Primary Care Trust, Dudley, West Midlands
Suzanne Roche	Research Assistant, South London and Maudsley NHS Trust, London
Gael Somerville	Occupational Health Nurse, British Broadcasting Corporation, London
Bella Stensnas	Research Assistant, South London and Maudsley NHS Trust, London

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Introduction

The aim of this review is to provide an evidence-based guideline on chronic fatigue syndrome (CFS) specifically focused on occupational issues. It is intended to assist occupational and other healthcare professionals, managers, employees and other interested parties in providing advice on the occupational aspects of CFS, based on current evidence. Where evidence does not exist or is not robust, recommendations for further research are made.

Importance of CFS in an occupational health setting

CFS represents a considerable public health burden with costs to the individual and the employer, as well as to the economy:

- *Costs to the employee:* individuals may find it difficult to perform their work duties to their usual standard. They may also have periods of sickness absence and in severe cases may be unable to continue working, resulting in loss of their livelihood.
- *Costs to the employer:* these include increased levels of sickness absence [1], impaired performance, both physical and cognitive [2], and possibly an increased risk of occupational injuries [3].
- *Economic costs:* a UK study of chronic fatigue and CFS in primary care has shown that both impose substantial economic costs on society, mainly in the form of informal care (care provided by friends and family) and lost employment [4]. A US study estimated a 37% decline in household productivity and a 54% reduction in labour force productivity among people with CFS. The estimated annual total value of lost productivity in the USA was \$9.1 billion, representing approximately \$20,000 per person with CFS [5].

With this level of impact, it is important that occupational health professionals are well informed about CFS to enable them to provide accurate occupational health advice to those concerned.

Background

Epidemiology of fatigue

The complaint of “feeling tired” or fatigue is relatively common. The Office of Population Censuses and Surveys (now part of the Office for National Statistics) conducted a large community survey in the United Kingdom (Meltzer H, Gill D, Petticrew M, Hinds K. The prevalence of psychiatric morbidity amongst adults living in private households. London HMSO, 1995), in which 27% of respondents (a third of women and a fifth of men) reported significant fatigue in the week before the interview [6]. In a postal survey of patients registered at six general practices in southern England, 18.3% of respondents reported substantial fatigue lasting six months or longer [7]. Identification of individual with abnormal fatigue may include indicators such as chronicity, functional impairment and a decision to seek help [8].

The term “chronic fatigue” is sometimes used, and has been defined as fatigue lasting more than six months but without the associated symptoms that are characteristic of CFS.

It is important to note that this guideline is focussed on CFS rather than fatigue or chronic fatigue. CFS has specific diagnostic criteria, as outlined below.

Definition of chronic fatigue syndrome

CFS is a medically unexplained illness. It is characterised by severe, disabling fatigue and other symptoms, including musculoskeletal pain, sleep disturbance, impaired concentration and headaches. While fatigue is commonly reported in primary care settings, the vast majority of patients who complain of fatigue do not suffer from CFS. CFS is defined by specific diagnostic criteria.

The two most widely used definitions of CFS are the International Centre for Disease Control (CDC) 1994 definition (this replaced the original CDC 1988 version) and the British (Oxford) definition. The CDC 1994 definition is based on an international consensus of researchers and simplified the original 1988 definition by reducing the number of symptoms required and requiring the exclusion of only a small number of specified psychiatric syndromes.

In addition, to the CDC and Oxford CFS definitions, there are also Australian and Canadian definitions. All five definitions include the requirement for severe, disabling fatigue to have been present for at least six months; they are summarised in **Appendix 1**.

Limitations of chronic fatigue syndrome definitions and research

These definitions are mainly used in the context of research into CFS rather than as diagnostic tools in clinical practice. A potential problem with the definitions stating that fatigue has to have been present for at least six months is that this will lead to delay in diagnosis and treatment. Many consider that the six-month time period is an “end point” by which stage the diagnosis of CFS should have been confirmed, rather than, the point at which it should first be considered.

Although there is no evidence base, many treating practitioners in the field of CFS believe that patients would benefit from earlier referral for treatment, for example at the three-month stage, rather than waiting until symptoms have been present for six months.

A major difficulty when looking at the research into CFS is that different studies have used different definitions of the syndrome. In addition, studies have used a wide variety of outcome measures to evaluate the severity of CFS. These include a number of different “fatigue scales”. As so many different outcome measures have been used, it can be difficult to draw comparisons between studies.

Historical context

Although the term “chronic fatigue syndrome” is a relatively new diagnostic label, similar syndromes have been described in the past. In the late nineteenth century, a syndrome was described which was characterised by severe fatigue, exacerbated by exertion and accompanied by other symptoms including poor concentration, irritability and muscle pain. This was known as “neurasthenia”, a condition of uncertain cause that at the time was commonly attributed to “the stresses of modern life on the human nervous system” [9]. In the 20th Century, the diagnosis of neurasthenia declined and eventually fell out of common use. It is possible that the incidence of these symptoms in the population also declined. However, it seems more likely that patients with similar symptoms were given alternative diagnoses. These included diagnoses that suggested aetiological agents or specific disease processes such as chronic brucellosis, chronic Epstein-Barr virus and myalgic encephalomyelitis (ME), as well as the psychiatric diagnoses of depression and anxiety.

The term “myalgic encephalomyelitis” (ME) was first used in 1956 after an outbreak of illness among nursing and medical staff at the Royal Free Hospital in London. The cause of this outbreak remains uncertain. The term implies a pathological process of inflammation of the brain and spinal cord which, to date, has not been shown to be present in individuals with CFS. However, the term “ME” is still often used, mainly by patients, as synonymous with CFS and patient organisations are increasingly using the term “myalgic encephalopathy”.

In the past 20 years, the medical profession has increasingly come to believe that the symptoms of individuals with CFS are not readily explained either by recognisable organic disease or by depression and anxiety. The term “medically unexplained” has been used to address the lack of a clearly understood aetiology [10].

Other medical conditions that have been categorised in this group include fibromyalgia, irritable bowel syndrome and chronic pain syndromes. Although chronic pain syndromes are characterised by pain, fibromyalgia by tender points and irritable bowel syndrome by altered bowel function, these syndromes are all accompanied by the symptom of fatigue. It has also been observed that an individual with one of the foregoing conditions is more likely than average to suffer from another in the group. This has led to the proposal that they share a common pathophysiology and are best grouped together [11].

Before a diagnosis of CFS is made, it is important that other medical conditions are excluded. These include conditions such as thyroid disorders and anaemia, which typically can present with tiredness. Other less common conditions that also cause fatigue, such as sleep apnoea and coeliac disease, may need to be considered. The initial investigations in individuals presenting with fatigue are likely to be undertaken by their general practitioner, with referral on to secondary care at a later stage, if appropriate.

Prevalence of chronic fatigue syndrome

Estimates of the prevalence of CFS vary considerably depending on the definition used and the population studied. Studies of CFS in the general adult population give prevalence figures ranging from 0.007% to 2.8%, while studies of adults in primary care or general practice have given estimates ranging from 0.006% to 3.0%. [12]. However, a recent study from the Netherlands estimated the prevalence of “CFS-like caseness” in the working population to be 3.6% [13]. The National Institute for Clinical Excellence (NICE) guidance on CFS, currently under development in the United Kingdom, is based on an estimated prevalence of 0.4% [14].

Similar CFS prevalence rates have been found in people of different socio-economic status and in all ethnic groups [15]. Women are at higher risk than men of developing CFS with a relative risk of 1.3–1.7, depending on the diagnostic criteria used [16]. Although CFS can affect any age group, including children, it commonly presents in those in their twenties, thirties or forties and therefore at a time of life when occupational issues are likely to be important.

What causes chronic fatigue syndrome?

As outlined above, the cause of CFS remains poorly understood. The nature, pathology and aetiology are controversial and so the descriptive term, CFS, is preferable to previously used terms such as “post-viral fatigue syndrome” or ME.

There is no established single cause of CFS, and in practice it is likely that the definition covers a heterogeneous group of conditions. One model that has been used to consider the possible contributing factors to the condition, and hence an approach to managing it, is the “biopsychosocial” model [10,17].

Biological factors

These are not fully understood. Patients often describe their symptoms as following a viral illness. One prospective cohort study in primary care found no evidence that common infective episodes, such as sore throats, influenza and gastroenteritis, are related to the onset of chronic fatigue or CFS [18]. However, several studies have shown that approximately 10% of individuals who are infected with Epstein-Barr virus, (EBV – also known as “glandular fever” or “infectious mononucleosis”) in adulthood go on to develop CFS or experience delayed recovery with prominent fatigue and hypersomnia [19,20]. This suggests that certain systemic infections can *trigger* CFS, with the strongest evidence being for EBV. However, available evidence suggests that abnormal persistence of infectious agents does not occur in CFS.

There is also evidence that patients are often advised to rest after a viral illness [21]. While a short period of rest is appropriate as part of normal convalescence, in some cases they may continue to follow this advice for long periods, after the illness has resolved. The resultant inactivity may cause physical deconditioning (reduced fitness levels) resulting in further feelings of weakness and fatigue.

Psychological factors

Although there is an association with depression and anxiety disorders, in most cases these do not fully explain the nature of CFS. However, if psychiatric conditions such as depression coexist in individuals with CFS, it is important that these are treated, in addition to pursuing treatment for CFS.

Avoidance of activity commonly arises from the experience of doing too much on a “good day”, resulting in a “crash” (worsening of symptoms) the next. The resultant avoidance of activity may cause physical deconditioning and further disability.

Social and occupational factors

A full assessment of any difficulties in the individual's social circumstances or working environment should also be undertaken. These factors should be addressed, if possible, in order to facilitate recovery.

Impact of CFS on work

Individuals with CFS may have difficulty undertaking their usual working hours and performing to their usual standard. They may also have recurrent or prolonged sickness absence. Uncertainty about the diagnosis may lead to friction with employers or colleagues who may lose sympathy over the length of absence.

Hypothetical causal model of CFS [10,17]

	Predisposing factors	Precipitating factors	Perpetuating factors
Biological	Genetic predisposition?	Viral infection	Consequences of inactivity (loss of fitness) Sleep disturbance
Psychological		Psychological response	Attributional style Fear of making symptoms worse Coping by avoidance of activity
Social	Stigma of psychiatric disease	Stress	Personal conflicts Occupational factors

Treatments

No one treatment has been shown to provide a "cure" for all cases of CFS. However, some studies have shown promising results for cognitive behavioural therapy (CBT) [22–30], and graded exercise therapy (GET) [31–38]. NICE is currently working on developing guidance on the diagnosis and treatment of CFS. This project is entitled "CFS/myalgic encephalomyelitis (or encephalopathy): diagnosis and management". This guidance is due to be issued in 2007. (See NICE website <http://www.nice.org.uk>)

While many studies have looked at whether a variety of treatments lead to an improvement in CFS symptoms and physical functioning, few have looked at the impact of treatment on work outcomes, despite most patients being of employment age. This guideline is focused on establishing which treatments have been shown to be effective in restoring an individual's ability to work.

Cognitive behavioural therapy

CBT for CFS focuses mainly on the factors that may be maintaining fatigue rather than those that may have initially triggered it. The treatment includes planned activity and rest, graded increases in activity, establishing a sleep routine, and cognitive restructuring of unhelpful beliefs and assumptions, in collaboration with the patient.

The duration of treatment with CBT varies between individuals, ranging from around six to 20 sessions over six to 12 months. A study of individuals who received 13 sessions of CBT showed that some of the positive outcomes from CBT persisted at 5-year follow-up, and that 25% regarded themselves as recovered at this time [23].

The following have been identified as possible predictors of poor response to CBT:

- poor social and occupational functioning prior to becoming ill [30]
- a low sense of control in relation to CFS complaints
- a very passive activity pattern
- a high level of focusing on bodily symptoms [27]
- taking medical retirement or making a new claim for a disability-related benefit during treatment, although the numbers involved are small [39].

Attributing CFS to physical causes, eg a virus, did not affect outcome in one particular study [39]. This contradicts a previous study which found that attributing the symptoms mainly to a physical cause predicted poorer outcome in CBT [40].

It should be noted that research into the predictors of response to CBT is still in the early stages and the above results require replication.

Graded exercise therapy (GET)

GET involves a structured activity management programme that aims for a gradual increase in aerobic activities, usually walking. Patients negotiate an exercise programme adapted to their own physical capacity. Patients are advised not to exceed the negotiated exercise duration or intensity. Randomised controlled trials (RCTs) evaluating GET have found an overall beneficial effect on fatigue and functional work capacity. However, one study out of five has shown higher drop-out rates for GET than for CBT.

A trial of different “dosages” of GET found that poor outcome was predicted by

- dysphoria [41].
- membership of a self-help group
- being in receipt of sickness benefit at the start of treatment

(membership of a self-help group and being in receipt of sickness benefit at the start of treatment may be a marker of severity)

It is important to note that GET is a carefully structured intervention. Simply advising an individual with CFS to exercise is unlikely to be helpful.

Pacing

This is a treatment in which individuals manage their energy levels within an “envelope”, and is based on the principle of balancing activity and rest [42]. There is no published trial evidence of its efficacy, but pacing is favoured by some patients. A large multicentre RCT, PACE is currently under way in the UK, comparing standardised specialist medical care with CBT, GET and pacing. PACE will include work outcomes. However, its results are not expected until 2009 [43].

Prolonged rest

There have been no RCTs of prolonged rest as a treatment for CFS, although in the past it was frequently recommended. While there is no direct evidence of harmful effects of prolonged rest, apart from those well described outside of CFS, such as muscle wasting, there is also no evidence that it is an effective treatment. A systematic review has shown that prolonged rest after a viral illness may actually perpetuate or increase fatigue [44].

Other treatments

A number of systematic reviews have shown that no other treatment receives consistent support [45].

Prognosis

Published studies have tended to focus on people attending specialist clinics. A recent systematic review of the prognosis of *untreated* CFS reviewed studies from 1980 to 2003 [46]. This review showed that although full recovery from CFS is rare, many individuals with CFS do improve with time. The median full recovery rate was 5% (range 0–31%) and the median proportion of patients who improved during follow-up was 39.5% (range 8–63%) The duration of follow-up in the studies included in this systematic review varied from six months to 10 years.

Predictors of an improved outcome included a lower severity of fatigue at baseline and the individual not attributing the illness to physical causes. Presence of a co-existing psychiatric disorder was associated with poorer outcomes. The review noted that few studies of prognosis looked at work outcomes and that when these were considered there was little detail given regarding hours of work or, if not currently employed, why the individual was not working (for example, medical reasons, personal preference, or lack of success with job applications).

A study published in 2003 [47] followed up 65 individuals with CFS for up to three years and showed that only 20–33% were classified as having CFS at follow-up. At some point in the follow-up period, 57% experienced partial or total remission; 10% sustained total remission and 23.1% received alternative diagnoses, of which 20% were sleep disorders.

There is evidence that CBT and GET can be helpful treatments, although there is little published evidence comparing the long-term prognosis of individuals who have received these treatments with individuals who have received no treatment or other treatments, apart from that of Deale, Husain et al [23]. This study compared the long-term outcomes of individuals with CFS who had received 13 sessions of CBT with those of individuals who had been treated with 13 sessions of relaxation. The participants were followed up five years after the completion of treatment. 53 out of the original 60 trial participants agreed to participate in the follow-up study. Significantly more of the CBT group met criteria for complete recovery and were free of relapse. Similar proportions of both groups were employed but the CBT group worked significantly more hours per week, ie 56% of the CBT group were in full- or part-time employment, compared to 39% of the relaxation group. The mean number of hours worked per week was 35.57 for the CBT group and 24 for the relaxation group. The mean number of relapses since completion of treatment was 2.58 for the CBT group and 4.08 for the relaxation group.

Methodology of evidence review

A multidisciplinary Guideline Development Group (GDG) was formed in 2004.

The following 10 questions were developed by the GDG Group Leader (GDGL) and discussed at the first meeting on 26 October 2004:

1. How is CFS diagnosed? (How is it distinguished from other causes of fatigue?)
2. What is the prevalence of CFS in the population of working age?
3. What is the prognosis of CFS in the workplace?
4. What treatments are effective in enabling individuals to return to work or remain at work?
5. How long does it take for treatments to be effective?
6. What is the risk of relapse, in terms of non-attendance or poor functioning at work?
7. What are the risk factors for relapse?
8. What are the predictive factors for a successful return to work in individuals who are currently absent from work?
9. What is the likelihood of return to previous level of functioning?
10. What is the best way to manage rehabilitation to work?

Employment outcomes

A preliminary literature search showed that, although there is a considerable body of research on CFS, few studies have looked at employment outcomes. During the first GDG meeting, a paper specifically focussing on work outcomes was identified: “Disability and chronic fatigue syndrome – a focus on function” by SD Ross et al. [48]. This paper summarises a systematic review of studies published in English from 1 January 1988 to 15 November 2001.

Interventional and observational studies of adults with CFS were eligible for inclusion in the Guideline Development Group’s evidence review if they reported measures of disability and employment. This identified 3,840 studies, of which 37 reported employment status and some measure of mental or physical impairment associated with disability. Most patients with CFS in these studies were unemployed. In 22 studies, the employment status of controls was also available. Only depression seemed to be associated with unemployment in patients with CFS. No other measurable impairment seemed to be consistently associated with disability or work outcomes. Only CBT, rehabilitation, and exercise therapy interventions were associated with restoring the ability to work. No specific patient characteristics were identified as best predictors of positive employment outcomes. The Ross paper concluded that for questions of disability and employment in CFS, the limitations inherent in the current literature are extensive.

Ross Review

All papers cited in the (SD Ross et al. paper) which fulfilled the criteria for the three key questions were retrieved and critically appraised by the GDG.

Key Questions

It was decided by the GDG to use the paper SD Ross et al. [48] as the basis for a systematic review and the original 10 key questions were revised down to the following three questions.

1. What treatments are effective in enabling individuals with chronic fatigue syndrome to return to or remain at work?

Population	Employees with chronic fatigue syndrome
Intervention	a) CBT b) Counselling c) GET d) Rehabilitation e) Pacing f) Individualised programmes
Outcomes	Return to work: a) full-time b) part-time c) modified duties
Study design	Randomised controlled trials, systematic reviews, case control and longitudinal studies

2. What is the risk of relapse and what are the risk factors for relapse, in terms of non-attendance or poor functioning at work?

Population	Employees with Chronic Fatigue Syndrome
Risk factors	a) age b) sex c) duration of CFS d) severity of CFS e) occupation f) co-morbid psychiatric diagnosis g) attributional style h) educational status
Outcomes	Sickness absence or poor functioning after return to work
Study design	Randomised controlled trials, systematic reviews, case control and longitudinal studies

3. What are the predictive factors for a successful return to work in individuals who are currently absent from work?

Population	Employees with chronic fatigue syndrome
Predictive factors	<ul style="list-style-type: none"> a) age b) sex c) duration of CFS d) severity of CFS e) occupation f) co-morbid psychiatric diagnosis g) attributional style h) educational status
Outcomes	Return to work
Study design	Randomised controlled trials, systematic reviews, case control and longitudinal studies

Literature Review

Search strategy

1. “chronic fatigue syndrome” and work*
2. “chronic fatigue syndrome” and employ*
3. “chronic fatigue syndrome” and occupation*
4. “chronic fatigue syndrome” and unemployment
5. “chronic fatigue syndrome” and “occupational health”
6. “chronic fatigue syndrome” and “sickness absence”
7. “chronic fatigue syndrome” and “ill health retirement”
8. “chronic fatigue” and work*
9. “chronic fatigue” and employ*
10. “chronic fatigue” and occupation*
11. “chronic fatigue” and unemployment*
12. “chronic fatigue” and “occupational health”
13. “chronic fatigue” and “sickness absence”
14. “chronic fatigue” and “ill health retirement”
15. (1) and “Cognitive Behavioural Therapy”
16. (1) and “counselling”
17. (1) and “Graded Exercise Therapy”
18. (1) and “rehabilitation”
19. (1) and “pacing”
20. (1) and “individualised programmes”
21. (2) and “Cognitive Behavioural Therapy”
22. (2) and “counselling”
23. (2) and “Graded Exercise Therapy”
24. (2) and “rehabilitation”
25. (2) and “pacing”
26. (2) and “individualised programmes”
27. (3) and “Cognitive Behavioural Therapy”
28. (3) and “counselling”
29. (3) and “Graded Exercise Therapy”
30. (3) and “rehabilitation”
31. (3) and “pacing”
32. (3) and “individualised programmes”
33. (4) and “Cognitive Behavioural Therapy”
34. (4) and “counselling”
35. (4) and “Graded Exercise Therapy”

36. (4) and “rehabilitation”
37. (4) and “pacing”
38. (4) and “individualised programmes”
39. (5) and “Cognitive Behavioural Therapy”
40. (5) and “counselling”
41. (5) and “Graded Exercise Therapy”
42. (5) and “rehabilitation”
43. (5) and “pacing”
44. (5) and “individualised programmes”
45. (6) and “Cognitive Behavioural Therapy”
46. (6) and “counselling”
47. (6) and “Graded Exercise Therapy”
48. (6) and “rehabilitation”
49. (6) and “pacing”
50. (6) and “individualised programmes”
51. (7) and “Cognitive Behavioural Therapy”
52. (7) and “counselling”
53. (7) and “Graded Exercise Therapy”
54. (7) and “rehabilitation”
55. (7) and “pacing”
56. (7) and “individualised programmes”

* indicates a truncated word

Terms inside inverted commas are text words (words in title, abstract or keywords)

Search dates

15/11/2001 to 30/11/2004

Method

The published literature was searched using the following databases:

- Medline
- PsycINFO
- EMBASE
- HSE Line
- Health Periodicals Database
- Evidence Based Periodicals Database
- Cochrane Library
- (CINAHL) Cumulative Index to Nursing and Allied Health Literature

Search Limitations

The search was limited to

- Human subjects
- English Language

Details were listed of all papers which met the search criteria abstracts and obtained wherever possible.

Inclusion criteria

- Employment/work outcomes.

Exclusion criteria

- Case reports
- Letters.

Selection of papers for critical appraisal

A librarian at the Department of Health undertook the literature search outlined above. This yielded a total of 188 abstracts, after removal of duplicates. The GDG also decided, at a group meeting on 18 February 2005, to repeat the search strategy above using the search terms “ME”, “myalgic encephalomyelitis” and “neurasthenia” instead of CFS. This yielded a total of 54 abstracts. All of these abstracts were reviewed independently by the GDGL and the Project Director to select papers which appeared to meet the criteria for the three key questions.

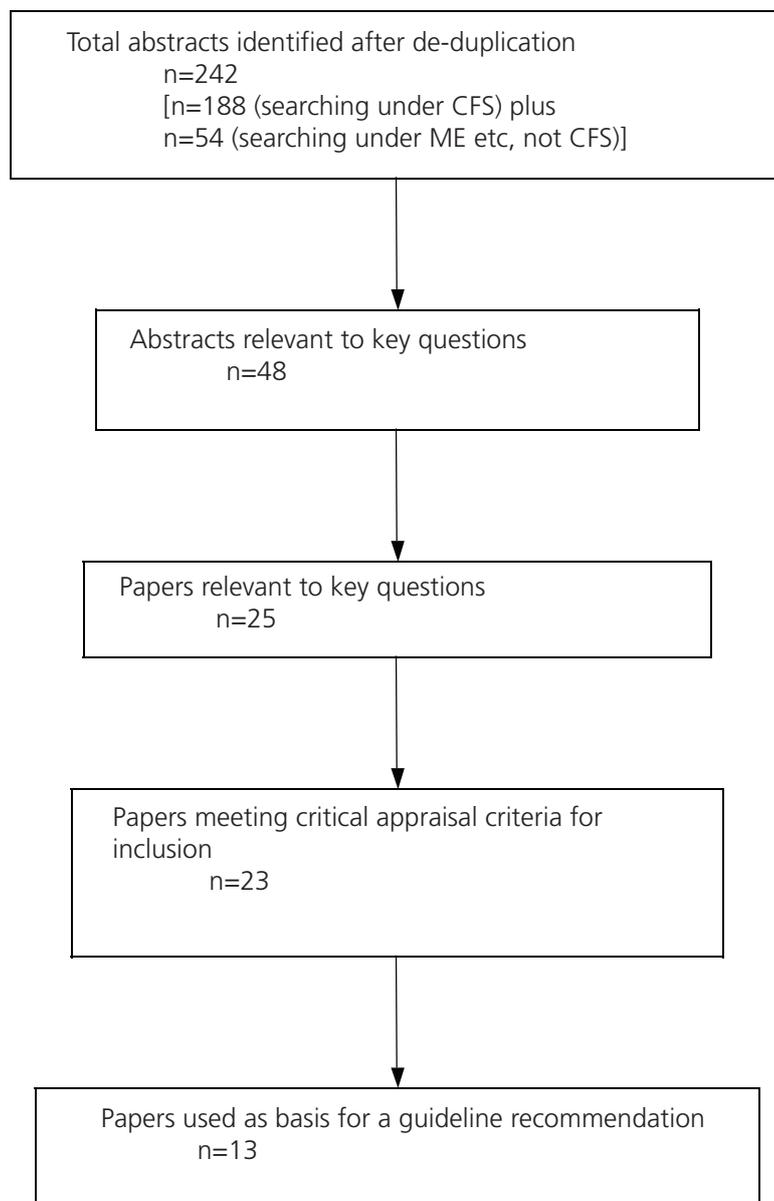
Full text of 48 papers was obtained. These included papers identified from review of the references cited in the SD Ross et al. paper as well as “in press” papers identified by GDG members. These 48 papers were read independently by the GDGL and Project Director to establish which met the criteria for the key questions. This process yielded 23 papers, which were critically appraised by six of the GDG members, working in pairs.

The appraisers were asked to identify any follow-on papers listed in the references of the papers they were appraising. None was identified. The papers were assessed for methodological quality, using a proforma developed by the Critical Appraisal Skills Programme (reproduced as **Appendix 2**). The revised Scottish Intercollegiate Guidelines Network (SIGN) grading system (2000) was used to grade each paper (see form reproduced as **Appendix 3**). In the event that a pair of appraisers could not reach agreement on the SIGN grading, the paper was passed to the GDGL for discussion with the Project Director to make a final decision.

Development of recommendations

Draft recommendations for the occupational health management of CFS were produced by the GDGL and circulated to the group for comments and feedback. The recommendations were then redrafted, incorporating this feedback, as well as that of the external assessors. As with NICE guidelines, papers with a “minus” grade were not used as a basis for a recommendation due to a high risk of bias or confounding.

Flow chart for study selection



Revised SIGN grading system: Levels of evidence

1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Grading system for recommendations

- A** At least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population; or
A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
- B** A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+
- C** A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++
- D** Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

Good practice points

Good practice points (GPPs) are practical points that the GDG wishes to emphasise but for which there is not, nor is there likely to be, any research evidence – for example, some aspect of management or treatment that is regarded as such sound clinical practice that nobody is likely to question it. These are not alternatives to evidence-based recommendations, and are only used where there is no other way of highlighting the issue.

The above gradings were used as a basis for the guideline's recommendations.

Limitations of the Literature Review

These include:

1. Publication bias – there is a tendency for only studies with positive results to be published.
2. Study bias – there is a bias towards CBT rather than other forms of psychotherapy.
3. Published studies have tended to focus on individuals with CFS who are attending specialist clinics. They may therefore exclude those least affected or more severely affected (who may not be ambulant).
4. Due to time and resource limitations, the “grey literature” on CFS was not comprehensively searched. The two external assessors are experts in the field of CFS and they indicated that they were content that all relevant research had been identified in the review.

Findings for occupational health management

This section lists the full evidence statements derived from the systematic literature review.

The findings are divided into eight sections:

1. Employees in the early stages of fatigue
2. Management of employees with CFS
3. Organising a return to work
4. Treatments for CFS that have been shown to improve work outcomes
5. Factors that predict work outcomes in individuals with CFS
6. Risk of relapse in CFS
7. Disability Discrimination Act 1995
8. Future research.

1. Employees in the early stages of fatigue

Recommendation	Grade	Evidence
Healthcare professionals should be aware that advice given to employees in the early stages of fatigue may have an adverse impact on their long-term outcome, including return to employment.	D	Rimes and Chalder 2005 [49]
Positive advice should include the recommendation to avoid excessive prolonged resting after a viral illness, once the acute systemic illness has passed.	D	Candy et al. 2002 [44]

2. Management of individuals with chronic fatigue syndrome

Recommendation	Grade	Evidence
Co-morbid psychiatric conditions, such as depression, should be identified and treated.	B	Ross et al. 2004 [48], Russo et al. 1998 [50]
If advice and education are not sufficient, individuals may benefit from referral to a health professional who is trained in CBT or GET and who has experience of working with individuals with CFS.	A (CBT) B (GET)	Butler et al. 1991 [40], Deale et al. 1997 [22] and et al. Deale 2001 [23], Prins et al. 2001 [27] Fulcher and White 1997 [32]
For individuals with more persistent fatigue, one paper has suggested that the following advice may be helpful: <ul style="list-style-type: none"> • The individual should be shown how to pace himself/herself with breaks, and targets should be set to help gradually build up activities again. • If impaired, the individual should be given help to build up activities gradually. An “all or nothing” approach to activity should be avoided. • 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 the individual has caused himself/herself harm or will relapse; rather, the symptoms will pass as the individual becomes fitter. • It is best to prepare the individual for the fact that he/she will probably experience setbacks. However, it should still be possible to apply the same principles, merely lowering targets temporarily. 	D	Rimes and Chalder 2005 [49]
Self-help material specific to chronic fatigue may be helpful.	D	Rimes and Chalder 2005 [49] Chalder et al. 1997 [51], Chalder 1995 [52]
Lifestyle factors such as diet, smoking and alcohol intake should be addressed.	GPP	

3. Organising a return to work

Recommendation	Grade	Evidence
<p>The systematic review did not identify any primary research on the best way to manage return to work in individuals with CFS.</p> <p>For employees with CFS who are currently off work but who have recovered sufficiently for a return to work, the following points should be considered:</p> <ul style="list-style-type: none"> • There should be liaison between the employee, occupational health, management and human resources. • The occupational health professional should liaise, with the employee's consent, with his/her general practitioner, consultant or treating practitioner. • Employer and employee should explore whether the employee perceives that any work issues have contributed to or are contributing to fatigue. This should include a full exploration of all aspects of the case, including work satisfaction and interpersonal issues. • An individualised return to work plan should be developed. One paper has suggested that this may include: <ul style="list-style-type: none"> • building up work or work-related skills at home or in a voluntary position initially • gradually increasing hours of work (the employee may need to start with a dramatically reduced workload and hours of work, gradually increasing both, depending on progress) • regular breaks • regular review by an occupational health professional. 	D	Rimes and Chalder 2005 [49]
As with all common health problems, a biopsychosocial approach to rehabilitation should be taken.	D	Waddell and Burton 2004 [53]

4. Treatments for CFS that have been shown to improve work outcomes

Recommendation	Grade	Evidence
<p>The two treatments with the highest quality of evidence of effectiveness in restoring ability to work in those currently absent from work are CBT and GET</p>	<p>A (CBT)</p> <p>B (GET)</p>	<p>Butler et al. 1991 [40], Deale et al. 1997 [22], Deale et al. 2001 [23]</p> <p>Prins and couper 1998 [27], and White 1997 Fulcher [32]</p>
<p>Note: in research trials, these treatments have largely been delivered by experienced therapists. If delivered by less qualified/ experienced therapists, there is less potential for favourable outcomes.</p>		
Ill health retirement should generally be deferred until such treatment has been explored.	D	Cairns and Hotopf 2005 [46]
Concurrent psychiatric conditions, especially depression, should be treated	B	Ross et al. 2004 [48], Russo et al. 1998 [50]

5. Factors that predict work outcomes in individuals with CFS

The following factors have been identified as predictors of poorer work outcomes:

Recommendation	Grade	Evidence
Concurrent depression	B	Ross et al. 2004 [48], Morantz et al. 2003 [54]
Current psychiatric diagnosis	C	Russo et al. 1998 [50]
Older age	C	Tiersky et al. 2001 [55]
Higher number of physical complaints	C	Tritt et al. 2004 [56]
Higher number of physical signs, such as lymphadenopathy	C	Russo et al. 1998 [50]

6. Risk of relapse in CFS

No studies have looked at the risk of relapse or risk factors for relapse in individuals with CFS specifically in terms of non-attendance or poor functioning at work.

Recommendation	Grade	Evidence
One RCT showed that individuals treated with CBT had a lower risk of relapse than a control group during the five years following treatment	A	Deale 2001 et al. [23]

7. Disability Discrimination Act 1995

Employers and occupational health professionals should bear in mind that most patients with CFS are likely to fall under the remit of the Disability Discrimination Act 1995 [57].

Workplace adjustments could include:

- changing location of work
- working from home
- limiting working hours
- reducing workload
- limiting or reducing physical tasks.

8. Future research

Current projects

1. The two CFS treatments for which there is the greatest weight of evidence are CBT and GET. A third treatment is “pacing” which involves managing the patient’s energy expenditure within an “envelope” (this is based on the principle of balancing activity and rest) [42]. Despite lacking any evidence of efficacy in published research trials, it is considered by many patients to be helpful and was recommended by the Chief Medical Officer’s Working Group in 2002 [58].

A large multi-centre RCT is currently under way, comparing these three treatments as supplements to medical care with medical care alone. The trial, “Pacing, activity and cognitive behaviour therapy: a randomised evaluation (PACE) will include work outcomes [43].

2. Another trial that is currently under way is the “Fatigue intervention by nurses evaluation (FINE) trial [43]. Treatments will be delivered in patients’ homes, so this trial is particularly suited to those who are too ill to attend specialist clinics. FINE will compare usual medical care with supportive listening delivered by a trained nurse and pragmatic rehabilitation.

Research recommendations

The following are recommendations for research that would help to improve the quality of the evidence base available to occupational health practitioners:

1. An evaluation of the optimum method of managing return to work in individuals who have been absent from work due to CFS.

Population	Individuals absent from work due to CFS
Intervention	Return to work and rehabilitation programmes
Control	Usual care
Outcome	Return to part- or full-time work

2. The role of CBT/GET in the prevention of further non-attendance at work.

Population	Individuals with CFS who have returned to work
Intervention	CBT/GET prior to return to work and/or “top-up” sessions on return to work
Control	No CBT/GET
Outcome	Attendance at work

3. Longitudinal studies assessing factors that predict a relapse of CFS following return to work.

Suggested audit criteria

Key priority for implementation	Audit criterion
Co-morbid psychiatric conditions, especially depression, should be identified and treated in employees with CFS.	% of individuals who have been clinically assessed for psychiatric conditions, especially depression.
If advice and education are not sufficient, employees may benefit from referral to a health professional who is trained in CBT or GET and who has experience of working with individuals with CFS.	% of individuals absent from work who have been offered CBT or GET.
For employees with CFS who are currently off work but who have recovered sufficiently for a return to work, there should be liaison between the employee, occupational health, management and human resources. The occupational health professional should liaise, with the employee's consent, with his/her general practitioner, consultant or treating practitioner.	% of cases where at least three of the key players have liaised.
An individualised return-to-work plan should be developed for employees with CFS who are currently off work but who have recovered sufficiently to return to work.	% with a written return-to-work plan.
Ill health retirement should be deferred until CBT/GET has been explored.	% of ill health retirement cases where CBT/GET has been offered.

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Appendix 1: Definitions of chronic fatigue syndrome

International Centre for Disease Control 1988 definition

Major criteria:

- new onset of persistent or relapsing, debilitating fatigue in a person without a previous history of such symptoms that does not resolve with bed rest and that is severe enough to reduce or impair average daily activity to less than 50% of the patient's premorbid activity level for at least six months
- fatigue that is not explained by the presence of other evident medical or psychiatric illnesses.

Minor criteria:

At least six symptoms plus at least two signs, or at least eight symptoms, from the lists below:

symptoms:

- mild fever or chills
- sore throat
- painful adenopathy (posterior or anterior, cervical or axillary)
- generalised muscle weakness
- myalgias
- prolonged generalised fatigue after previously tolerated levels of physical activity
- generalised headaches
- migratory arthralgia without swelling or redness
- neuropsychologic complaints
- sleep disturbance
- main symptom complex developing over a few hours to a few days.

physical signs:

- low grade fever
- nonexudative pharyngitis
- palpable or tender anterior or posterior, cervical or axillary lymph nodes.

From: Holmes GP, Kaplan JE, Gantz NM et al. Chronic fatigue syndrome: a working case definition. *Annals of Internal Medicine* 1988, **108**:387–389.

International Centre for Disease Control 1994 definition

Clinically evaluated, unexplained, persistent or relapsing chronic fatigue lasting more than six months

- of new or definite onset
- not the result of ongoing exertion
- not substantially alleviated by rest
- including substantial reduction in previous levels of occupational, social or personal activities

Clinical evaluation should include history, physical examination, mental state examination and laboratory tests, including FBC, ESR, LFTs, total protein, albumin, globulin, calcium, phosphate, glucose, urea, electrolytes, TSH and urinalysis.

Four of the following symptoms concurrently present for at least six months

- sore throat
- tender cervical or axillary lymph nodes
- muscle pain
- multi-joint pain
- new headaches
- unrefreshing sleep
- post-exertion malaise.

Exclusion criteria:

- active, unresolved, or suspected disease likely to cause fatigue
- psychotic, melancholic or bipolar depression
- psychotic disorders
- dementia
- anorexia or bulimia nervosa
- alcohol or other substance misuse
- severe obesity.

From: Fukuda K, Straus SE, Hickie I et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of Internal Medicine* 1994, **121**:953–959.

Oxford definition

Severe, disabling fatigue lasting at least six months that:

- affects both physical and mental functioning
- is present more than 50% of the time

Other symptoms possibly present:

- myalgia
- sleep disturbances
- mood disturbance.

Exclusion criteria:

- active, unresolved or suspected disease likely to cause fatigue
- psychotic, melancholic or bipolar depression (but not uncomplicated major depression)
- psychotic disorder
- dementia
- anorexia or bulimia nervosa.

From: Sharpe MK, Archard LC, Banatvala JE, et al. A report – chronic fatigue syndrome: Guidelines for research. *Journal of the Royal Society of Medicine* 1991, **84**:(2)118–121.

Australian definition

Disabling and prolonged feelings of physical tiredness or fatigue, exacerbated by physical activity, and:

- present for at least six months
- unexplained by an alternative diagnosis reached by history, laboratory, or physical examinations
- accompanied by new onset of neuropsychological symptoms including impaired short-term memory and concentration, decreased libido, and depressed mood. These symptoms usually have their onset at the same time as the physical fatigue, but are typically less persistent than those seen in classic depressive illness.

Exclusion criteria:

- chronic medical condition that may result in fatigue

- history of schizophrenia, other psychotic illnesses, or bipolar affective disorder.
- Drug or alcohol dependence makes CFS very unlikely.

From: Lloyd AR, Hickie I, Broughton CR, et al. Prevalence of chronic fatigue syndrome in an Australian population. *Med J Aust* 1990, **153**:522-528.

Canadian definition

A patient with ME/CFS will meet the criteria for fatigue, post-exertional malaise and/or fatigue, sleep dysfunction and pain (items 1–4); have two or more neurological/cognitive manifestations (item 5) and one or more symptoms from two of the categories of autonomic, neuroendocrine and immune manifestations (item 6); and adhere to item 7.

1. *Fatigue*: The patient has a significant degree of new onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level.
2. *Post-exertional malaise and/or fatigue*: There is an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post-exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. There is a pathologically slow recovery period—usually 24 hours or longer.
3. *Sleep dysfunction*:* There is unrefreshed sleep or sleep quantity or rhythm disturbances such as reversed or chaotic diurnal sleep rhythms.
4. *Pain*:* There is a significant degree of myalgia. Pain can be experienced in the muscles and/or joints, and is often widespread and migratory in nature. Often there are significant headaches of new type, pattern or severity.
5. *Neurological/cognitive manifestations*: Two or more of the following difficulties should be present: confusion, impairment of concentration and short-term memory consolidation, disorientation, difficulty with information processing, categorising and word retrieval, and perceptual and sensory disturbances – eg spatial instability and disorientation and inability to focus vision. Ataxia, muscle weakness and fasciculations are common. There may be overload phenomena: cognitive, sensory – eg photophobia and hypersensitivity to noise – and/or emotional overload, which may lead to “crash” periods and/or anxiety.

* There is a small number of patients who have no pain or sleep dysfunction, but no other diagnosis fits except ME/CFS. A diagnosis of ME/CFS can be entertained when this group has an infectious illness type onset.

6. *At least one symptom from two of the following categories:*
 - a. *Autonomic manifestations:* orthostatic intolerance – neurally mediated hypotension, postural orthostatic tachycardia syndrome, delayed postural hypotension; light-headedness; extreme pallor; nausea and irritable bowel syndrome; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmias; exertional dyspnoea.
 - b. *Neuroendocrine manifestations:* loss of thermostatic stability – subnormal body temperature and marked diurnal fluctuation, sweating episodes, recurrent feelings of feverishness and cold extremities; intolerance of extremes of heat and cold; marked weight change – anorexia or abnormal appetite; loss of adaptability and worsening of symptoms with stress.
 - c. *Immune manifestation:* tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms, general malaise, new sensitivities to food, medications and/or chemicals.
7. *The illness persists for at least six months.* It usually has a distinct onset,** although it may be gradual. Preliminary diagnosis may be possible earlier, three months is appropriate for children.

To be included, the symptoms must have begun or have been significantly altered after the onset of this illness. It is unlikely that a patient will suffer from all symptoms in 5 and 6. The disturbances tend to form symptom clusters that may fluctuate and change over time. Children may have numerous prominent symptoms but their order of severity tends to vary from day to day.

Exclusions: Exclude active disease processes that explain most of the major symptoms of fatigue, sleep disturbance, pain and cognitive dysfunction. It is essential to exclude certain diseases, which would be tragic to miss: Addison's disease, Cushing's syndrome, hypothyroidism, hyperthyroidism, iron deficiency, other treatable forms of anaemia, iron overload syndrome, diabetes mellitus, and cancer. It is also essential to exclude treatable sleep disorders such as upper airway resistance syndrome and obstructive or central sleep apnoea; rheumatological disorders such as rheumatoid arthritis, lupus, polymyositis and polymyalgia rheumatica; immune disorders such as AIDS; neurological disorders such as multiple sclerosis, Parkinsonism, myasthenia gravis and B12 deficiency; infectious diseases such as tuberculosis, chronic hepatitis, Lyme disease, etc; primary psychiatric disorders and substance abuse. Exclusion of other diagnoses, which cannot be reasonably excluded by the patient's history and physical examination, is achieved by laboratory testing and imaging. If a potentially confounding medical condition is under control, then the diagnosis of ME/CFS can be entertained if the patients meet the criteria otherwise.

** Some patients have been unhealthy for other reasons prior to the onset of ME/CFS and lack detectable triggers at onset and/or have more gradual or insidious onset.

Co-morbid entities: Fibromyalgia syndrome (FMS), myofascial pain syndrome, temporomandibular joint syndrome, irritable bowel syndrome, interstitial cystitis, irritable bladder syndrome, Raynaud's phenomenon, prolapsed mitral valve, depression, migraine, allergies, multiple chemical sensitivities, Hashimoto's thyroiditis, sicca syndrome, etc.

Such co-morbid entities may occur in the setting of ME/CFS. Others such as IBS may precede the development of ME/CFS by many years, but then become associated with it. The same holds true for migraines and depression. Their association is thus looser than between the symptoms within the syndrome. ME/CFS and FMS often closely connect and should be considered to be "overlap syndromes."

Idiopathic chronic fatigue: If the patient has unexplained prolonged fatigue (six months or more) but has insufficient symptoms to meet the criteria for CFS/ME, it should be classified as idiopathic chronic fatigue.

From: Carruthers, BM et al. myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. *Journal of Chronic Fatigue Syndrome* 2003, **11**(1):11–13.

Appendix 2: Critical appraisal form

Author, title etc.

Study type (tick all that apply)

- Randomised controlled trial
- Systematic review
- Meta-analysis
- Qualitative research
- Literature review
- Case study
- Cohort study
- Other

(please describe)

SCREENING QUESTIONS

1. Does the paper have a clearly focused aim or research question?

Yes No Can't tell

Consider:

- *population studied*
- *interventions delivered*
- *outcomes*
- *relevance of research.*

2. Is the chosen method appropriate?

Yes No Can't tell

Consider whether:

- *the authors explain their research design*
- *the chosen methods address the research question.*

3. Is it worth continuing?Yes No **PLEASE EXPLAIN****DETAILED QUESTIONS****4. Has the research been conducted rigorously?**Yes No Can't tell *Consider:*

- *search strategy described*
- *inclusions and exclusions*
- *more than one researcher*
- *resolving issues of bias.*

5. Is it clear how data has been analysed?Yes No Can't tell *Consider:*

- *were study results combined*
- *if so was this reasonable*
- *in-depth description of the analysis process*
- *all participants accounted for*
- *contradictory findings explained.*

6. Is there a clear statement of findings?Yes No Can't tell *Consider:*

- *sufficient evidence to support conclusions*
- *do findings support the research question*
- *precision of results*
- *all important variables considered.*

7. How are the results presented?*Consider:*

- *numerically, ie p-value, OR (odds ratio)*
- *narratively.*

8. What is the main result?

Consider:

- *how large is the size of the result*
- *how meaningful is the result*
- *how would you sum up the bottom-line result in one sentence.*

9. Are there limitations to the research?

Yes No Can't tell

Consider:

- *was the sample size large enough*
- *were all important outcomes considered*
- *was the intervention process adequately described*
- *was there any follow-up data*
- *do the authors acknowledge weaknesses.*

10. Can the results be applied to a UK context?

Yes No Can't tell

Consider:

- *any discussion on how the findings can be used*
- *findings considered in relation to current practice*
- *estimation of benefits and costs.*

ACCEPT FOR INCLUSION AS EVIDENCE?

Yes No Can't tell

REFER TO GUIDELINE DEVELOPMENT GROUP LEADER?

Yes No

Appendix 3: Recording form for appraisal and grading

Title:

Author:

DISCUSSED (tick as appropriate)

1. Electronically
2. By telephone
3. Face-to-face

DISCUSSED (tick as appropriate)

1. Once only
2. Twice
3. Several times

APPRAISAL (attach completed forms)

(tick as appropriate)

1. Complete agreement
2. Negotiated agreement
 - a. Process ?
3. Referral to guideline leader
 - a. Outcome?

GRADING (tick as appropriate)

- 1. Complete agreement
- 2. Negotiated agreement
 - a. Process?
- 3. Referral to third party?
 - a. Outcome?

CONCLUSION

Level of evidence (circle one)

1++ 1+ 1- 2++ 2+ 2- 3 4

Appendix 4: Evidence table for included papers

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results
Butler [40]	Cohort	2+	50 patients at outpatient clinic in London	Cognitive behaviour therapy in CFS.	<p>Two sets of outcome measures were used:</p> <ul style="list-style-type: none"> self-administered questionnaires, including General Health Questionnaire and Hospital Anxiety and Depression Scale functional disability instruments, including a visual analogue scale covering the ability to work. <p>Scores for ability to work were:</p> <ul style="list-style-type: none"> 6.31 before treatment (95% CI = 5.57-7.05) 2.72 after treatment (95% CI = 1.77-3.65) <p>Range = 0 to 8 where 8 is most impaired.</p>
Cairns [46]	Systematic review	2++ for prognosis 4 for opinion on deferring ill health retirement until treatment has been given	28 Studies met inclusion criteria for the study. 14 of which met operational criteria for CFS	A systematic review describing the prognosis of CFS.	<p>Full recovery from untreated CFS is rare. The prognosis for improvement in symptoms is less gloomy.</p> <p>There is increasing evidence for the effectiveness of CBT and GET.</p> <p>Medical retirement should be postponed until a trial of such treatment has been given (opinion of authors).</p>

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results
Deale 1997 [22]	RCT	1++	<p>Patients with CFS (Oxford or CDC definition) who were referred from both primary care and consultants to a UK hospital clinic specializing in CFS.</p> <p>60 patients were randomly allocated to CBT (graded activity and cognitive restructuring) or relaxation.</p> <p>53 completed the treatment (three dropped out of CBT and four from relaxation)</p>	CBT for CFS: a randomised controlled trial.	<p>This was an RCT which compared the effectiveness of 13 sessions of CBT with 13 sessions of relaxation. The study looked at 10 different outcome measures, one of which was the Work and Social Adjustment Scale (WASAS). This scale measures impairment in work, home management, social activities and private leisure. Impairments are measured on a scale of 0–8. 8 represents maximum impairment.</p> <p>Pre-treatment mean WASAS was 6.0 for the 30 CBT patients and 6.1 for the 30 relaxation patients.</p> <p>At 6 months after treatment, mean WASAS was 3.3 for the CBT group and 5.4 for the relaxation group.</p> <p>At six months follow-up, 70% of those who had completed CBT achieved substantial improvement in physical functioning compared with 19% of the relaxation group.</p>
Deale 2001 [23]	RCT	1+	<p>60 patients who met UK criteria for CFS and who had been randomised to receive either CBT or relaxation therapy five years previously.</p> <p>Patients completed self-rated outcome questionnaires and a structured interview with an assessor blinded to which treatment they had received.</p>	Long term outcome of CBT versus relaxation therapy – a five-year follow-up study.	<p>53 out of the original 60 patients consented to participate in this follow-up study.</p> <p>Significantly more of the CBT group met criteria for complete recovery and were free of relapse.</p> <p>Similar proportions of both groups were employed but the CBT group worked significantly more hours per week.</p> <p>56% of the CBT group were in full or part-time employment, in comparison to 39% of the relaxation group.</p> <p>Mean number of hours worked per week:</p> <ul style="list-style-type: none"> CBT group – 35.57 Relaxation group – 24 <p>Mean number of relapses since completion of treatment:</p> <ul style="list-style-type: none"> CBT group – 2.58 Relaxation group – 4.08

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results
Fulcher [32]	RCT	1+	66 patients with CFS in a general hospital department of psychiatry in London. Mean age = 37.2. 74% were women. Median duration of illness = 2.7 years.	RCT of graded exercise in patients with CFS. Patients were randomly allocated to 12 weeks of either graded aerobic exercise or flexibility exercises and relaxation therapy.	Patients were followed up by questionnaire approximately one year after supervised treatment stopped. 66% of patients who completed exercise treatment were working or studying at least part-time, compared with 39% of all 66 patients before treatment (95% confidence interval of difference 9% to 44%).
Glozier [57]	Commentary on in-depth review of CFS for occupational health professionals (non-systematic review of literature)	4 (expert opinion)	Individuals with CFS	Gives overview of CFS, including definitions, prognosis and treatments. Mentions Disability Discrimination Act (DDA) case and suggests adjustments.	Useful expert opinion on possible workplace adjustments to comply with DDA. States that "making disability claims or taking medical retirement also predicts poorer treatment outcome, although this may reflect condition severity."

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results
Morantz [54]	Systematic review	2++	A systematic review was performed from 1 January 1988 to 15 November 2001. Observational and interventional studies of CFS were included. Studies accepted for inclusion were required to report CFS diagnosed by one of the following four definitions – CDC 1988, CDC 1994, Oxford 1991 or Australia 1990. Studies also had to report at least one measure of physical or mental impairment.	Systematic review of literature 1988–2001.	A systematic review of CFS studies from 1988 to 2001 identified 37 papers that looked at work outcomes. This review is relevant to both key questions 1 and 3. The paper concludes that: <ol style="list-style-type: none"> 1. Some CFS patients who underwent a variety of interventions ranging from no treatment to individualised rehabilitation programmes were able to return to work, but the sample sizes are too small and the study designs too disparate to allow comparisons of different treatments in their association with returning CFS patients to work. 2. No patient characteristics in any impairment domain have been consistently identified that best define or predict improvement or positive work or functional outcomes in the CFS population. 3. <i>Depression</i> was the only impairment that appeared to be consistently associated with disability or work outcomes.
Prins [27]	RCT	1+	278 patients with CFS (CDC criteria) at an outpatient clinic in Maastricht were randomly assigned as follows: <ul style="list-style-type: none"> • CBT – 93 • support group – 94 • natural course – 91 CBT consisted of 16 sessions of one hour over eight months. Guided support groups consisted of 11 meetings of 1.5 hours over eight months.	Cognitive behaviour therapy for CFS: a multicentre randomised controlled trial.	Multidimensional assessments were made at baseline, eight months and 14 months. This included fatigue severity (checklist individual strength CIS is the name for a commonly used fatigue scale) – often referred to in CFS research functional impairment (sickness impact profile) and hours working in a job. In the sample of 278 patients, 33% had a job at baseline whereas 76% had been employed prior to the onset of CFS. Although at 14 months CBT was significantly more effective than both control conditions for fatigue severity, differences in the time spent working in a job did not reach the 5% level of significance.

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results
Rimes [49]	Literature search	4	Search strategy was chronic fatigue or post-viral fatigue or myalgic encephalitis or myalgic encephalomyelitis and trial or treatment or intervention.	Treatments for CFS. The study discusses CBT, GET, pharmacological, immunological, nutritional supplements, complementary/alternative treatments and prolonged rest.	<p>Predictors of response to CBT:</p> <ul style="list-style-type: none"> • poor social and occupational functioning prior to becoming ill (predicted poor outcome in one study) • low sense of control in relation to CFS complaints • a very passive activity pattern • a high level of focusing on bodily symptoms • taking medical retirement • making a new claim for a disability-related benefit during treatment. <p>In one study, attributing CFS symptoms mainly to a physical cause predicted poorer outcome in CBT. However, in another study, attributing CFS to physical causes (eg a virus) did not affect the outcome.</p> <p>The study discusses possible precipitating factors and perpetuating factors in CFS.</p> <p>The authors suggest advice that can be given to individuals in the early stages of fatigue, including self-help material specific to chronic fatigue.</p> <p>They also recommend regular review.</p> <p>The authors advise liaison between the patient (employee), his/her manager, occupational health and human resources. It is important to explore whether any work issues may be contributing to fatigue.</p> <p>They advise an individualised return-to-work plan, such as:</p> <ul style="list-style-type: none"> • building up work or work-related skills at home or in a voluntary position initially • gradually increasing hours of work • taking regular breaks.

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results
Ross [48]	Systematic review	2++	A systematic review was performed of studies dating from 1 January 1988 to 15 November 2001. Observational and interventional studies of CFS were included. Studies were required to report CFS in one of four definitions – CDC 1988, CDC 1994, Oxford 1991 or Australia 1990. Studies also had to report at least one measure of physical or mental impairment	<p>A multidisciplinary expert panel developed four questions to guide the review:</p> <ol style="list-style-type: none"> 1. What is the evidence that some individuals with CFS have discrete impairments that are associated with disability? 2. What is the evidence that, in the CFS population, current neuropsychological tests reliably detect cognitive or affective impairments associated with decreased ability to work? 3. What is the evidence that, in individuals with CFS, treatments are effective in restoring the ability to work? 4. What are the patient characteristics that best define improvement or positive outcomes in the CFS population such that they experience improvement in functioning? Where it occurs, how is this improvement in functioning related to the ability to engage in work activity? 	<p>Of 3,840 studies identified, 37 reported employment status and some measure of physical or mental impairment.</p> <p>Only <i>depression</i> seemed to be associated with unemployment in patients with CFS. No other measurable impairment seemed to be consistently associated with disability or work outcomes.</p> <p>Only CBT, rehabilitation and exercise therapy interventions were associated with restoring the ability to work.</p> <p>No specific patient characteristics were identified as best predictors of positive employment outcomes.</p> <p>Note: The Morantz (p.48) and Ross papers used the same data, although Morantz was published in 2003 and Ross in 2004. Despite using the same data, the papers have drawn slightly different conclusions.</p>

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results
Russo [50]	Longitudinal No intervention	2+	<p>98 of 100 consecutive patients seen at the Chronic Fatigue Clinic at the University of Washington.</p> <p>Patients were not required to meet the CDC case definition for CFS but were required to had at least six months of fatigue.</p> <p>78 of the 98 patients who completed self-report questionnaires, had a psychiatric interview and physical examination at two evaluation points, Time 1 and Time 2, which were an average of 2.5 years apart.</p>	<p>Longitudinal changes associated with improvement in chronic fatigue patients.</p> <p>The aim of the study was to examine changes in symptoms, CFS criteria, physical signs, functioning, and psychiatric disorders over a 2.5 year period, and to determine which of these changes were most related to return to work.</p>	<p>29.5% of patients returned to work by Time 2. Changes in the number of <i>physical signs</i> and changes in <i>psychiatric diagnoses</i> were significant predictors of resuming work:</p> <ul style="list-style-type: none"> • 42.2% of patients with less than two physical signs resumed work. • None of patients with two or more physical signs at Time 1 and Time 2 had resumed work by Time 2. <p>Only 4.3% of those with a current psychiatric diagnosis at Time 2 or at both Time 1 and Time 2 resumed work. 40% of patients in three other subgroups (no current psychiatric diagnosis, a prior history of psychiatric illness only having had a psychiatric diagnosis only at Time 1) resumed work.</p>
Tiersky [55]	Cohort	2+	<p>Patients who met the 1988 and 1994 CDC criteria for CFS at a fatigue research centre in the USA.</p> <p>47 patients underwent a physical and psychological assessment at baseline (Time 1) This included employment status (full- or part-time, unemployed or retired due to ill health).</p> <p>The evaluation was repeated on 35 patients (74.5% of the original sample) at a mean of 41.9 months after time 1 (Time 2).</p>	<p>Longitudinal assessment of neuropsychological functioning, psychiatric status, functional disability and employment status in CFS.</p>	<p>The sample did not change significantly in employment status from Time 1 to Time 2. 68% of participants were unemployed at both times.</p> <p>Two baseline factors were identified as predictors of employment status:</p> <ul style="list-style-type: none"> • Being <i>older</i> at baseline lowered the odds of being employed at Time 2 • Having a <i>concurrent psychiatric diagnosis</i> at intake increased the odds of being employed at Time 2. <p>The authors postulate that one reason why patients with a concurrent psychiatric history may demonstrate better outcomes than CFS patients with no such history is that the aetiology of their CFS may differ.</p> <p>Participants in this study also showed some improvement in neuropsychological functioning with time and the authors therefore suggest periodic re-evaluation of patients to establish their current level of functioning.</p>

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results
Tritt [56]	Cross-sectional	2+	<p>1,000 randomly selected patients at a psychosomatic inpatient clinic in Germany. Psychosomatic clinics in Germany treat a wide spectrum of conditions, including CFS.</p> <p>83.9% agreed to participate in the study by completing a questionnaire that looked at 141 variables including age, sex, life situation and life satisfaction.</p> <p>Patients with CFS who were fit for work were compared with those with CFS who had been off work for six months or more ("employment disabled") to look for predictors of long-term employment disability.</p>	Chronic fatigue and indicators of long-term employment disability in psychosomatic inpatients.	<p>This study aimed to investigate how CFS patients who are capable of working differ from those who are incapable of working. It also aimed to establish if there are any predictors of long-term employment disability in fatigued patients.</p> <p>In comparison to those who were fit for work, the employment-disabled CFS group had significantly more physical complaints, more frequently reported difficulties getting along with other people (superiors and colleagues) at work and in dealing with the public and considered that "work is not an important part of life".</p> <p>The employment-disabled group also reported severe restrictions in strenuous activities, eg running fast for over 1km, and in concentrating for longer periods.</p>

Appendix 5: Evidence table for excluded papers

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results
Agaki [59]	Longitudinal	2-	<p>Patients referred to Department of Psychological Medicine in Oxford between 1991 and 1997, aged 16–65.</p> <p>94 patients who met criteria for CFS (Oxford)/ neurasthenia were offered treatment.</p> <p>58 completed treatment which included shared understanding of the problem, graded exercise, cognitive challenge and problem solving. These 58 patients completed a median of six sessions (range 1–39) over a median six-month period (range 1–41)</p>	CBT for CFS in a general hospital – feasibility and effectiveness.	<p>All patients offered CBT were included in follow-up, whether or not they had accepted treatment. All patients had been discharged at least three months before they were contacted and asked to complete a questionnaire.</p> <p>Patients were asked to rate (on a four-point scale) their symptoms, functional impairment and effects on social life (1) over the previous month and (2) when their CFS was at its worst.</p> <p>88% (45 out of 51) in the treatment group had changed occupation and 76% (39 out of 51) attributed this to CFS.</p> <p>At follow-up, 53% were in work or study in comparison to 29% pre-treatment. 65% mentioned occupational stress as a contributory factor in their illness.</p>

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results
Bombardier [60]	Longitudinal no intervention	2-	<p>445 out of 498 consecutive patients who underwent an initial evaluation at a chronic fatigue clinic in Seattle. Patients were either self-referred or referred by a physician. Patients were classified as having CFS if they met the CDC 1988 criteria.</p> <p>Mean age was 39 years and 331 (74%) were women. Average length of education was 14 years.</p> <p>At the initial clinic visit, average duration of fatigue was five years, and 226 (51%) met the case definition for CFS.</p>	Outcome and prognosis of patients with chronic fatigue versus CFS.	<p>A follow-up questionnaire was sent to 498 consecutive clinic patients at on average 1.5 years (range = one month to 2.7 years) after the initial evaluation.</p> <p>Outcome measures included employment status during the previous three months and whether in full- or part-time work.</p> <p>Patients were divided into two groups, chronic fatigue and CFS, based on whether they met the CDC definition at initial evaluation.</p> <p>The aim was to determine which demographic and clinical variables predicted subsequent improvement and return to work.</p> <p>At follow-up 103 (46%) of the CFS group met criteria for CFS.</p> <p>In the <i>chronic fatigue group</i>, <i>age</i> and <i>duration of fatigue</i> were negatively correlated with return to work. Those who returned to work were significantly less likely to have a current diagnosis of major depression at the initial evaluation.</p> <p>However, in the <i>CFS group</i>, none of the initial demographic, clinical or psychiatric variables were predictive of return to work.</p>
Huibers [61]	RCT	1-	<p>151 employees on sick leave with fatigue in Dutch general practice.</p> <p>One group was offered five to seven 30-minute sessions of CBT by a GP. The control group was offered no treatment.</p>	CBT by general practitioners for unexplained fatigue among employees.	<p>There was no significant difference in outcomes between the experimental and control groups.</p> <p>Outcome measures were fatigue severity, self-reported absenteeism, registered absenteeism and clinical recovery. These were assessed at four months, eight months and 12 months.</p> <p>As study population was heterogeneous with only 44% of the employees meeting criteria for CFS at baseline. In addition, the duration of CBT was shorter than other studies which have shown CBT to be effective in CFS.</p>

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results
Marlin [62]	Cohort	4	<p>Canadian private clinic treating patients with chronic disability, including CFS. Patients are referred mainly by employers and disability benefits providers, for assessment and treatment.</p> <p>Patients with CFS undergo a multidisciplinary assessment by a physician, a psychiatrist, a psychologist and a physiotherapist.</p> <p>An individualised treatment programme is developed that includes structured physical exercise, sleep management strategies, activity management, regulation of stimulant intake, cognitive intervention, participation of patient's family and establishment of vocational and avocational goals.</p> <p>71 patients entered the study – 51 had multidisciplinary treatment and 20 were left untreated. Patients were not randomly selected for either assessment or intervention.</p> <p>The average duration of treatment was six months (range 2–12 months).</p>	An evaluation of multidisciplinary intervention for CFS with long-term follow-up and a comparison with untreated controls.	<p>Of 51 treated patients, meeting the Fukuda definition of CFS, 31 returned to full-time gainful employment, 14 were functioning at a level equivalent to employment and 6 remained significantly disabled. Untreated patients showed improvement in only a minority of cases.</p> <p>Limitations of this study:</p> <ul style="list-style-type: none"> • Patients were not randomly selected for either assessment or intervention. • There is very limited data on the work outcomes of those patients who were not treated. • The individualised treatment programme contained many different treatments so it is very difficult to assess to which extent each contributed to improvement in work outcomes.

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results
Masuda [63]	Cohort	2-	<p>18 patients who met the CDC criteria for CFS and who attended clinics in Kagoshima University Hospital, Japan.</p> <p>Nine patients had developed CFS after a definite infection. The other nine had no history of infection during the preceding three years.</p>	Prognosis after multidisciplinary treatment for patients with post-infectious CFS and non-infectious CFS.	<p>Both groups of patients underwent three-stage treatment programmes, including medication (vitamin C, “herbal” medicine, and psychotropic medication for symptoms such as insomnia, anxiety and depression) CBT and exercise therapy.</p> <p>Two years after completion of treatment, eight of the post-infectious group had returned to work (five of these patients had changed occupation or workplace). In the non-infectious group, only three patients had returned to work.</p> <p>Limitations of this study:</p> <ul style="list-style-type: none"> • small numbers • ambiguous selection criteria. • no control group • a mixture of treatment strategies used, making it difficult to draw a conclusion.
McDermott [64]	Cohort	2-	98 consecutive patients attending a UK rheumatology department who fulfilled the 1994 CDC criteria for CFS were offered a place in a lifestyle management group led by a senior occupational therapist. Of these, 74 chose to participate.	Evaluation of a lifestyle management programme focusing on the outcome of return to work or training.	<p>The programme consisted of six two-hour group sessions at fortnightly intervals. Additional sessions were held at six weeks, six months and one year. The aim was to empower patients to gain greater control of their symptoms by explaining and exploring some of the complex interactions of the condition. The programme used pacing as its core strategy but also applied techniques derived from CBT and, in some patients, GET.</p> <p>42% of the 74 patients who participated in the programme had returned to new employment, voluntary work or training when followed up at a median of 18 months.</p> <p>The authors of this non-randomised study highlight the need for an adequately powered RCT to compare lifestyle management with CBT and GET.</p> <p>Limitations of this study:</p> <ul style="list-style-type: none"> • no control group • a mixture of treatment strategies used a making it difficult to draw a conclusion.

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results
Ranjith [8]	Non-systematic literature review	2-	Individuals with CFS as well as those with fatigue.	Epidemiology of CFS.	<p>Fatigue as a symptom is very common but CFS is relatively rare.</p> <p>The paper looks at prevalence and incidence of both fatigue and CFS.</p> <p>Some occupational groups have traditionally been held to have higher rates of fatigue than control groups. These include healthcare workers, shift workers and airline pilots. However, much of the literature refers to fatigue as a symptom and therefore may not be applicable to CFS.</p>
Taylor [65]	Expert opinion	4	Included inpatient, outpatient and community-based treatment studies of children, adolescents and adults with unexplained chronic fatigue or CFS (both 1994 and CDC Oxford criteria)	CFS: traditional and community-based approaches to rehabilitation.	<p>This is a literature review comparing traditional approaches (CBT with graded activity, GET, “activity pacing and energy conservation” and “supportive counselling and multidisciplinary inpatient programmes”) with community-based approaches such as social support programmes and multidisciplinary programmes.</p> <p>The author summarises and critically reviews these studies as well as comparing and contrasting the benefits and limitations of traditional and community-based approaches.</p> <p>The paper is narrative rather than being a systematic review.</p> <p>The only reference to employment outcomes is a summary of a study by Marlin et al. (1998), “Community-based multi-disciplinary treatment programme”, which looks at percentages of subjects returning to gainful employment. This paper had already been identified in our literature search and has been critically appraised by the group.</p>

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results
Wallman [36]	RCT	1++	<p>61 patients with CFS (1994 CDC definition) recruited from notices placed in medical surgeries and adverts in local newspapers in Australia.</p> <p>Patients were randomised to 12 weeks of graded exercise (32 patients) or 12 weeks of relaxation/flexibility therapy (29 patients).</p>	RCT of graded exercise in CFS.	<p>This paper does not contain any work outcomes although it does comment on “improvements in physical work capacity”.</p> <p>The paper also comments that improvements may be associated with the abandonment of avoidance behaviours.</p>

First author	Study design	Research quality (sign grading)	Study population	Research topic	Main results



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