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IN-DEPTH REVIEW

A systematic review describing the prognosis of chronic fatigue syndrome

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Aim To perform a systematic review of studies describing the prognosis of chronic fatigue (CF) and chronic fatigue syndrome (CFS) and to identify occupational outcomes from such studies.

Method A literature search was used to identify all studies describing the clinical follow-up of patients following a diagnosis of CF or CFS. The prognosis is described in terms of the proportion of individuals improved during the period of follow-up. Return to work, other medical illnesses and death as outcomes are also considered, as are variables which may influence prognosis.

Results Twenty-eight articles met the inclusion criteria and, for the 14 studies of subjects meeting operational criteria for CFS, 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%). Less fatigue severity at baseline, a sense of control over symptoms and not attributing illness to a physical cause were all associated with a good outcome. Return to work at follow-up ranged from 8 to 30% in the three studies that considered this outcome.

Conclusions Full recovery from untreated CFS is rare. The prognosis for an improvement in symptoms is less gloomy. This review looks at the course of CF/CFS without systematic intervention. However, there is increasing evidence for the effectiveness of cognitive behavioural and graded exercise therapies. Medical retirement should be postponed until a trial of such treatment has been given.

Key words Chronic fatigue syndrome (CFS); outcomes; prognosis.

Introduction

Chronic fatigue syndrome (CFS) is characterized by persistent or relapsing unexplained fatigue of new or definite onset lasting for at least 6 months. Its prevalence has been reported as 0.1–2.6% in community- and primary care-based studies, depending on the criteria used [1]. Operational criteria developed for research purposes by the US Centers for Disease Control and Prevention [2] and from Oxford [3] are now widely used to define CFS. Although there are a number of similarities between the two, important differences are also apparent. The British criteria require the presence of both mental and physical fatigue whereas the American criteria include a requirement for several physical symptoms, reflecting the belief that an infective or immune process underlies the syndrome [4]. Despite this, the aetiology of CFS remains poorly understood and it appears to be a heterogeneous disease process that can be caused by a number of factors.

Both chronic fatigue (CF) and CFS are associated with significant disability and dysfunction both at home and at work. Kroenke *et al.* found this to be comparable with the disability experienced in well-recognized medical conditions such as untreated hyperthyroidism and following myocardial infarction [5]. Rates of unemployment for patients attending a CF clinic in Washington and meeting operational criteria for CFS were 37% [6]. One previous literature review has been concerned with the prognosis of CF and CFS [7]. The authors found that studies used a wide variety of definitions of CF and CFS and relatively few studies used operational criteria for CFS. There has been an upsurge in research concerning CFS in recent years and operational criteria have been used in an increasing number of studies looking at the prognosis of CFS. This review therefore aims to build on the work of the previous authors.

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Aims

This review will update the previous work by Joyce, Hotopf and Wessely and will describe the prognosis of CFS in terms of the proportion of individuals improved during the period of follow-up [7]. It will also describe other reported outcomes such as additional medical illnesses and deaths. Consideration will be given to return to work as an outcome measure when these data are available. Finally, many studies concerned with prognosis have simultaneously examined variables which may influence prognosis and these data will also be included.

Method

A comprehensive search of the relevant literature was undertaken using electronic databases (MEDLINE, EMBASE and PSYCHINFO from January 1980 until October 2003), reference lists and personal contact. The search strategy was any of CFS, myalgic encephalitis, asthenia and neurasthenia in addition to (chronic OR persistent OR postviral) and (fatigue OR exhaustion OR tiredness) for journals published between 1980 and 1996. The latter terms were not included for journals from 1996 onwards as it was judged that the now widespread acceptance of operational criteria would allow identification of relevant studies using a narrower search. All references were checked in title and abstract.

Inclusion/exclusion criteria

Studies were included whether they contained original data describing the clinical follow-up or outcomes of patients following a diagnosis of CFS or CF from an English-language peer-review journal. Exclusion criteria included data concerned with CFS in childhood or adolescence, papers which used mixed diagnostic categories (other than fatigue on the continuum with CFS) or mixed target symptoms (e.g. fatigue and pain) as entry criteria. Where patients were receiving treatment as usual (ranging from acknowledging the reality of illness to pharmacological treatment of co-morbid depression or the recommendation of moderate exercise), the papers were included. However, papers whose main theme was the systematic investigation of active biological or psychological therapy were not included, unless they included a placebo group and follow-up was greater than 12 months.

Data extraction

Studies were categorized according to their design and then further analyzed using a checklist constructed for the purpose of the review. This focused upon variables such as social demographic characteristics of the sample, the setting of the study, inclusion criteria, sample size, patients lost to follow-up and the main outcome measures used.

A wide range of instruments and variables were used to measure outcomes in the different studies. Although this heterogeneity made direct comparison of study outcomes difficult, it was possible to extract information from each paper about global or overall patient outcomes. The data are therefore summarized in terms of the proportion of patients 'recovered', 'improved', 'remaining the same' or 'worse' at the point of follow-up. The results are presented in table form, according to diagnostic criteria and study setting, to allow more detailed presentation of the outcome measures used and other reported outcomes. Separate tables contain information related to variables that may modify prognosis and occupational data/outcomes.

Results

Twenty-eight articles met the inclusion criteria for containing satisfactory data. Fourteen of these studies contained only subjects meeting operational criteria for CFS and 14 contained mixed subjects (a combination of CF and CFS). Twenty-three studies were naturalistic or prospective cohort studies, three were retrospective cohort studies and two were randomized controlled trials (RCTs). In the previous review by Joyce *et al.* [7], only four of the 22 studies looking at fatigue in adults were concerned with operationally defined CFS.

The quality of the studies was varied and 50% (7/14) of the mixed diagnostic group studies failed systematically to exclude psychiatric and/or organic diagnoses. The sample size ranged from 20 to 3201 (median 78.5%) and the response/follow-up rate ranged from 50 to 100% (median 82.5%). The duration of symptoms at study outset and duration of the follow-up period varied considerably. As would be expected from the epidemiology of CFS, the gender distribution was predominantly female in the majority of the studies.

Outcome of studies

Mortality and medical illnesses

Twelve of the 25 studies reported the presence or absence of alternative outcomes of either death or a newly diagnosed medical condition. In the remaining studies, where no report was made, it was often not clear whether this information was collected and these outcomes may have been under-reported.

Eight deaths were recorded: two of these were unrelated to CFS [8], one was by suicide [8] and the circumstances of the other five were unclear [10–12]. Newly diagnosed medical illnesses were reported in seven studies and there were 26 cases of new organic

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diagnosis in total. Wilson *et al.* reported one case of dementia and a case of systemic lupus erythematosus from 103 patients re-contacted [13]. Hill *et al.* reported one case of newly diagnosed hypothyroidism amongst 23 patients followed-up, although the patient's fatigue persisted despite treatment for this [14]. Bates *et al.* reported newly diagnosed hypothyroidism in three of 26 patients recruited to the study [15]. Amongst those followed after an outbreak of unexplained fatigue, 13% [3] were diagnosed with significant other disorders (bladder cancer, ulcerative colitis and asthma) and 17% [4] were found to have severe hepatomegaly, including one with prolonged jaundice [8]. In a community sample of 74 patients, previously undiagnosed medical conditions associated with fatigue were documented in five patients [16]. Five patients developed 'other diseases' during the multi-centre RCT of cognitive behavioural therapy (CBT) versus support and natural course groups [17]. Finally, Deale *et al.* recorded three newly diagnosed medical conditions during follow-up (two cases of coeliac disease and one case of cancer) [34].

Global Improvement

Table 1 presents the main outcomes of the 14 studies that used operational criteria to define cohorts of patients with CFS. Ten of the studies report the outcome of recovery and improvement separately while two describe self-reported improvement that presumably encompasses full recovery as an outcome [17,19] and two describe only recovery as an outcome [20,21]. The median full recovery rate during the follow-up periods was 7% (range 0–48%) and the median proportion of patients who improved during follow-up was 39.5% (range 8–63%). Recovery rate varied according to duration of follow-up with the study of Reyes *et al.* showing 31% recovery at 5 years compared with 48% at 10 years [20]. In five studies, a worsening of symptoms during the period of follow-up was reported in between 5 and 20% of patients. Three studies reported notably higher recovery rates than others. The reported 20% recovery rate and 60% improvement in Saltzstein *et al.*'s naturalistic study of CFS among women may be partly explained by its primary care setting, suggesting that the severity or chronicity of symptoms may be less than in secondary care [22]. Sixty-three percent (65/103) of subjects in Wilson *et al.*'s longitudinal study of patients from a chronic fatigue referral centre reported improvement but complete recovery rates of 6% were more consistent with other reports [13]. The longer duration of follow-up for this study may be important and may suggest that improvement does occur in CFS, albeit gradually. Similar rates of improvement were also seen in Ray *et al.*'s naturalistic study of 147 patients from a hospital outpatient clinic but presumably this value of 63% also includes patients who achieved a full recovery [19].

Table 2 shows similar data for the 14 studies that included patients fulfilling operational criteria for CFS and patients with chronic fatigue but not meeting operational criteria. The results are presented according to the study setting. The outcomes of the four primary care studies are difficult to compare in a meaningful way due to different diagnostic categories and a variety of outcomes. The outcomes reported by Skapinakis *et al.* show rates of remission ranging from 61 to 80% in an international sample of primary care attenders, depending on the severity of fatigue experienced [23]. Similarly promising results are reported by Levine *et al.* with 'almost all' study subjects able to return to pre-illness activity after 3 years follow-up [24]. The improvement reported in 22% of patients in Valdini *et al.*'s study and recovery of 23% in the study of Bates *et al.* are more consistent with the outcomes reported in Table 1 [15,25].

The secondary care studies in Table 2 reported a median recovery rate of 23.5% (range 2–70%). The median proportion of patients who improved during follow-up was 44% (range 38–64%) for the four studies that reported this as an outcome. Three studies reported a worsening of symptoms in 13%, 24% and 26% of patients at follow-up [11,26,27]. It is of note that the 70% recovery rate was reported in a study concerned with 28 mixed cases of fatigue followed up 10 years after an outbreak of unexplained fatigue [8]. The authors comment that the clinical course of CFS in this cluster of patients appears to be much better than that for sporadic cases of CFS. They also suggest that this study of the West Otago cluster provides evidence to support the validity of similarly high recovery rates found in the earlier primary care study looking at the northern Nevada/California cluster [24]. Interestingly, this is not reflected in Strickland *et al.*'s 10-year follow-up of the outbreak in Northern Nevada/California [12].

Two community-based studies are included in Table 2. Both reported on the resolution of symptoms rather than improvement. Forty-nine percent of patients had recovered after 3 years in the study of Taylor *et al.* compared with only 22% after 12 months in Buchwald *et al.*'s study [16,28].

Factors related to recovery

As in Joyce *et al.*'s previous review [7], predictors of outcome were considered in terms of demographic, psychological and physical variables as well as characteristics of the initial illness. These are summarized in Table 3.

Demographics: No clear patterns emerged. Four studies suggested that older age was predictive of a worse

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Table 1. Design of included studies

Study	Setting and definition	Duration of symptoms at outset	Main outcome used	Detailed notes on outcome
Peterson *et al.* [32]	CFS clinic. 75 CFS (CDC 1988) patients	1–18 years	Postal questionnaire at 12 months follow-up	91% contact: no recoveries; 40% improved; 10–20% worsening of symptoms
Hinds and McCluskey [29]	Immunology clinic. 393 CFS (CDC 1988) patients	Not known	Postal questionnaire (duration of follow-up unclear)	74% followed-up: 54/291 (19%) recovered; 35% improving; 5% worse; remainder relapses and remissions
Tirelli *et al.* [33]	CFS referral centre. 265 CFS (CDC 1988) cases	Median 3 years, range 6 months–10 years	Followed at mean of 24 months	100% followed-up: 8/265 method of FU unclear, 3% recovery; 22/265 (8%) substantial decrease in symptoms. Symptoms persisted in remainder
Wilson *et al.* [13]	CFS referral centre. 139 CFS patients meeting Australian criteria	Mean 9.2 years, range 3–30 years	Mean of 39 months follow-up (self-report, Karnofsky score, disability benefits received, GHQ-30)	103 (74%) contacted; six completely recovered; 65/103 improved and 31/103 unable to work. Karnofsky rating 76.3 (disability measure). Two new diagnoses: one dementia, one SLE
Vercoulen *et al.* [10]	Hospital sample of 296 self-referred CFS (Oxford) patients	Median 4.5 years, range 2–54 years	Mean follow-up at 18 months. Postal questionnaire for patients' self-report, BDI, SIP and functional impairment	83% followed-up: 3% reported full recovery; 17% reported improvement; 20% worse
Ray *et al.* [19]	Hospital outpatient clinic. 147 CFS (Oxford) patients	No more than 6 years—no further detail	Twelve month follow-up (fatigue severity, functional impairment, rating of overall change).	93% followed-up: 63% perceived improvement; 24% no change; 13% worse
Saltzstein *et al.* [22]	20 CFS (CDC) patients in primary care	Seven less than 2 years; four between 2 and 5 years; four between 6 and 8 years	Postal questionnaire 24 months after initial interview	15/20 (75%) contact: 20% worse or the same; 60% improved; 20% recovered. All treated by the same doctor in primary care
Reyes *et al.* [20]	Referrals to CDC surveillance by physicians in four US cities. 160 CFS (1988 case definition prior to 1994 and then CDC criteria) patients	Median 4.4 years, range 0.65–32.8 years	Telephone interviews every 6 months for 3.5 years. Outcomes presented as cumulative probabilities of recovery	97% took part in follow-up, response rate 91% for all seven interviews: 31% perceived recovery within first 5 years of illness, 48% reported recovery within 10 years. Recovery reported with respect to last 4 weeks—no adjustment for whether permanent/temporary. No deaths

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Table 1. (*continued*)

Study	Setting and definition	Duration of symptoms at outset	Main outcome used	Detailed notes on outcome
Hill *et al.* [14]	CFS research centre. 23 CFS (1988 case definition—all substantial or worse in severity) patients	Median 2.4 years, range 0.8–4.4	Follow-up by postal questionnaire at time 2 (6 months–2 years after enrolment) and by assessment at time 3 (1–3 years after time 2). Outcome categories based on reports of activity reduction and severity of minor symptoms present	Data for 23 patients: one recovered (4%); nine improved but still met CFS criteria (39%); 13 remained the same (57%). One patient diagnosed with hypothyroidism but fatigue continued despite treatment
Deale *et al.* [34]	Chronic fatigue clinic. RCT of 60 CFS (Oxford) patients randomized to receive either CBT or relaxation therapy (as a control)	Not known	Five year follow-up with assessor blind to treatment received. Measures of global improvement, fatigue, physical functioning, GHQ, relapse frequency and predetermined criteria for 'complete recovery'	53/60 (88%) agreed to take part: 17/25 (68%) CBT group much or very much improved at 5-year follow-up compared with 10/28 (36%) of control group. Complete recovery in 24% and 4% of CBT and control groups, respectively. 3/25 (12%) of CBT group had new medical diagnosis at 5-year follow-up—one cancer; two coeliac disease
Prins *et al.* [17]	University medical centre. RCT of 270 CFS (CDC) patients randomized to CBT, support or control (natural course) groups	Not known	Multidimensional assessments at 8 and 14 months (fatigue severity, functional impairment, self-rated improvement). Not clear whether rater was blind to treatment received	196/270 (73%) followed-up at 14 months. Intention to treat analyses: self-rated improvement in 28/58 (50%) of CBT group; 9/62 (15%) of support group; 24/76 (32%) of natural course group. Significant differences also seen in fatigue severity and Karnofsky rating
Van der Werf *et al.* [18]	Medical outpatient clinic. 79 CFS (CDC) patients	Mean 1.4 years, range 6–24 months	12-month follow-up (self-reported change, fatigue severity)	99% followed-up: 8% recovered; 46% improved; 37% no change; 17% worse. Limited information about patient recruitment
Tiersky *et al.* [30]	CF research centre. 47 CFS (CDC 1988 & 1994) patients with symptoms of at least moderate severity	No more than 4 years	Interview at time 2 (mean 41.9 months after baseline) with physical, neuropsychological and psychiatric assessments. CFS severity rated by trained research assistant and self-report fatigue severity and CFS disability scales	74.5% followed-up (35/47): 3% (1/35) no longer met CDC criteria; 57% demonstrated improvement and 43% no improvement in CFS severity and fatigue
Pheley *et al.* [21]	341 (1994 CDC) CFS patients referred to a regional CFS research programme	Mean 9.4 years (5.3 SD)	Self-completed postal questionnaire including visual analogue scale rating of both fatigue in last month and degree of recovery since illness onset—'conservative' cut-off for recovery established by the authors using these measures	52% (177/341) follow-up/response: 12% (21/177) recovered

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Table 2. Outcome of chronic fatigue and CFS

Study	Setting and definition	Duration of symptoms at outset	Main outcome used	Detailed notes on outcome
Primary care				
Valdini *et al.* [25]	Primary care: 22 patients with fatigue for over 1 year. No organic exclusions made	Mean 12 years	Clinical visits, mean 7 months after	100% followed-up: 5/22 (22%) improved
Levine *et al.* [24]	31 primary care patients identified following one of four outbreaks of post-viral fatigue syndrome in USA. Defined on the basis of severe persistent fatigue	Not known	Postal questionnaires for 12 and 44 month follow-up and telephone survey at 23 months—questioned about the course of their illness and degree of recovery	84% followed-up at 2 years: 12/26 functioning without limitation. After 3 years 'almost all' study subjects were able to return to pre-illness activity
Bates *et al.* [15]	Primary care: 22 patients with medically unexplained fatigue lasting >6 months of which 17 met operational criteria for CFS	Not known	Follow-up assessment at 12 months	86% (23/26) followed-up: 16/17 CFS cases remained fatigued, five no longer fatigued. (Of original 26 patients, one was found to have schizophrenia and three patients were found to be hypothyroid)
Skapinakis *et al.* [23]	International sample of primary care attenders: 3201 patients identified by three screening questions and a fourth question to assess fatigue severity relating to fatigue of 1 month duration. Categorized into three groups reflecting severity of fatigue. No systematic psychiatric exclusions	Not known	Interviewed in person at 12 month follow-up. Outcome in terms of fatigue persistence (meeting case criteria or in remission)	Overall response rate 68% (2182/3201): 61%(801/1306) prolonged unexplained fatigue in remission; 79% (385/487) substantial unexplained fatigue in remission; 80% (313/389) neurasthenia in remission. No information about new organic diagnoses during follow-up period
Secondary care				
Hellinger *et al.* [26]	60 secondary care CF patients with or without raised EBV titres. No systematic psychiatric exclusions	Not known	Postal questionnaire at 6–17 months	30 (50%) followed-up, of which: 2/30 resolved, 14/30 improved, 4/30 worsened. New medical diagnoses in four during follow-up
Gold *et al.* [35]	Viral disease clinic: 26 patients with at least 9 months fatigue with physical symptoms and raised EBV titres. No systematic psychiatric exclusions	Mean 3.5 years	Mean duration of follow-up 11.3 months, patients seen a mean of four times. Patient's assessment of improvement and symptom score	81% followed-up: 4/21 (19%) felt normal/recovered; 8/21 (38%) significantly improved
Sharpe *et al.* [31]	Infectious diseases clinic. 177 patients with at least 6 weeks fatigue, impaired function and somatic symptoms. No systematic psychiatric exclusions	Median 25 months, range 6 months–25 years	Median duration of follow-up 1 year (range 6 weeks–4 years) by postal questionnaire	81% followed-up: 62/82 (76%) of those followed for <1 year reported functional impairment with 69% of those followed for 1–2 years and 33% of those followed for >2 years reporting impairment. Only 13% perceived themselves to be fully recovered

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Table 2. (*continued*)

Study	Setting and definition	Duration of symptoms at outset	Main outcome used	Detailed notes on outcome
Bombardier and Buchwald [6]	University CFS clinic: 498 mixed cases of CF (6 months fatigue but not full CFS) and CDC CFS	Mean 5 years for CF, mean 5.2 years for CFS	Follow-up by postal questionnaire sent 1–31 months after initial visit	89% followed-up: 2% (10/445) reported complete resolution of symptoms; 64% (281/445) improved and 24% (107/445) were worse
Clark *et al.* [9]	CFS clinic: 78 patients with chronic fatigue (6 months or more), 19 of whom met CDC CFS criteria. No systematic psychiatric exclusions	Mean 5.5 years	Self-report follow-up questionnaire of current symptoms, level of functioning and amount of change at 12 months	100% followed-up: 32/78 (41%) reported moderate to complete recovery; 46/78 (59%) significantly worse or no change. Of CFS patients 7/19 (37%) recovered and 12/19 (67%) did not
Levine *et al.* [8]	Patients recruited from the private practice of one doctor working in the locality of an outbreak of unexplained fatigue. Retrospective diagnoses for 28 mixed cases of fatigue including eight CFS (CDC) patients	Study undertaken 10 years after the outbreak	Personal and telephone interviews at 10-year follow-up	82% contact: 3% (23/28) contact: 70% no residual restriction including 5/8 with CFS diagnosis; 30% modified activities to avoid relapse. 3/23 patients developed other significant medical disorder subsequent to the initial outbreak
Russo *et al.* [11]	Chronic fatigue clinic: 98 mixed patients with at least 6 months of fatigue, either CFS (CDC 1988) or CF	Mean 5.5 years	Assessment at mean follow-up time of 2.5 years (range 27–32 months). Data collection for a range of variables including CFS follow-up questionnaire	80% (78/98) contact: 3% (2/78) 'fully recovered'; 41% (32/78) moderate to complete recovery; 26% (44/78) worse
Strickland *et al.* [12]	Patients known to two practitioners from a private practice in Northern Nevada/California following an outbreak of CF: 259 mixed cases, either CFS, idiopathic CF or prolonged fatigue	Study undertaken 10 years after the outbreak	Self-administered follow-up questionnaire including questions concerned with recovery	58% response rate (123/213) 43 questionnaires returned due to incorrect address and three patients had died. 28% (34/123) recovered: 50% (2/4) of those with prolonged fatigue; 36% (25/69) of those with idiopathic CF and 14% (7/50) CFS patients
Community based				
Taylor *et al.* [28]	Community-based sample: 67 patients with chronic fatigue for 6 or more months identified by a screening question. No systematic organic exclusions	Not known	Retrospective cohort: mean follow-up at 3 years	76% (51/67) followed-up: 51% (26/51) experienced fatigue for past 6 months or more; 49% (25/51) no longer experiencing fatigue
Buchwald *et al.* [16]	Community sample of 74 patients: 71 cases of CF (6 months of new onset fatigue causing impairment with exclusion of physical and psychiatric causes of fatigue) and three CDC CFS	Not known	Self-report measures at 12 and 24 month follow-up and interview at 12 months	100% followed-up: 16/74 reported resolution of fatigue but no improvement in the three CFS cases

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Table 3. Risk factors for poor prognosis

Study	Demographic	Initial illness	Psychological	Physical
Hellinger *et al.* [26]	No report	No report	No report	EBV serology not associated with outcome
Sharpe *et al.* [31]	Gender, age, marital status not related to outcome	Better outcome with longer duration of follow-up	Emotional disorder and belief in viral cause associated with a poor outcome	No report
Hinds and McCluskey [29]	Patients under 20 had better outcome	No report	No report	No report
Wilson *et al.* [13]	Age at onset not associated	Duration of illness not associated	Psychiatric disorder developing during the illness and strong belief in physical cause related to a poor outcome	No association with cell-mediated immunity
Bombardier and Buchwald [6]	Older age did worse	Longer duration of symptoms and shorter duration of follow-up associated with worse outcome	Lifetime dysthymia associated with poor outcome	Raised oral temperature associated with poor outcome
Clark *et al.* [9]	Older age and less education associated with poor outcome	Multiple physical symptoms, longer duration of fatigue associated with poor outcome	Lifelong dysthymia associated with poor outcome	No report
Vercoulen *et al.* [10]	No association	Lower fatigue scores and shorter duration of fatigue associated with a good outcome	Not attributing to a physical cause and positive self-efficacy associated with a good outcome	No report
Ray *et al.* [19]	No association	Longer illness duration and more somatic symptoms associated with poor outcome	Subjective cognitive difficulty and low internal locus of control associated with poor outcomes	No report
Russo *et al.* [11]	Younger age associated with better outcomes	Physical examination signs at enrollment and follow-up associated with poor outcomes	Psychiatric disorder at follow-up associated with poor outcomes	No report
Saltzstein *et al.* [22]	Social support associated with good outcome	No report	Physician validation of illness associated with good outcome	No report
Hill *et al.* [14]	No report	Mode of illness onset not predictive of outcome	Psychiatric co-morbidity not predictive of outcome	Chemical sensitivity not associated
Taylor *et al.* [28]	No association	Fatigue severity, worsening of fatigue with exertion and post-exertional fatigue lasting >24 h predictive of poor outcome	No report	No report
Van der Werf *et al.* [18]	No report	Fatigue severity at baseline predictive of poor outcome	Less concentration problems and more psychosocial attributions predictive of better outcome	No report
Skapinakis *et al.* [23]	No association	Severity of fatigue associated with poor outcome	Psychiatric morbidity associated with poor outcome	No report
Tiersky *et al.* [30]	Older age associated with less improvement in disability status	No association	Comorbid psychiatric diagnosis at baseline associated with greater odds of improvement	No association
Pheley *et al.* [21]	No association	No relationship between duration of illness and recovery. Less severe illness at the time of diagnosis associated with a better prognosis	Lower baseline ratings of anxiety, compulsiveness and psychoticism in those individuals who were recovered at follow-up	No report
Strickland *et al.* [12]	No association with gender	No report	No report	No report

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outcome [9,27,29,30] but this finding was not supported by three other studies that reported no association between age and outcome [13,21,31].

Initial illness: The associations between improved outcome with a longer duration of follow-up and with less fatigue severity at baseline emerged but were not consistent across all the studies.

Psychological: Psychiatric disorder and illness attributions were both reported as important indicators of follow-up. Four studies showed that having a sense of control over symptoms and not attributing illness to physical causes was associated with a good outcome.

Physical: There were no clear physical predictors of outcome.

Occupational outcomes

Eight of the 25 studies that were included considered work-related outcomes of CFS or CF and these are shown in Table 4. A further six studies (also in Table 4) provided information about the numbers of patients who were functionally impaired and unable to work as a result of their illness. The percentages of patients not working varied considerably, but ranged from 27 to 65% at the point of entry to the study, and 15 to 52% at the point of follow-up. Information about numbers of patients in receipt of disability benefits was given in only two instances with 25 and 42% of patients receiving benefits at 39 month follow-up [13] and 18 month follow-up [10], respectively. Prognosis in terms of return to work was also variable. Russo *et al.* reported that 30% of patients had returned to work at follow-up and Bombardier and Buchwald reported that in the last 3 months 14 and 11% had returned to full- or part-time work, respectively [11,27]. In the smaller study of Hill *et al.*, only two of 23 patients (8%) had returned to (part-time) work at follow-up [14]. Taylor *et al.* found that work status was a significant predictor of continued fatigue with fatigued patients more likely to have been on disability benefits or working part-time at baseline than the patients who had improved [28]. Bombardier and Buchwald found no significant predictors of return to work in CFS patients but showed that patients with CF who returned to work were significantly less likely to have a diagnosis of major depression at baseline [27].

Discussion

This review shows considerable variability between the conclusions of different studies concerned with the prognosis of both CF and CFS. This is to some extent understandable in view of the heterogeneity of the condition itself. The different methods used to research this area are also likely to be responsible for some of the discrepancies: the variability of illness duration and severity, and length of follow-up makes direct comparison of results across studies difficult; patient selection and recruitment methods and poor response/follow-up rates will have introduced bias into many of the studies; and a number of the studies have relied on retrospective self-report at a single or two points in time. This cross-sectional assessment of clinical condition has not allowed for detection of the unpredictable course of CFS, particularly whether questions concerning recovery related to recent weeks rather than months: reports of continued fatigue do not equate to continuous illness and conversely subjects whose symptoms have remitted are not necessarily completely recovered. Finally, the results of statistical analyses performed on small samples, or without correction for multiple comparisons, need to be viewed with caution and it should be recognized that as many of the studies used samples from secondary care settings the findings cannot necessarily be generalized to other patient populations.

Despite the variability of the studies reviewed, a number of conclusions can be drawn from the available data. As previously described by Joyce *et al.* [7], this review also suggests that CF or CFS is not associated with an increased mortality rate and that it rarely constitutes a missed medical diagnosis when an attempt has been made to exclude organic illness prior to making the diagnosis. This review was concerned with the course of CF/CFS without systematic biological or psychological intervention. Full recovery from CF/CFS is rare, although less so in chronic fatigue that does not meet full CFS operational criteria. The natural course appears to be different for CF/CFS occurring in outbreaks or epidemics and two of three studies concerned with such cases showed that the prognosis is much better with many patients achieving full recovery [8,24]. For CF/CFS patients in general, an improvement in symptoms is a more commonly reported outcome than full recovery and the prognosis for this is less gloomy, especially amongst patients seen in primary care. However, the natural history of CF/CFS is still of concern: many patients reported either residual symptoms or disability at follow-up and a progression or worsening of symptoms was seen in some. It undoubtedly led to functional impairment and work disability in a considerable number of patients and the prognosis in terms of return to work is poor and occurred in less than a third of patients when it was reported.

Predictors of an improved outcome included less fatigue severity at baseline and not attributing the illness to physical causes. Psychiatric disorder was associated with poorer outcomes. Importantly, the evidence does suggest that irrespective of the biology of CFS, patients' beliefs and attributions about the illness are intricately linked with the clinical presentation, the type of help

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Table 4. Work-related outcomes

Study	Work-related outcomes
Gold *et al.* [35]	At enrolment 13/24 (54%) patients were functionally impaired by their illness: 9/24 (38%) were unable to work and 4/24 (17%) worked part-time. Only 2/13 were not working after 12 months follow-up
Sharpe *et al.* [31]	At follow-up 38% had left or changed their job (or studies) because of illness and 31% (44/144) of subjects reported occupational impairment. No baseline data available for comparison
Wilson *et al.* [13]	30% (31/103) patients unable to perform any work at follow-up and 25% (26/103) were receiving disability benefits because of CFS. Information not available to allow comparison with situation at study outset
Bombardier and Buchwald [27]	At follow-up 14% and 11% had returned to full or part-time work in the last 3 months, respectively and 19% reported improved work performance. However, 34% of total sample were still unable to work and 23% reported decreased performance while remaining at work. Univariate analyses showed that those with chronic fatigue who returned to work were significantly less likely to have a diagnosis of major depression at enrolment. No significant predictors of return to work in CFS patients
Vercoulen *et al.* [10]	At initial assessment 12% patients were unemployed, 28% worked and 43% were on sick leave or receiving disability benefits. At follow-up assessment 12% were unemployed, 29% worked and 42% were on sick leave. The remaining subjects were at school, housewives or retired
Russo *et al.* [11]	Number of subjects not working at enrolment not given but 23 (30%) had returned to work at time 2. A reduction in the number of physical signs and no psychiatric diagnosis were significant predictors of resuming work
Saltzstein *et al.* [22]	All subjects were in full-time employment before becoming unwell but at the initial interview only 40% were working full-time, 33% were working part-time and 27% were unemployed
Hill *et al.* [14]	65% (15/23) were not working at enrolment and 52% were still unable to work at time 3 (two had returned to part-time work and one had retired)
Deale *et al.* [34]	49% of subjects were not working on entry to the study. At 5-year follow-up 14/25 (56%) from the CBT group and 11/28 (39%) from the control group were in either full- or part-time employment. This was not significantly different between the two groups but patients from the CBT group worked significantly more hours per week
Prins *et al.* [17]	76% of the sample were employed before the onset of CFS compared with only 33% at entry to the study. No employment rates from 14 month follow-up
Van der Werf *et al.* [18]	75% of sample were in paid employment before illness onset compared with 29% who had worked in paid employment in the month preceding the initial assessment. No employment data available from follow-up
Taylor *et al.* [28]	Work status was found to be a significant predictor of continued fatigue: a greater proportion of the fatigued group were on disability benefits or working part-time at baseline compared with the 'improved' group who were more likely to be retired, working full-time or unemployed at baseline
Tiersky *et al.* [30]	68% of the sample were unemployed at times 1 and 2. Older age at baseline was associated with lower odds of employment at time 2 whereas a comorbid psychiatric diagnosis at baseline was associated with higher odds of employment at time 2

sought and prognosis [4]. An association between poor outcomes and the attribution of CFS to a physical cause has been shown in a number of studies [10,13,31] and having little sense of control over the symptoms has also been associated with a poor prognosis [19]. The recognition of these and other relevant cognitions in CFS has led to an increased understanding of the condition using a cognitive behavioural model.

Occupational outcomes are a critical measure of prognosis and the cost of illness and this is particularly pertinent in the case of illnesses, such as CFS, with a chronic course. Somewhat surprisingly, prognosis studies to date have placed little emphasis on return to work or other related outcomes. Moreover, where it has been considered, general terms such as 'return to work' and 'not working' leave the reader unsure about specifics such as the number of hours worked and why the patient is not currently working. These are important differences and reasons for not working range from longstanding unemployment, to job loss as a direct result of CFS, to being on sickness leave of variable duration. Another important consideration is the provision and extent of financial support in the case of sickness leave or disability benefits as this may have an impact on prognosis. Future studies should consider occupational outcomes in an attempt to improve further our understanding of CFS

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and in turn to guide clinicians and employers in their approach to the occupational disability associated with this condition.

Many of the studies showing poor prognosis followed individuals who had been ill for many years at the start of the study. It is not clear whether return to work under these circumstances is determined by the disorder itself or by social or cultural factors, such as the familiarity of employers in taking on staff with previous prolonged periods of sickness absence. What is indisputable is that it is easier to return to work after shorter periods of sickness absence. Numerous studies in this issue (reviewed by Rimes and Chalder [36]) demonstrate the effectiveness of cognitive behavioural and graded exercise therapies in CFS. It is therefore vital that services are available to provide early treatment and rehabilitation.

From a clinical perspective, we recommend that serious and possibly irreversible actions, such as medical retirement, are postponed until a trial of treatment has been given. Although many sufferers of CFS are eventually retired, such action should be a last resort. The current situation, where it often becomes a 'solution' after a period of prolonged sickness absence for untreated CFS, is not tenable in the light of treatment studies.

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