The Royal Australasian College *of* Physicians

Chronic fatigue syndrome

Clinical practice guidelines — 2002

Produced by a Working Group convened under the auspices of the Royal Australasian College of Physicians

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The guidelines are available on the world wide web <http://www.mja.com.au/public/guides/cfs/cfs2.html>

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Preface

THESE GUIDELINES are primarily aimed at assisting general practitioners, but they are also relevant to specialist physicians and other healthcare professionals involved in managing people with fatigue states, including physiotherapists, occupational therapists, psychologists and social workers. They are based on information available at the date of publication, and are intended to provide a general guide to best practice. However, it should be emphasised that evidence-based clinical practice involves not only use of the best available research evidence, but also exercise of the practitioner's clinical judgement, taking account of individual patient preferences.

Background

In 1990, the Royal Australasian College of Physicians (RACP) published a brief position paper on the investigation and management of chronic fatigue syndrome (CFS) in the RACP magazine, *Fellowship Affairs*. In 1993, as a result of perceived variations in clinical practice, the then Commonwealth Minister for Health (Senator Graham Richardson) established a CFS Review Committee (comprising Dr David Watson [general physician], Dr Bryce Phillips [general practitioner] and Associate Professor Graeme Stewart [clinical immunologist]) to make recommendations on "diagnostic and management regimens that the medical profession would regard as appropriate for sufferers of CFS". The Review Committee approached the RACP for an up-to-date position, and the College passed the request to the Australasian Society of Clinical Immunology and Allergy (ASCIA). In 1994, a fully revised discussion paper prepared by ASCIA[1] was circulated to all specialist physicians in *Fellowship Affairs*, together with a questionnaire, and the paper and survey results were subsequently made available to the Ministerial Review Committee.

In 1995, as a result of the Review Committee's recommendations, the Commonwealth Department of Health funded the Royal Australian College of General Practitioners to conduct a survey of general practitioners' opinions and practices in relation to CFS. The Ministerial Review Committee also recommended the production of consensus guidelines for distribution to all medical practitioners in Australia. Fortuitously, in October 1995, the National Health and Medical Research Council (NHMRC) published *Guidelines for the development and implementation of clinical practice guidelines*,[2] which provided an ideal framework for this purpose. Consequently, in 1996, a multidisciplinary Working Group (including a Consumer Health Forum representative) was established under the auspices of the RACP to develop and disseminate evidence-based guidelines, following the procedures recommended by the NHMRC. The Commonwealth Department of Health and Family Services provided funding.

A: Quality-of-evidence ratings

I Consistent evidence obtained from more than two independent, randomised and controlled studies or from two independent, population-based epidemiological studies. Studies included here are characterised by sufficient statistical power, rigorous methods and inclusion of representative patient samples. Alternatively, a meta-analysis of smaller, well-characterised studies may support key findings.

II Consistent evidence from two randomised controlled studies from independent centres, a single multicentre randomised controlled study or a population-based epidemiological study. Data included here have sufficient statistical power, rigorous methods and the inclusion of representative patient samples.

III-1 Consistent evidence obtained from two or more well-designed and controlled studies performed by a single research group.

III-2 Consistent evidence obtained from more than one study, but where such studies have methodological constraints, such as limited statistical power, or the inclusion of patient samples which may be non-representative.

III-3 Evidence obtained from a single case–control study or a selected cohort study.

III-4 Conflicting evidence obtained from two or more well-designed and controlled studies.

IV Consensus opinions of respected authorities, based on clinical experience and/or descriptive reports.

Guideline development

The Working Group conducted an extensive review of the relevant scientific literature on prolonged fatigue, chronic fatigue and CFS, and the evidence was rated according to a modification of the schema recommended by the NHMRC. In addition, the Ministerial Review Committee report and a variety of other local and international public domain documents were examined.

Submissions were invited from interested practitioners, consumers and patient support groups. Eighty submissions were received from people with CFS, carers, concerned individuals and CFS Societies. The Consumer Health Forum representative produced two documents: *A compilation of submissions made by people with chronic fatigue syndrome and others to the Royal Australasian College of Physicians for the investigation of chronic fatigue and management of chronic fatigue syndrome clinical practice guidelines*,[3] and *A CFS health consumer perspective*.[4] Quotations for the *perspective* boxes in these guidelines were drawn from these documents.

The working group prepared draft guidelines that were widely circulated in early 1998. Comments were sought from relevant specialist societies, Royal Colleges, the National Health and Medical Research Council, patient support groups, complementary practitioner associations, and interested individual practitioners and consumers. The draft was also made available on the *MJA* website <http://www.mja.com.au/public/guides/cfs/cfs1.html>.

The draft guidelines attracted widespread comment both as a result of the initial public consultation and over the four years that they remained available on the *MJA* website. They were subsequently extensively revised and updated, and underwent a limited second round of public consultation. This final version of the guidelines is the result of revisions carried out in the light of comments received.

Literature review and evidence ratings

The evidence contained within published studies was evaluated according to the process outlined in the NHMRC *Guidelines for the development and implementation of clinical practice guidelines* (see Box A).[2] The quality-of-evidence ratings were modified to provide an integrated system for evaluating diagnostic, epidemiological and pathophysiological studies, as well as treatment trials.

Studies were rated primarily according to the rigour of the research methods used. However, since the interpretation of individual studies is often constrained by selection and other biases, replication across different studies performed in independent research centres was considered a key factor in assessing the reliability of evidence. When the available evidence from several well-conducted studies on a particular topic was conflicting, the quality-of-evidence ranking indicated this uncertainty (Level III-4).

Level IV evidence represents consensus opinions of experts, including working group members, based on clinical experience and limited scientific data. Although such statements may inform current practice, they should be interpreted cautiously, as they may undergo future modification in the light of new evidence.

Clinical Overview

FATIGUE CAN BE DEFINED as a pervasive sense of tiredness or lack of energy that is not related exclusively to exertion. It is a common complaint in the community and is usually transitory. If fatigue is prolonged beyond six months, is disabling, and is accompanied by other characteristic constitutional and neuropsychiatric symptoms, then a diagnosis of *chronic fatigue syndrome* (CFS) should be considered.

What is CFS?

"CFS" is a descriptive term used to define a recognisable pattern of symptoms that cannot be attributed to any alternative condition. The symptoms are currently believed to be the result of disturbed brain function, but the underlying pathophysiology is not known. Therefore, CFS cannot be defined as a specific "disease" entity at present. Indeed, there is growing evidence that the disorder is heterogeneous, and it will probably prove to have no single or simple aetiology.

It is important for practitioners to appreciate the distinction between disease, illness and disability.

Diseases are defined and categorised according to our contemporary understanding of causal mechanisms and pathophysiology. As new knowledge emerges, disease definitions and terminology change. *Illness*, by contrast, is the subjective experience of suffering and, as such, can only be defined by reference to the sick person. *Disability* is the functional impairment — physical, psychological and social — caused by disease and illness.

Even though an underlying *disease* process cannot presently be defined in patients with CFS, the suffering and disability caused by the *illness* can be very considerable — in many cases comparable to that seen in multiple sclerosis and rheumatoid arthritis. It is therefore important that doctors acknowledge the reality and seriousness of the suffering and disability experienced by people with CFS. Our goal as physicians is not only to identify and treat disease, but also to help relieve suffering and disability, whatever the cause.

Diagnosis

CFS is diagnosed on clinical grounds. It relies on the presence of characteristic symptoms (see Box B), and the exclusion of alternative medical and psychiatric diagnoses. In individual patients, the symptoms of CFS may overlap with other common syndromes such as fibromyalgia and irritable-bowel syndrome, and the primary diagnosis will depend on which symptoms are the most dominant and disabling. People with CFS often have concurrent depression, and this need not exclude the diagnosis.

As similar symptoms can also occur in a range of other disorders (eg, thyroid disease, anaemia, major depression), the first priority in clinical assessment is to exclude alternative explanations. This can be achieved by careful history-taking, physical examination and a restricted set of laboratory investigations.

"To study the phenomena of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all."[5]

Clinical history

It is important to take careful note of the character of the fatigue. In people with CFS, fatigue is typically exacerbated by relatively minor physical or mental activity, and is associated with a protracted recovery period lasting hours or days. The fatigue should be differentiated specifically from weakness (neuromuscular disease), dyspnoea and effort intolerance (cardiac or respiratory disease), somnolence (primary sleep disorders), and loss of motivation and pleasure (major depression).

Additional clues which could point to alternative diagnoses include unexplained weight loss (occult infection, malignancy, thyrotoxicosis, Crohn's disease); dry skin and cold

B: Diagnostic criteria for chronic fatigue syndrome[6]

1. Fatigue

Clinically evaluated, unexplained, persistent or relapsing fatigue persistent for six months or more, that:

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

and

2. Other symptoms

Four or more of the following symptoms that are concurrent, persistent for six months or more and which did not predate the fatigue:

- Impaired short term memory or concentration
- Sore throat
- Tender cervical or axillary lymph nodes
- Muscle pain
- Multi-joint pain without arthritis
- Headaches of a new type, pattern, or severity
- Unrefreshing sleep
- Post-exertional malaise lasting more than 24 hours

intolerance (hypothyroidism); snoring and daytime sleepiness (sleep apnoea); risk factors for transmission of blood-borne infections (HIV, hepatitis C); prior episodes of depression or anxiety (vulnerability to psychiatric disorder); arthralgia or rash (connective tissue disease); and prescribed or illicit drug misuse. A history of altered bowel habit may indicate an underlying gastrointestinal infection (eg, giardiasis), coeliac disease, thyroid disease, or inflammatory bowel disease.

Examination

Characteristically, there are no abnormal physical findings in people with CFS. The physical examination and mental state examination are therefore primarily directed towards excluding other disorders. A careful assessment for neurological deficits or signs of anaemia, cardiac failure, respiratory disease, hidden infection, connective tissue disease or tumour should be conducted. The presence of persistent fever, lymphadenopathy, or enlargement of the liver or spleen are not features of CFS and always warrant further investigation.

The behavioural signs of psychiatric disorder should also be sought, including psychomotor slowing (major depression), physiological arousal (anxiety states and panic disorder) and cognitive deficits (delirium or dementia).

Investigation

There are currently no validated laboratory tests to confirm the diagnosis of CFS, assess its severity or monitor progress. Hence, the purpose of laboratory investigation is to help exclude other disorders.

Recommended screening investigations are:

- full blood count and erythrocyte sedimentation rate;
- serum electrolyte, calcium and creatinine levels;
- biochemical liver function tests;
- thyroid function tests (TSH); and
- urinalysis for blood, protein and glucose.

Additional investigations should be ordered only if the history or examination plausibly suggests other diagnoses (eg, autoimmune connective tissue disease, coeliac disease), or if abnormalities are found in the screening investigations. Routine analysis of immune function (lymphocyte subsets, immunoglobulin levels), infectious disease serology, or environmental toxins are not recommended.

Unvalidated diagnostic tests should only be performed in the context of an appropriately designed and ethically approved clinical trial.

Specialist referral

In most cases, a general practitioner should be able to diagnose CFS. However, if, after a careful history, examination and screening investigations, the diagnosis remains uncertain, the opinion of a specialist physician, adolescent physician or paediatrician should be sought. Referral to a psychiatrist may also be useful for people with profound or prolonged depression or anxiety states. Specialist referral may also help in formulating an appropriate management plan (see below).

Management

In the early stages reassurance and supportive care is generally all that is required, as most prolonged fatigue states will resolve spontaneously. In people with established CFS, providing a definite diagnosis, along with general information about the illness and its natural history, are important starting points for good clinical care.

A definitive diagnosis also serves to validate the patient's experience of illness and suffering. Doctors who display empathy, acceptance of their patient's suffering, a non-judgemental style and a commitment to continued care are likely to establish a beneficial therapeutic relationship. Conversely, doctors who reject or trivialise the patient's illness experience are likely to promote feelings of alienation and to perpetuate ill health.

In managing people with CFS it is important to:

- develop an individualised management plan for physical and social rehabilitation;
- discourage excessive rest and minimise social isolation;
- maintain regular contact;
- evaluate the basis of any new symptom or deterioration in function; and
- provide support for the person and his or her family, including access to social security, educational assistance and disability services where appropriate.

To date, no pharmacological agent has been reliably shown to be effective treatment for CFS. Management strategies are therefore primarily directed at relief of symptoms (eg, headache, muscle pain) and minimising impediments to recovery (loss of functional capacity, disruption of the sleep–wake cycle, intercurrent depression and social isolation). Additional elements of good clinical management are the development of a clear and mutual understanding of the nature of the illness; a sensible approach to physical and mental activity; and realistic expectations about long-term outcome possibilities.

Understanding the illness

Helping people with CFS understand the nature of their illness is an important element of good clinical management. For example, some people harbour fears that an occult infection, environmental pollutants or electromagnetic fields may be causing irreversible neurological or immunological damage. Others may have been led to believe that any physical activity at all could be harmful. Unwarranted concerns of this kind may lead to maladaptive attitudes and behaviours that may increase disability and retard recovery.

Doctors should also avoid simplistic attributions of CFS to "chronic infection", "immune dysfunction", "malingering", or "mere depression". Instead, it should be recognised that the illness is likely to be multifactorial in origin. A broad perspective that encompasses medical, psychological, and social aspects is more appropriate.

Physical activity

In general, people with CFS should be encouraged to undertake physical and intellectual tasks, starting at a level that is tolerated without significant exacerbation of symptoms. This should initially be in divided sessions of relatively short duration. As exercise tolerance improves, duration and intensity of activity can be gradually increased. Graded exercise programs have been shown to be beneficial for some people with CFS, and can improve functional status.

It is important to discuss with the patient the vicious circle whereby initial avoidance of physical activity may lead to longer-term avoidance of all activity. In the early stages of the illness, many people with CFS put off chores or social engagements until they feel better, then push themselves excessively on "good days" to make up for lost time. The subsequent worsening of symptoms and delayed recovery can establish a cyclic pattern of illness and disability.

An individualised management program should be carefully negotiated between the patient and doctor, with particular attention to:

- starting at a level of activity that can be achieved without exacerbation of symptoms — abrupt resumption of strenuous activity after prolonged periods of inactivity should be discouraged;
- undertaking activity on a regular basis, with sessions of limited duration; and
- planning for regular reviews to achieve feasible increases in activity over a realistic time-frame (eg, several months).

In formulating a management plan, it is important to be aware that in many people with CFS the degree of fatigue can fluctuate unpredictably from day to day and week to week. Flexibility in the level of physical and mental activity undertaken to allow for such fluctuations ("pacing") should be explicitly discussed.

Sleep

Unrefreshing sleep is extremely common in people with CFS. Patients usually report a longer time to fall asleep, an increased time in bed awake, and a broken and restless sleep pattern. A shift from regular night-time sleep to daytime naps and a late-night to late-morning sleep cycle is sometimes noted. It is known that chronic disruption of the normal sleep pattern can induce symptoms in healthy volunteers, including fatigue, musculoskeletal pains, irritability and impairment of concentration.

The general goals of sleep management are to establish a regular, unbroken, night-time sleep pattern and to improve perceptions of the quality of sleep. Although direct evidence of benefit in CFS is currently lacking, the following strategies may be helpful:

- establishing a regular bed-time routine — going to bed when "sleepy" rather than "tired"; putting the light out immediately rather than reading or watching television in bed; and "anchoring" the sleep routine by setting the alarm to the same rising time every day;
- judicious use of sedative-hypnotic medication to achieve sleep;
- use of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) for relief of musculoskeletal pain;
- avoiding (preferably) daytime naps or keeping them under 30 minutes;
- gentle exercise during the day (within the limits of the individual's functional capacity).

Where appropriate, the advice of a specialist sleep physician should be sought, either to exclude a primary sleep disorder or to manage the sleep disturbance. Sleep hygiene strategies can also be incorporated into a "cognitive behaviour" therapy program (see Chapter 3). Clinical experience suggests that sleep interventions in people with CFS may reduce symptoms and improve functional capacity, although direct evidence for this is lacking.

Symptomatic drug treatment

No medication has yet been shown to provide long term remission or "cure" in people with CFS. However, there is a place for symptomatic treatment for relief of specific symptoms if they are sufficiently distressing. As such treatments for CFS are empirical, each patient should be monitored carefully to ensure that the symptomatic benefits outweigh any side effects.

Many people with CFS report an increased susceptibility to drug side effects, and it is advisable to begin with small doses when introducing new agents.

Although depression is a common symptom in people with CFS, the disorder as a whole cannot be regarded simply as a "somatised" variant of a depressive illness. Overall, clinical trials of antidepressant drugs show no consistent pattern of improvement. However, judicious use of particular agents may provide symptomatic improvement in subjective energy (moclobemide), sleep disturbance (amitryptyline, nefazodone), muscle and joint pain (amitryptyline), and depressed mood (sertraline, paroxetine, nefazodone). A reasonable approach is to consider undertaking an "N = 1" therapeutic trial of a selected drug based on this broad pattern of effects on brain function. Given that these drug therapies are increasingly varied and complex, there is an important role for the specialist physician or psychiatrist to guide the choice of drugs and their monitoring.

In people with the overlapping syndrome of fibromyalgia, the use of symptomatic treatments such as analgesics and NSAIDs, in combination with tricyclic agents, can be effective in reducing pain and improving sleep.

Psychological and social support

As with other chronic illnesses, managing people with CFS requires consideration of the psychological and social impacts of the illness.

People with CFS may be unable to continue full-time work, so financial difficulties may rapidly develop. Similarly, CFS frequently disrupts high school or university studies. Successful return to work or school after a prolonged illness with CFS often requires a rehabilitation program incorporating medical treatments, psychological support and occu-

pational therapy. Doctors may need to coordinate the help of other healthcare and educational professionals to implement this.

The impact of the illness on the person's family should also be considered. In some circumstances it may be useful for people with CFS to bring their spouse or partner to a consultation, both to help them better understand the illness and to discuss their difficulties in coping. Parents of children and adolescents with CFS should be seen regularly, and may require additional support and counselling.

Doctors should be prepared to act as advocates for their patients in negotiations with employers, educational institutions and social welfare organisations. For instance, part-time work or school alternatives may need to be arranged, or disability allowances may need to be sought.

Joining a patient support group may be valuable for some people. CFS societies can offer individual and group support, education, and advice about access to social welfare agencies (Box C). Individuals may also benefit from the opportunity to exchange information on how to cope with the many practical day-to-day difficulties that arise for those living with this debilitating condition. However, the quality of advice given can vary and it is therefore useful for the doctor to have ongoing knowledge of the activities and attitudes of local support groups.

Special considerations in children and adolescents

Children and adolescents are in a dynamic developmental state, and issues such as self-concept, autonomy, body image, socialisation, sexuality and academic goals are of central importance. Early intervention in those with persistent fatigue is therefore especially important. For this reason, many experts believe that in children and adolescents a diagnosis of CFS should be considered when unexplained fatigue persists for three months, rather than the six months stipulated in the adult case definition.

The family practitioner or paediatrician should seek the cooperation of the parents and other carers in devising a supportive rehabilitation plan. Information should be provided to young people, their family and teachers to help them gain an appropriate understanding of the illness, and in some cases visiting the school and talking to classmates might be helpful. Although there is considerable variation, prognosis in children and adolescents is better than in adults, with recovery likely to occur within two to four years.

An individualised plan should be developed over the week for:

- maintenance of peer contact and relationships with friends;
- academic and recreational activity; and
- physical activity, rest periods and sleep.

Adjustments to schooling may involve limiting the number of subjects taken, or the number of days per week at school (particularly if travel to and from school is causing exhaustion). Occasionally, a mixture of distance education and school attendance for one or more subjects allows both social contact and maintenance of academic progress. Those in Years 11 and 12 who are hoping to qualify for university entrance may need to apply for special consideration, and consider a 12-month extension.

Appropriate psychosocial support throughout the illness is particularly important. Prolonged absence from school may lead to anxiety about falling behind with classwork, and young people may become frustrated and depressed by their inability to participate in sporting and social activities. These issues should be discussed explicitly.

Psychiatric labelling is generally unhelpful. In most cases, there is little evidence that the disorder is "psychosomatic", and inappropriate speculation about "school phobia" may be damaging and counterproductive. Early correction of such misunderstandings leads to fewer difficulties in the long-term.

Those at the more severe end of the disability spectrum may require a more intensive, multidisciplinary approach to rehabilitation and psychosocial support. Where there are obvious behavioural problems or major disturbances in family functioning, the assistance of a child psychologist or psychiatrist may be of value.

C: Support and resources for people with CFS[14]

CFS = chronic fatigue syndrome; HACC = home and community care.

1: What is chronic fatigue syndrome?

PROLONGED AND DISABLING FATIGUE is present in 10%–25% of patients presenting to general practitioners.[7-13] Fatigue syndromes lie along a continuum of severity,[8,14-16] from ubiquitous transient and mild states to the more severe and prolonged fatigue disorders, including CFS.[17-19] As with many other problems in clinical medicine (such as blood pressure and body weight), the challenge is to identify the point at which the problem becomes clinically significant. In relation to fatigue states, it is important to focus on those in whom the disorder is associated with ongoing disability[20,21] and significant social or economic cost.[22]

Epidemiology

- Prolonged fatigue is common in primary care, with a prevalence of 10%–25% (Level I).
- The prevalence of CFS in the community is 0.2%–0.7% (Level III-2), and 0.5%–2.5% in primary care (Level I).
- CFS predominantly affects young adults (Level I).
- CFS occurs in individuals from all socioeconomic groups (Level I).

For an explanation of the rating of levels of evidence, see *page S21.*

Natural history

- Most fatigue syndromes are of short duration and resolve spontaneously (Level II).
- People with CFS for more than five years tend to remain symptomatic, although function may improve slowly over time (Level II).
- People meeting diagnostic criteria for CFS rarely develop another medical condition that explains their symptoms, but are at increased risk of developing psychological disorders (Level II).
- Concurrent psychological disorder, somatic symptoms, high levels of fatigue and a low sense of control over symptoms are associated with poorer outcomes (Level II).
- A supportive doctor–patient relationship is an important component of managing people with CFS (Level III-3).

For an explanation of the rating of levels of evidence, see *page S21.*

Diagnostic criteria

In 1988, the United States Centers for Disease Control proposed the term "chronic fatigue syndrome" to describe a clinical condition defined by a cluster of constitutional and neuropsychiatric symptoms occurring in a distinctive pattern.[23] Current diagnostic criteria (see Box B) describe CFS as a syndrome of physical and mental fatigue, usually of acute onset, which is markedly exacerbated by physical activity. Other common symptoms include headaches, myalgia, arthralgia, and post-exertional malaise; cognitive difficulties, with impaired memory and concentration; unrefreshing sleep; and mood changes.[16,24-27] The diagnostic criteria also require that the person must have been ill for more than six months and that the symptom complex is associated with substantial disability.

Delineating CFS as a clinical syndrome has facilitated descriptive clinical research to test the validity of the concept, epidemiological studies to document prevalence and to formulate aetiological hypotheses, laboratory studies to test hypotheses about underlying pathophysiology, and research into a range of treatment strategies.[28,29] Although a variety of research definitions have been proposed,[6,23,24,27,30-33] the current international consensus criteria for CFS[6] have gained wide acceptance in the scientific literature.[34,35] In routine clinical practice, a diagnosis of CFS may be appropriate even though the requirement of four out of eight additional symptoms is not formally met (see Box B). Such patients (with "idiopathic chronic fatigue"[6]) can have comparable levels of disability,[27] and may also benefit from the assessment and intervention strategies described in these guidelines.

In primary care, up to two-thirds of people presenting with persistent fatigue have some other identifiable medical or psychiatric disorder that accounts for the symptom,[36-41] and careful assessment to exclude these is essential before making a diagnosis of CFS.[6]

"Disease" or "illness"?

Syndromal diagnoses like CFS have a long history of use in clinical medicine.[42] In the absence of a clear understanding of the underlying pathophysiology, CFS is best regarded as an "illness" — a subjective state that can only be defined by reference to the sick individual — rather than a "disease".[43-45] "Disability" arises when illness interferes with the individual's ability to function normally. People with CFS are clearly *ill*, and are often significantly *disabled*, even though an underlying *disease* process has not yet been identified.[46]

What other terms are commonly used for CFS?

In the United Kingdom the earlier term "myalgic encephalomyelitis" ("ME")[47] is still in use, and in the United States the term "chronic fatigue and immune dysfunction syndrome" (CFIDS) is in widespread popular use. Both names inappropriately suggest that the cause or mechanism of illness is understood (inflammation of the brain, spinal cord and muscles; or immune deficiency). Most research groups prefer the term "CFS", as it leaves open the question of aetiology and pathogenesis.[6,23]

Neurasthenia (literally meaning "nervous exhaustion") is a diagnosis included in the *International classification of diseases* (ICD-10) to describe a syndrome of mental and physical fatigue of at least three months' duration. The term has a long tradition of use in psychiatric classification,[48] but the extent of its overlap with CFS, and with common psychological disorders such as anxiety and depression, remains to be determined.[49] Although patients are rarely

labelled as having neurasthenia in Australia, the UK or the US, the diagnostic term is widely used in Europe and elsewhere. Neurasthenia has a prevalence of 5.4% (range, 2%–10%) in primary care settings worldwide.[50]

How common is CFS?

The reported prevalence estimates of CFS differ as a consequence of variations in sampling methods, survey instruments and diagnostic criteria, particularly with regard to duration of illness and the extent to which alternative medical and psychiatric diagnoses were excluded (Box 1.1). Early attempts to record the community prevalence suggested a range of 0.002% to 0.04%.[30,55,56] These figures appear to be substantial underestimates as a consequence of limitations in sampling or diagnostic protocols.

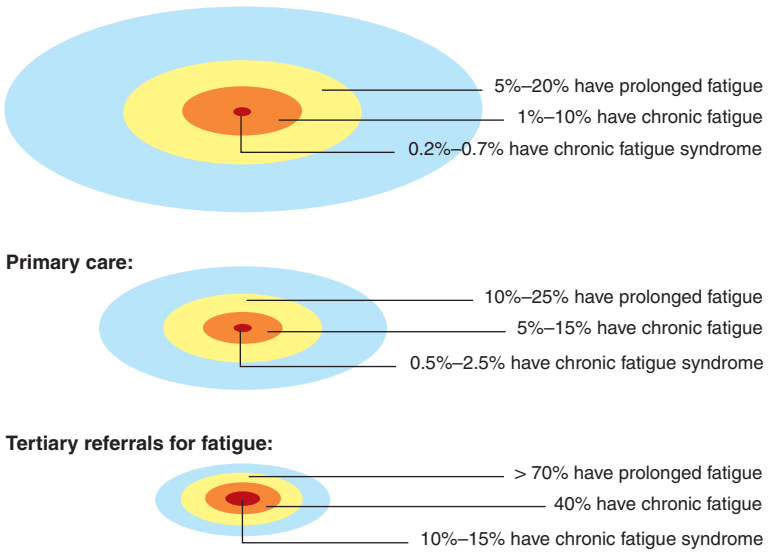
The true prevalence of CFS can only be determined in large-scale community studies employing adequate case detection and characterisation techniques. In the US and UK, four studies have provided a more realistic estimate of 0.2% to 0.7% (that is, 200–700 cases per 100 000 people).[39,40,57,58] In Japan, the community prevalence has been reported to be 1.5%.[59]

In primary care settings, estimates of the prevalence of CFS are between 0.5% and 2.5%, depending on the intensity of medical, psychiatric and laboratory evaluation (Box 1.1). Preliminary estimates of the incidence of new cases per year of prolonged fatigue or chronic fatigue in primary care are 3%–5%,[40,60,61] whereas the incidence of CFS is about 0.4%.[40]

Who is at risk of CFS?

CFS predominantly affects young adults, with a peak age of onset between 20 and 40 years.[30,40,57,62] In samples of patients from treatment centres, CFS appears to be more common in women (typically in a ratio of 2–3:1[30]), but this may be because women attend all levels of medical care more frequently than men.[63] CFS does not preferentially affect individuals from upper socioeconomic groups (contrary to the notion of "yuppie flu").[30] Rather, some studies suggest that fatigue syndromes may be more common in people from more socially disadvantaged groups.[13,40,62,64] One study has suggested that nurses have a high rate of CFS, indicating that specific occupations may be at risk.[65]

1.1: The prevalence of fatigue states



Definitions:

Prolonged fatigue — prolonged and disabling fatigue lasting at least one month.

Chronic fatigue — prolonged and disabling fatigue lasting at least six months.

Chronic fatigue syndrome — prolonged and disabling fatigue lasting at least six months, unexplained by other medical or psychological conditions.

Prevalence of prolonged fatigue (PF), chronic fatigue (CF) and chronic fatigue syndrome (CFS) in primary care

Study	PF	CF	CFS
Buchwald et al, 1987, USA[51]	—	21%	—
Kroenke et al, 1988, USA[7]	23.8%	—	—
David et al, 1990, UK[8]	10.5%	—	0.16%
Cathebras et al, 1992, Canada[9]	13.6%	5.7%	—
Bates 1993, USA[52]	—	27%	0.3%–1.3%
Katerndahl 1993, USA[10]	6.9%	—	—
McDonald et al, 1993, UK[53]	—	112%	2.5%
Walker et al, 1993, USA[11]	6.7%	—	—
Pawlikowska et al, 1994, UK[15]	—	18.3	—
Buchwald et al, 1995, USA[39]	—	19%	0.1%–0.3%
Hickie et al 1996, Australia[13]	25%	—	0.3%–1.3%
Wessely et al 1997, UK[54]	—	11.3%	0.5%–2.6%

It is unlikely that common, non-specific viral illnesses trigger the onset of CFS, but specific infections, such as mononucleosis, quite commonly do so. A large controlled study in general practice[66] found that people presenting with minor symptomatic infections were no more likely to report chronic fatigue subsequently than those presenting for other reasons. By contrast, a prospective cohort study following

individuals with serologically confirmed Epstein–Barr virus infection documented the development of a chronic fatigue state that was independent of psychiatric diagnoses.[67] In the Australian context it appears that infections such as Q fever and Ross River virus infection may also trigger CFS.[68-71]

Does CFS overlap with other illnesses?

Fatigue is a central feature of many clinical syndromes (see Box 1.2), including CFS, fibromyalgia, irritable bowel syndrome, major depression, anxiety and somatoform disorders.[72-82] These syndromes also share other, non-specific symptoms, including musculoskeletal pain, sleep disturbance, neurocognitive impairment and mood changes.[83] Fibromyalgia, in particular, is a closely related syndrome, differing mainly in its relative emphasis on musculoskeletal pain rather than fatigue.[73,84-89]

The number of non-specific medical symptoms reported by people with CFS is strongly correlated with the presence of psychological symptoms.[16,90] Up to two-thirds of adults with CFS have either prior or concurrent major depression,[36,40,60,74,91-98] as do people with fibromyalgia[99] and irritable-bowel syndrome.[100,101] By comparison, the lifetime rate of comparable depressive disorders in the general community is 15%–25%.[102-106] The high rate of comorbidity is not surprising, as current diagnostic criteria for both CFS and major depression (DSM-IV;[107] ICD-10[108]) include fatigue, sleep disturbance and cognitive impairment, and the presence of mood changes is no longer an exclusion criterion for the diagnosis of CFS.

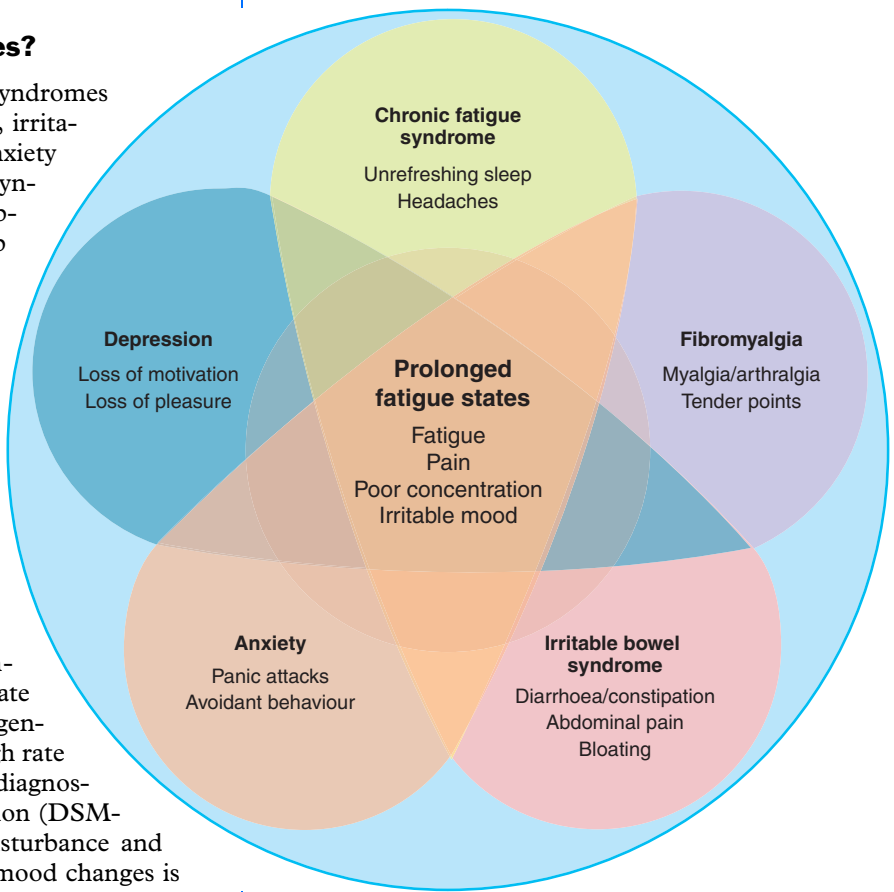
Perhaps the most difficult diagnostic uncertainty between CFS and psychological illness is in relation to "somatoform" disorders (DSM-IV[107]). In these disorders, people present with medically inexplicable physical symptoms that are hypothesised to be the result of underlying psychological processes. As the causes of CFS are "unexplained", there is an obvious overlap between the diagnostic criteria for the somatoform disorders and CFS.[16,90,109-112]

A recent international multicentre study attempted to stratify patients diagnosed with CFS in tertiary referral centres, without prior clinical assumptions.[113] The results suggested heterogeneity, with variation between centres, but it was not possible to determine whether the hypothesised subgroups (with "classical CFS" versus "multiple somatic" symptoms) lie on a continuum or represent truly distinct aetiological categories. Nor was it clear whether somatic symptoms were the result of a constitutional vulnerability or were secondary to chronic illness. It was concluded that, although stratification was likely to be important in future research, the basis for allocating subcategories remains controversial.

Whether it will ever be possible to neatly separate a "core condition" of CFS[16,33] from other "functional somatic syndromes"[114] or to successfully delineate aetiological subcategories of CFS patients remains unclear.[18,83] Whatever the case, however, in everyday clinical practice "somatisation" and "somatoform" are unhelpful diagnostic labels which are best avoided in patients with CFS (see Chapter 5).

1.2: Overlapping diagnoses

Prolonged fatigue states are found in fibromyalgia, irritable bowel syndrome, anxiety and depression, as well as in chronic fatigue syndrome



Food and environmental intolerances

Though not considered a "cause" of CFS, some patients with chronic fatigue report food intolerances that can exacerbate symptoms.[115,116] If food intolerance is suspected on clinical grounds, dietary investigation under the supervision of an appropriately qualified physician and dietitian may be warranted.

Some studies have suggested an overlap between CFS and multiple chemical sensitivity (MCS)[82,87,117-124] Gulf War syndrome[124,125-128] and "sick building" syndrome.[129] The existence of these as valid diagnostic or ontological entities is highly contentious[82,130-138] and their consideration is beyond the scope of these clinical practice guidelines.

1.3: Evaluation of the evidence for infections as factors in the pathophysiology of CFS

Non-specific infections

- Raised titres of IgG antibodies directed against common viruses (eg, herpesviruses, enteroviruses) are common, but are of no pathophysiological or diagnostic significance[51,173,184] (Level I).
- Common, non-specific infections (eg, upper respiratory tract infections) are not likely to trigger CFS[66] (Level II).

Epstein–Barr virus

- Infectious mononucleosis can trigger CFS[67,185-188] (Level I).
- Reactivation of EBV is not more prevalent in CFS[94,190-192] (Level II).

Enteroviruses

- Earlier reports of enteroviral RNA particles in the muscles have not been confirmed by more comprehensive studies[192-200] (Level I).

Retroviruses

- There is strong evidence against a role for retroviruses in CFS[201-208] (Level I).

Human herpesvirus-6

- There is conflicting evidence for reactivation of HHV-6 replication[176,184,191,209-216] (Level III-4).

Ross River virus

- Retrospective studies suggest CFS may follow RRV infection[30,70,217] (Level III-2).

Borna disease virus

- There is conflicting evidence of Borna disease virus infection in patients with CFS[184,218-222] (Level III-4).

Non-viral infections (Q fever, Lyme disease, *Mycoplasma*)

- Retrospective studies suggest CFS may follow adequately treated Q fever or Lyme disease[68,69,223-228] (Level IV).
- The existence of Lyme disease in Australia has not been confirmed[229] (Level III-3).
- An increased prevalence of colonisation by non-pathogenic mycoplasmal commensal species has been detected by polymerase chain reaction in the blood of a proportion of patients with CFS[230-232] (Level III-2).

Comment: Many studies that have suggested a link between infections and CFS have relied upon the detection of antibodies against the viral or other agent as an indirect means of implicating the organism in the pathophysiology of CFS. These studies have suggested that "high" titres of IgG antibodies directed against viruses such as EBV, HHV-6 or enteroviruses reflect chronic, active viral infection. However, case–control studies indicate that such "elevated" antibody titres are also found in healthy individuals many years after the original infection. Those studies which have sought direct evidence of chronic viral replication have not found an increased prevalence of viral isolation in people with CFS.

1.4: Evaluation of the evidence for immunological factors in the pathophysiology of CFS

General

- Despite numerous studies there is no consensus on the pattern and prevalence of immunological disturbance in people with CFS[165,233] (Level III-4).
- Preliminary evidence of an HLA association[234] has not been confirmed[235] (Level III-4).

Lymphocytes

- Reduced lymphocyte proliferation and natural killer cell cytotoxicity are common, but findings are non-specific[94,149,198,236-252] (Level I).
- Despite numerous studies there is no consensus on the pattern and prevalence of changes in peripheral blood lymphocyte subpopulations or activation status[149,198,240-242,246,247,249,253-259] (Level III-4).

Immunoglobulins

- There is conflicting evidence for reduced serum immunoglobulin G (IgG) and IgG subclass levels[239,260-264] (Level III-4).

Atopy

- There is conflicting evidence for an increased prevalence of atopy[174,265-272] (Level III-4).

Delayed type hypersensitivity skin responses

- There is conflicting evidence for impaired DTH skin responses[24,198,239,245,273-275] (Level III-4).

Cytokines

- Numerous studies using different methods have yielded conflicting evidence for increased serum levels of cytokines or cytokine production[94,198,237,276-292] (Level III-4).

Antiviral immunity

- Alterations in the 2-5A synthetase/ribonuclease (RNase L) antiviral pathway have been described in a significant proportion of patients with CFS[293-295] (Level II).

Autoimmune/inflammatory conditions

- There is conflicting evidence of a role for autoantibodies[296-299] (Level III-4).
- Sicca symptoms are common and a subset of people with CFS meet clinical but not laboratory criteria for Sjögren's syndrome[26,300-302] (Level II).
- An increased prevalence of elevated serum angiotensin-converting enzyme levels has been reported in patients with CFS[303] (Level III-3).

Comment: Numerous studies have sought evidence for a disturbance in immunity in people with CFS, but no consensus has emerged. The divergent results are likely to have arisen from variations in methodology, as well as inadequate attention to important confounding variables such as the effects of sleep disturbance, diurnal variation, medication, mood (and others) on laboratory measures of immunity.

1.5: Evaluation of the evidence for disturbance of central nervous system function as a factor in the pathophysiology of CFS

Neuroendocrine function

- Impaired hypothalamic–pituitary–adrenal (HPA) axis activation has been shown[304-323] (Level III-2).
- There is conflicting evidence for reduced levels of insulin-like growth factors (IGFs)[324-327] (Level III-4).

Sleep

- Disturbances of sleep maintenance (eg, frequent awakenings) are prevalent[81,328-331] (Level III-2).
- There is conflicting evidence of disturbed circadian rhythm[332,333] (Level III-4).
- Sleep disruption or circadian rhythm disturbance may perpetuate musculoskeletal symptoms[77,334,335] (Level III-3).

Sympathetic nervous system function

- Altered blood pressure responses to postural change, consistent with neurally mediated hypotension, have been shown[336-345] (Level III-2).
- There is conflicting evidence for reduced sympathetic nervous system markers[340,346-348] (Level III-4).

Neurotransmitter function

- There is conflicting evidence for increased sensitivity of serotonin and dopamine receptors to antagonists[305-307,349] (Level III-4).

Brain structure/function

- There is conflicting evidence for an increased prevalence of white matter abnormalities on magnetic resonance imaging[176,350-363] (Level III-4).
- Regional cerebral blood flow studies (eg, single photon emission computed tomography [SPECT]) have produced conflicting results[176,350-361,364-366] (Level III-4).
- Gait and motor abnormalities have been described[367,368] (Level III-2).

Cognitive performance

- Attention, concentration and other measures of cognitive function are impaired[361,369-383] (Level I). Interpretation of findings is uncertain.[384]
- There is conflicting evidence for impaired visual and auditory memory[361,369-378] (Level III-4).

Psychological/psychiatric factors

- Changes in biological markers (eg, HPA axis function, immunity, sleep architecture) in patients with major depression are different from those in patients with CFS[81,245,307] (Level III-2).
- There is conflicting evidence of a role for personality factors.[385-390] There were no differences in perfectionism, attitudes towards mental illness, defensiveness, social desirability or measures of neuroticism when patients with CFS were compared with a control group with rheumatoid arthritis[391] (Level III-4).
- Increased measures of suggestibility have been reported[392] (Level III-3).
- Childhood sexual or physical abuse were not found to be risk factors for development of CFS[393] (Level III-3).
- In a retrospective study, patients with CFS were more likely than controls to have experienced critical life events, infections and high fatigue levels during the three months before onset of CFS[394] (Level III-3).
- There is conflicting evidence of rates of premorbid psychiatric disorders (depression, anxiety, somatisation disorder) in patients with CFS[91-99,395] (Level III-4).

Comment: Several lines of evidence suggest that a disturbance of central nervous system function is present in people with CFS. This disturbance is reversible and, as yet, poorly characterised. The pattern of alteration seen in people with CFS in these studies contrasts with that seen in people with major depression, suggesting different pathophysiological processes in these two syndromes.

What is the natural history of fatigue states?

In the early stages of an illness characterised by prolonged fatigue, spontaneous recovery is common.[139] After infectious mononucleosis 41% of patients reported prominent fatigue during the acute illness, of whom 71% had prolonged fatigue one month later, 43% at two months, and 9% at six months.[67]

By contrast, full recovery in patients with established CFS is less common. In prospective studies, rates of self-reported improvement vary from 11%–64%,[140-143] and worsening at 12–18 months was reported in 15%–20%.[140,143] A US population surveillance study estimated a cumulative five-year recovery rate of 31%.[144]

The long-term outcome of CFS has been evaluated mostly in people treated within tertiary referral settings.[140,145-150] Such patient samples are biased towards chronic illness and limited patterns of recovery.[60,91,139] Patient reports drawn from self-help group populations show similar biases with respect to functional impairment.[146] In an Australian study conducted in a specialist setting,[150] 65 of 103 patients (63%) who had had symptoms for about five years reported abatement of symptoms and improvement in functional capacity over the next three years, but complete recovery was uncommon (6%). During follow-up, patients were very unlikely to develop other medical disorders (2%), but a significant

Phenomena associated with CFS

- CFS does not typically follow common, non-specific viral illnesses (Level II).
- Specific infections such as infectious mononucleosis can trigger CFS (Level I).
- There is currently no convincing evidence that retroviruses cause CFS (Level I).
- Immunological alterations are common in people with CFS (Level III-4), but are of uncertain pathophysiological significance.
- Neuroendocrine changes indicating hypothalamic–pituitary-axis disturbance are common in people with CFS (Level III-4), but are of uncertain pathophysiological significance.
- Sleep disturbance is very common in people with CFS (Level I), but is of uncertain pathophysiological significance.
- Neurocognitive performance in people with CFS is impaired (Level I).
- Neuromuscular performance in people with CFS is normal, implicating the central nervous system as the likely site of pathophysiological disturbance (Level I).

For an explanation of the rating of levels of evidence, see *page S21*.

1.6: Evaluation of the evidence for other factors proposed to contribute to the pathophysiology of CFS

Genetic factors

- Studies in twins suggest a genetic vulnerability to idiopathic chronic fatigue and possibly CFS[396,397] (Level III-2).

Neuromuscular disorder

- Muscle strength, endurance and recovery are normal[179,398-402] (Level I).
- Conflicting evidence for a disturbance in mitochondrial function[403,404] (Level III-4).
- The hypothesis that CFS is the result of channelopathy is not supported by empirical data[405,406] (Level IV).

Cardiac abnormality

- Subtle abnormalities of cardiac function with exercise have been described[407-409] (Level III-2).

Metabolic disturbance

- Urinary excretion of protein metabolites may be altered[410-412] (Level III-2).
- Serum acylcarnitine deficiency has been reported[413] (Level III-3).
- Differences in total body potassium levels between patients with CFS and control patients have been reported[414] (Level III-3).

Poisoning

- Levels of chlorinated hydrocarbons may be increased[415,416] (Level III-3).
- Chronic exposure to industrial solvents, insecticides or pesticides may cause an illness resembling CFS[417-419] (Level IV).
- Silicone breast implants may be associated with a syndrome resembling CFS[75,84,118,420-423] (Level IV).
- Ciguatera poisoning may precipitate a syndrome resembling CFS[424,] (Level IV).

Comment: Apart from the strong evidence indicating that the muscle is not the site of pathophysiological disturbance giving rise to fatigue in people with CFS, these studies provide only very limited preliminary evidence of other possible factors linked to CFS.

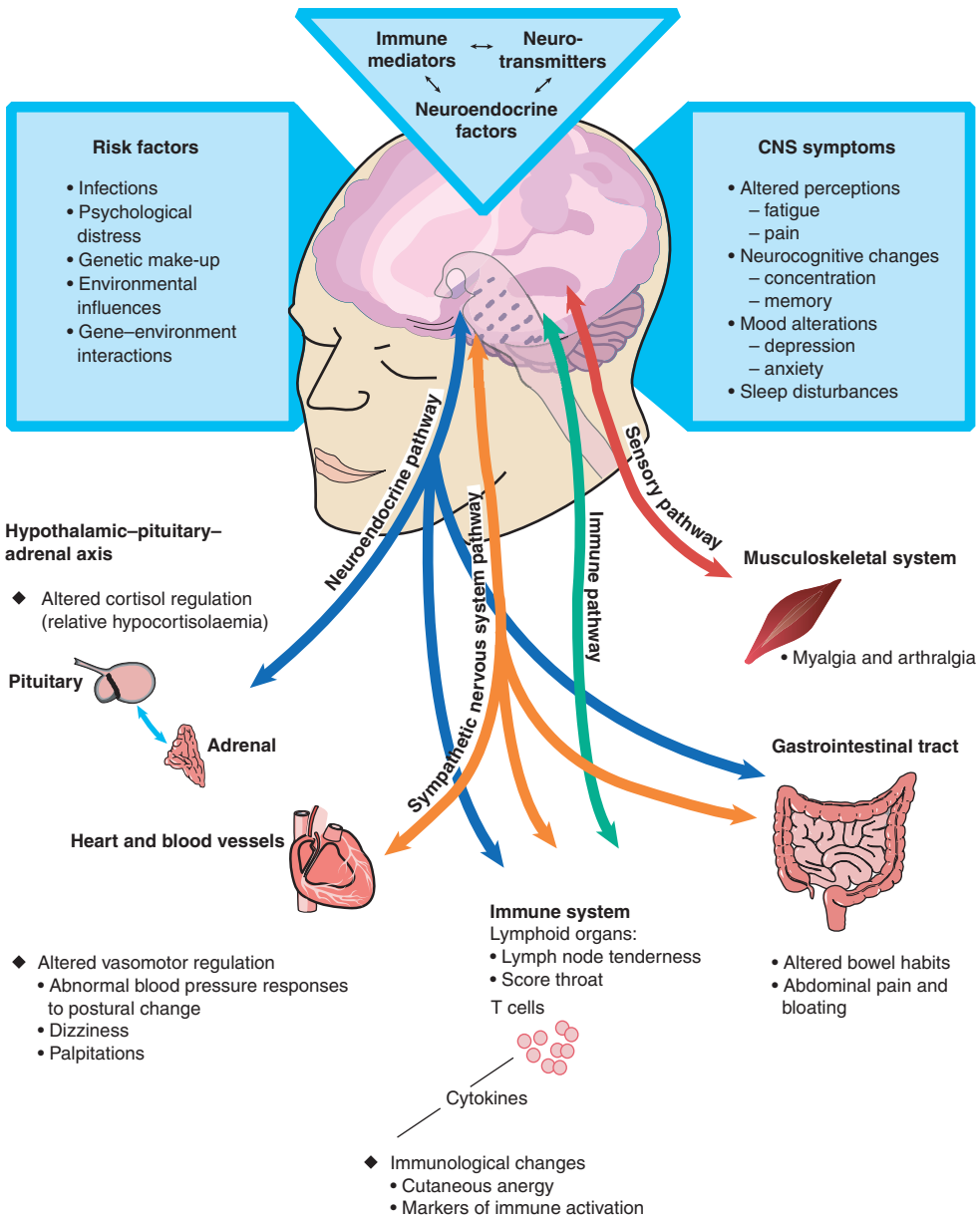
number did develop other psychological disorders (19%), notably major depression and anxiety. Similar outcomes were confirmed in several other retrospective studies from tertiary referral centres.

Factors associated with poorer outcomes include illness duration, subjective cognitive impairment and somatic symptoms,[143-151] as well as high levels of fatigue or functional impairment and a low sense of control over symptoms.[140] Outcome has not been found to be associated with sex or life stress events,[146-152] or with laboratory parameters, such as viral antibody titres and immunological measures (including T-cell-subset measurements).[153]

At the more severe end of the clinical spectrum, although improvement over time can occur, the prognosis for recovery is poor.[154,155] Patients who have had CFS for more than 10 years are more disabled than those with shorter-duration illness, and have significantly more severe symptoms (particularly cognitive impairment) and more frequent symptoms of fibromyalgia.[156]

Among 2075 people followed up in 19 published studies of the outcome of prolonged fatigue and CFS, there was one

1.7: Potential central nervous system pathways to chronic fatigue syndrome



death by suicide and two unrelated deaths.[139] These studies included mean follow-up periods ranging from six months to four years, suggesting that suicide rates and overall mortality are not increased in people with CFS.

In studies of children and adolescents with CFS the outcome is significantly better than in adults. Two studies evaluating chronic fatigue in children reported that 77%–94% recovered or their condition improved.[157,158] The average duration of illness is 2–4 years [see Chapter 4].[159-163]

What is known about the pathophysiology of CFS?

The pathophysiological basis of CFS is unclear. The leading hypotheses put forward over the past decade are summarised in Boxes 1.3 to 1.7 and include:

- a unique pattern of infection with a recognised or novel pathogen;[164]
- altered central nervous system (CNS) function resulting from an abnormal immune response against a common antigen;[16,165,166]
- a neuroendocrine disturbance;[167,168]
- a neuropsychiatric disorder with clinical and neurobiological aspects suggesting a link to depressive disorders;[169] and
- a psychologically determined response to infection or other stimuli occurring in "vulnerable" individuals.[110,170-172]

Other hypotheses exist but have not been scientifically evaluated. The probable heterogeneity within patient groups labelled as having CFS[18,28,82,83,113] makes it highly likely that there are multiple contributing factors in the disorder.

What is the cost of CFS to the community?

The financial impact of CFS on those affected and on the community has been evaluated.[22] A conservative Australian estimate of the direct costs (those incurred in diagnosis and management) was $1936 per case per annum (in 1988/89 dollars). After inclusion of indirect costs (from lost productivity associated with the disorder) the aggregate annual cost of CFS was $9436 per case (1988/89 dollars). In 2000/01 dollars, this represents a direct cost of $2764 per case and an annual aggregate cost of $13 471 to the community. Based on a conservative assumption of a community prevalence of CFS of 0.2% (200 cases per 100 000 population), this implies an annual cost to the Australian community of $525 million.

2: Evaluating people with fatigue

What is "fatigue"?

Patients who complain of persisting "fatigue" or "tiredness" may be describing any one of a diverse range of clinical phenomena, ranging from muscle weakness to dyspnoea or depressed mood. The initial task is to clarify the nature of the "fatigue". Fatigue, like pain, is intrinsically a brain-mediated sensation. As with pain, most people report that the fatigue is experienced as a peripheral phenomenon, apparently occurring in musculoskeletal regions. When questioned closely, most people with CFS report that they also experience "mental fatigue", typically precipitated by complex neuropsychological tasks.[74,426]

To differentiate the various causes of mental and physical fatigue, doctors should focus on the description of the complaint (Box 2.1). Fatigue in people with CFS is typically exacerbated by physical tasks previously achieved with ease, and recovery from periods of worsened fatigue can take hours or even days. Pathological fatigue can be differentiated from:

- somnolence (or "sleepiness"), as it is not relieved by sleep;
- neuromuscular weakness, as people with CFS can generate muscle strength and endurance when circumstances demand;[24,400,427] and
- the lack of motivation and loss of pleasure from usual daily activities that characterise depressive illness.

Diagnosis

Clinical diagnosis

- A diagnosis of CFS is made on clinical grounds (Level IV).
- Diagnosis relies on the presence of characteristic symptoms and exclusion of alternative medical and psychiatric disorders (Level IV).
- The physical examination in people with CFS is normal (Level I).
- People with CFS commonly have concurrent depression (Level I), which does not necessarily represent an alternative primary diagnosis.
- CFS frequently overlaps with other common syndromes such as fibromyalgia and irritable bowel syndrome (Level III-2).

Laboratory investigation

- There is no validated diagnostic test for CFS (Level I).
- The purpose of laboratory investigation is to exclude other conditions that may cause fatigue (Level IV).
- For most patients the following investigations are sufficient: blood count and ESR, serum levels of electrolytes (including calcium and phosphate), standard biochemical tests of liver and kidney function, thyroid function tests (TSH) and urinalysis for protein, blood and glucose (Level I).
- Symptoms or signs that are not typical of CFS (eg, fever, weight loss, enlargement of liver, spleen or lymph nodes) should be investigated separately, as indicated clinically (Level IV).

Specialist referral

- An experienced general practitioner should be able to make a diagnosis of CFS in most patients. Specialist medical or psychiatric referral is only required if the diagnosis remains in doubt (Level IV).

For an explanation of the rating of levels of evidence, see *page S21*.

How should fatigue be evaluated?

CFS is distinguished from similar fatigue-related illnesses not only by carefully characterising the fatigue itself, but also by evaluating associated symptoms and signs. People with CFS also report:

- unrefreshing sleep;
- myalgia:
- arthralgia;
- loss of concentration;
- memory impairment;
- irritable mood, and
- postexertional malaise (may be delayed).

Any of these associated features may be exacerbated by minor physical activity.

2.1: What can a person with "fatigue" or "tiredness" be describing?

In most instances the symptoms of chronic fatigue syndrome can be distinguished from the closely related phenomena of somnolence, muscle weakness, neuromuscular fatigability, depressed mood or anhedonia.

Person describes:	Interpretation
■ Reduced muscle power at rest ■ Difficulty walking or lifting weights	→ Muscle weakness (eg, myopathy; polymyositis)
■ Loss of muscle power over time with activity	→ Neuromuscular fatigability (eg, myasthenia gravis)
■ Physical and mental fatigue at rest	→ Central fatigue (eg, multiple sclerosis)
■ Lack of motivation to commence tasks ■ Lack of pleasure from tasks undertaken	→ Anhedonia (eg, major depression)
■ Daytime sleepiness ■ Short sleep latency	→ Somnolence (eg, sleep apnoea, narcolepsy)
■ Breathlessness at rest *or* on exercise	→ Dyspnoea → Weakness (eg, airflow limitation; cardiac failure; anaemia)
■ Muscle pain, joint pain ■ Fever, malaise	→ Inflammation (eg, systemic lupus erythematosus) → Infection (eg, influenza)

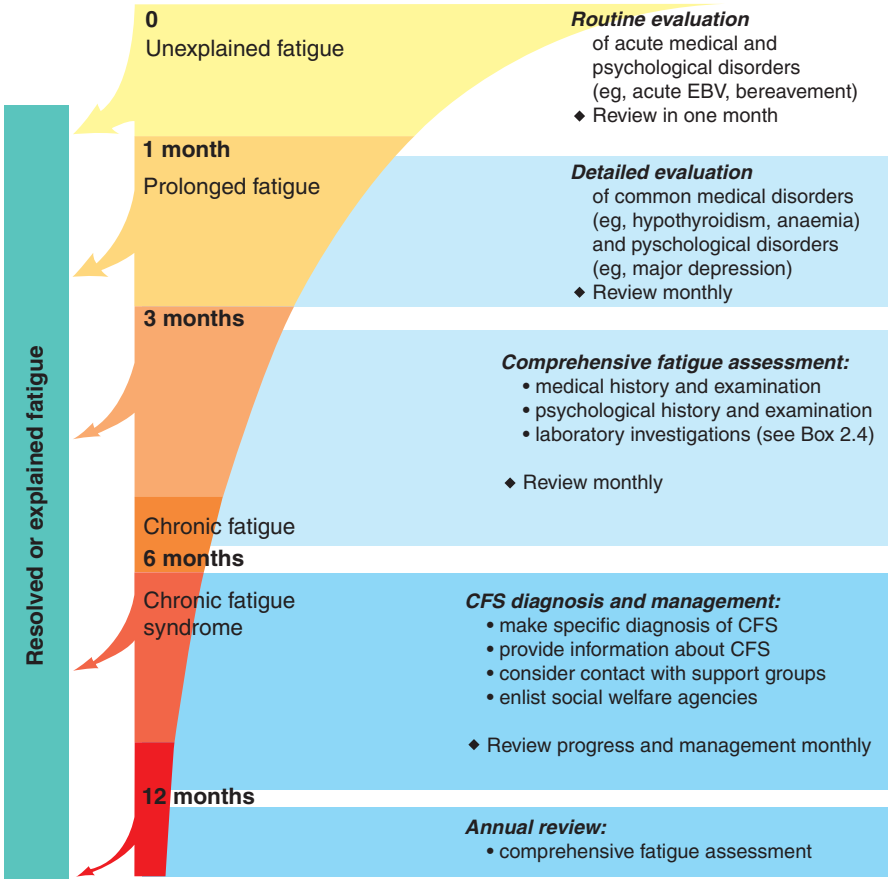
Although these symptoms are common in people with CFS, they are not specific and may occur in a range of other medical and neuropsychiatric disorders. In adults presenting for medical assessment with fatigue states the most common alternative diagnosis to consider is major depression.[25,36,39,40,66,74,92-94,96,97] Other commonly detected disorders (Box 2.3) are sleep apnoea, hypothyroidism, anaemia, coeliac disease, chronic hepatitis, panic disorder, generalised anxiety, and somatoform disorders.[16,27,39,40,78,81,90,109]

When taking a medical history, the questions should focus on key symptoms that might suggest alternative explanations for the fatigue state (see Box 2.1 and Box 2.3). Fatigue accompanied by fever, malaise and weight loss suggests an inflammatory or infective process, and fatigue accompanied by weight gain and cold intolerance may indicate hypothyroidism. Fatigue commonly accompanies many other medical conditions, particularly those directly involving the central nervous system and affecting information processing, the sleep–wake cycle, or arousal mechanisms (eg, multiple sclerosis). Many commonly prescribed medications (such as antihistamines and sedatives) and other substances (such as alcohol, marijuana and amphetamines) cause fatigue directly, or indirectly by disturbing the sleep–wake cycle.

Similarly, physical examination should be directed towards elucidating alternative diagnoses. Apart from minor, non-specific signs of illness, the physical examination in people with CFS is normal.[6] Evidence of objective muscle weakness, hard neurological signs, cardiorespiratory disease or fever should alert the doctor to diagnoses other than CFS (see Box 2.3). Although people with CFS often complain of tender cervical lymph nodes, demonstrable lymphadenopathy is not a feature.[6]

When patients have been definitively diagnosed with a medical or psychiatric condition known to be associated with marked fatigue, a separate diagnosis of CFS is generally not justified.

2.2: Flow chart for the evaluation of persistent fatigue



What psychological evaluation is required?

A formal diagnosis of CFS should not be made without an appropriate psychological evaluation of the patient.[6] Although this need not be done by a specialist psychiatrist or psychologist, referral can be useful in selected cases for both diagnostic and treatment purposes. Like the medical evaluation, the psychiatric assessment consists of two distinct parts: the history and the mental state examination.

Brief standardised approaches to psychological evaluation in primary care are available and have been shown to be effective.[429] These include self-report questionnaires such as the GHQ-30[430] and SPHERE,[61,431] or structured interview schedules such as PRIME-MD.[432] Important features of the history include prior episodes of anxiety or depression; a past history of multiple, unexplained physical symptoms; and prior alcohol or other substance misuse.

Many people with depressive disorders complain of fatigue or pain, rather than overt psychological symptoms such as tearfulness or sadness. The family history should be reviewed for depressive disorder, self-destructive behaviour or substance misuse. The relationship between the onset of the fatigue state and relevant psychosocial stressors should be noted. Whenever possible, an independent, corroborating history should be sought from a spouse, partner or other family member.

The characteristic mood state of people with CFS is irritation, frustration and transient depression, rather than persistent and profound sadness. This is unlike people with major depression, who report marked anorexia, weight loss, self-reproach and guilt, suicidal plans, persistent loss of motivation or a pervasive loss of pleasure.[25,107,108,111]

A careful review of the history of ill-health before the onset of CFS is the key to resolving the differential diagnosis

of somatoform and somatisation disorders. A long-standing history of frequent medical investigation and treatment for unexplained physical symptoms, persistent fear of medical ill-health despite adequate assessment, preoccupation with unusual physical explanations of illness, and persistent rejection of the potential relevance of psychosocial factors may suggest the diagnosis.[107,108]

The mental state examination of people with prolonged fatigue should focus on the observed behavioural features rather than simply those reported by the person. These include psychomotor slowing (which may suggest a serious depressive disorder),[433,434] demonstrable cognitive impairment (suggesting intoxication, delirium or a dementia syndrome), odd or bizarre interpersonal behaviour (suggesting a psychosis), and hostile, angry or excessively irritable responses (suggesting a personality disorder).

Evaluating a person's risk of suicide is an important task. The major psychological risk factor for suicide is untreated depression. Most people who attempt suicide first present to a healthcare agency, although they typically complain of non-specific symptoms such as poor sleep, poor appetite and tiredness rather than depressed mood.[435-437] Other risk factors for suicide include being male, social isolation, concurrent drug and alcohol use and access to lethal means.[438,439]

How should the context of the illness be assessed?

As in the management of other chronic medical conditions, assessing the social circumstances and interpersonal relationships of the patient with CFS is a key component of the medical evaluation.

Important issues to be addressed include:

- the effect of the illness on the person's ability to participate in work or school;
- the effect of the illness on key relationships (eg, partner, parents, friends); and
- the financial impact of the illness on the person with CFS and family.

The functional impairment of people with CFS has been shown to be similar to or greater than that of people with other chronic disabling medical conditions (eg, multiple sclerosis)[440] and psychological conditions (eg, major depression).[20,21] Accordingly, the patient's current level of disability should be carefully assessed, with a review of the duration and intensity of physical activity that can be undertaken without precipitating prolonged fatigue. For example, it may be evident that an adolescent's 45-minute walk to school produces fatigue and other symptoms that last all day. At the severe end of the spectrum of CFS, people may be housebound and experience profound fatigue simply from the necessities of self-care, such as showering or dressing.

A diagnosis of CFS is made after six months or more of disabling symptoms. By this time, people with CFS are commonly in crisis with their school or workplace because of the accumulated time lost as a result of the illness. Similarly, by the time of diagnosis, parents, friends and partners of people with CFS are often questioning the nature of the unexplained illness. The effect of the illness upon the patient's key interpersonal relationships,[441-443] work or educational activities should be specifically evaluated. This will enable doctors to act as advocates for their patients by providing appropriate information to relevant individuals and institutions.

2.3: Alternative causes of chronic fatigue*

Physiological
- Sedentary lifestyle
- Sleep deprivation

Drugs
- Medication (eg, β-blockers)
- Alcohol and drug dependence

Infectious diseases
- HIV/AIDS
- Chronic hepatitis B or C

Autoimmune disorders
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Sjögren's syndrome

Endocrine disorders
- Hypothyroidism
- Diabetes mellitus

Cardiorespiratory disorders
- Chronic airflow limitation
- Cardiac failure

Gastrointestinal disorders
- Coeliac disease
- Inflammatory bowel disease

Haematological disorders
- Anaemia

Sleep disorders
- Obstructive sleep apnoea

Neuromuscular disorders
- Myasthenia gravis
- Multiple sclerosis

Metabolic disorders
- Hypercalcaemia

Psychiatric and psychological disorders
- Major depression
- Anxiety disorder
- Somatisation disorder
- School phobia

Occult malignancy

Occupational and environmental factors

(eg, organic solvents, heavy metals)

* Not an exhaustive list.

What laboratory tests are appropriate?

Despite the wide range of serological, immunological, virological, psychometric and neuroimaging investigations that have been reported in case–control series of people with CFS (see Boxes 1.3–1.6), no specific diagnostic test for the disorder has emerged.[6] For any laboratory test to be accepted as having diagnostic validity, it would need to demonstrate both high sensitivity (ie, almost all people with CFS have a positive result — few false negatives) and high specificity (ie, almost all healthy persons, and people with fatigue not due to CFS, have a negative result — few false positives). In fact, as the diagnosis of CFS currently identifies a heterogeneous group of people,[16,113] it is unlikely that a single, reliable diagnostic test will emerge.

The only laboratory tests currently recommended for the routine evaluation of people with fatigue states (Box 2.4) are aimed at detecting alternative medical conditions. The diagnostic yield of investigations beyond this restricted list is very low.[444-447]

Perspectives

"We have had members of our support group who have been diagnosed with CFS, but who in fact did not have CFS but another disease. One woman endured five years of suffering until the correct diagnosis of systemic lupus erythematosus was made. She experienced substantial relief from drugs given to treat her lupus."

— a patient support group

Perspectives

"CFS is a sufficient indignity by itself; do not compound it. It takes considerable time and infinite patience to take an accurate history from a frail patient with impaired memory and concentration, especially if that history is long and complex. Resist the temptation of a hurried, superficial evaluation."

— Thomas English, MD[428]

"My cognitive difficulties were frightening and confusing. I often feared I was going crazy. I was ordinarily an intelligent man and avid learner, but suddenly my thinking was clouded and confused. I forgot things extremely easily. I mixed up words and I couldn't think of phrases I wanted to use. My concentration span was extremely short and my mathematical ability almost disappeared."

— a person with CFS

If specific alternative diagnoses are suggested by the clinical history or examination (eg, sleep apnoea or multiple sclerosis), further investigations may be warranted.

Many other laboratory procedures have been proposed as "diagnostic tests" by non-medical or alternative practitioners, but have not been subjected to rigorous evaluation. Such "tests" (eg, dark field blood testing for red cell morphology or "candida" identification; stool tests for "dysbiosis"; environmental sensitivity testing) have no basis in evidence and are not recommended.

When should another opinion be sought?

Given the lack of diagnostic certainty in people with CFS and the reliance on clinical history and examination, it may be appropriate to seek another medical opinion during evaluation or treatment. Another opinion by an experienced primary care practitioner may be sufficient, but specific issues in diagnostic assessment or treatment planning sometimes require consultation with the specialist most relevant to the individual's needs.

Perspectives

"CFS is one of the loneliest illnesses in the world, because we don't have anything to show for it."

— a person with CFS

For example, a history of snoring and daytime somnolence is an appropriate indication for assessment by a sleep physician, which may be followed by overnight sleep study. People with severe or prolonged depression, severe anxiety symptoms, or those assessed as being at risk of self-harm may require psychiatric evaluation. Adolescents who are absent from school or occupational training for prolonged periods may benefit from assessment by a paediatrician. People who are persistently housebound with severe disability arising from CFS may require the assessment and advice of a team, including specialists in rehabilitation medicine, pain management, physiotherapy, occupational therapy, and social work.

2.4: Laboratory investigations for evaluation of people with chronic fatigue*

Recommended

- Full blood count and film
- Erythrocyte sedimentation rate
- Urea, electrolyte and creatinine levels
- Serum calcium and phosphate levels
- Liver function tests
- Thyroid-stimulating hormone level
- Urinalysis for protein, blood and sugar

Not recommended†

Serological tests for:

- Epstein–Barr virus (Level II);
- Enteroviruses (Level II);
- Lyme disease in Australia (Level IV);
- Tests of immunity, including T lymphocyte subset measurements and functional assays (Level I);
- Urinary protein metabolite screening (Level III-3);
- Neuroimaging studies, including magnetic resonance imaging or radionuclide studies (Level III-3);
- Autoantibody assays (Level III-3); or
- Serum creatine kinase (Level II).

*Tests to exclude other diagnoses may be performed if indicated by the clinical evaluation

† Available evidence indicates that these tests have no role in standard laboratory evaluation of people with CFS.

3: Managing patients with CFS

Principles of management

Once the diagnosis of CFS is made, the doctor should establish an individualised management plan through a process of active discussion with the patient. The available pharmacological and non-pharmacological approaches should first be outlined, along with the role of continuing medical care and the place for physical, social and workplace (or school) rehabilitation programs. The importance of a collaborative approach between patient and doctor should be stressed. The plan should be designed within the framework of the patient's attitudes towards different modes of treatment, bearing in mind the limitations of existing evidence.[448]

The goal of treatment should be improvement towards and maintenance of maximal achievable functional capacity. While it is very unlikely that any single treatment will provide a "cure", current treatment approaches can result in significant reduction in disability over time.

It is important to give the patient a clear expectation that *sustained improvements are rarely achieved in short time frames* (days to weeks), but many patients can return to acceptable levels of functioning over longer periods (eg, three to six months).

Sustained improvements are rarely achieved without some setbacks and exacerbations of symptoms along the way. Frequent switching from one form of treatment to another in search of an elusive "cure" should be discouraged, as it is likely to result only in frustration and continuing disability. If patients are made aware of these possibilities at the outset, they will be less likely to abandon useful treatments prematurely.

To facilitate the reduction of disability, active control of key symptoms (eg, pain, sleep disturbance and depressed mood) with standard treatments should be explored. These may include the use of analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants or hypnosedatives. If these pharmacological agents prove helpful for the patient, their ongoing use should be reviewed regularly and coordinated with appropriate non-pharmacological forms of care. For example, short-term use of hypnosedatives may assist at the beginning of a structured sleep–wake cycle modification program.[449] Similarly, use of analgesics, NSAIDs or both may be necessary during the early phase of a physical rehabilitation approach. Or, if an antidepressant agent (eg, moclobemide) improves a patient's subjective sense of energy and wakefulness,[450] this can provide an opportunity to embark on a return to school or work, or a social activity program.

As with other chronic disorders, the patient's attitude to his or her illness experience, understanding of the nature of the disorder and its likely course over time, and the relationship between doctor and patient, are all likely to have a significant impact on long-term outcome.[451] Doctors who take an active approach to providing accurate information and to discussing key issues with their patients on an ongoing basis are likely to achieve the best results. This does not mean that the patient and doctor need necessarily agree about all treatment decisions (eg, the use of alternative therapies). It does, however, mean that they should agree on realistic goals for the outcomes of conventional medical treatments. The significant non-specific (placebo) response rate in some controlled treatment trials for people with CFS is likely to be a reflection of these essential components of good clinical practice.[452,453]

As a general principle of good management of patients with CFS, it can be useful to introduce the concept of self-monitoring of key symptoms and associated disability. This can be achieved through a variety of standardised instruments (eg, SPHERE,[431] Brief Disability Questionnaire) and activity, sleep–wake cycle or pain diaries. These allow both the doctor and patient to develop an accurate picture of whether progress is being made with a particular treatment, or whether there has been spontaneous improvement over time. Such monitoring may also alert the doctor to the emergence of a change in key symptoms or disability.

When people with CFS develop significant new symptoms, or experience a marked change in symptoms, they should be carefully reassessed. New symptoms should not automatically be assumed to be part of the CFS symptom complex. Within this context the emergence of depression and other psychiatric complications is particularly relevant.[450]

Management

- No single pharmacological treatment has been shown to be effective for people with CFS (Level I).
- Cognitive–behaviour therapy may be effective for some people with CFS (Level I).
- Physical and intellectual activities should be "paced" according to the individual's functional capacity (Level IV).
- Graded exercise may be effective for some people with CFS (Level II).
- Antidepressant drugs may provide symptomatic relief of pain, sleep disturbance, and depressed mood in people with CFS (Level IV).

For an explanation of the rating of levels of evidence, see *page S21*.

Perspectives

"We believe that the management and treatment of psychological symptoms in people with CFS should be similar to that for people with other chronic medical illnesses. Psychological symptoms in CFS can include depression, anxiety, and panic attacks among others."

— a patient support group

Pharmacological treatments for CFS

A range of antiviral, immunoregulatory, antidepressant and metabolic drug regimens have been evaluated in double-

blind, placebo-controlled trials in people with CFS. Although limited positive responses have been reported, no agent has consistently shown long-term efficacy in well-designed studies.[35]

Intravenous immunoglobulin (IVIG): Four double-blind, placebo-controlled trials of therapy with IVIG (based on a hypothesis of disturbed immunity in people with CFS) have been published.[264,273,454,455] Two of these trials conducted by one research group in Australia produced conflicting results, with the larger, dose-ranging study showing no significant benefit.[273,455] IVIG is not recommended for adults with CFS.

Antidepressants and other CNS agents: Given the high rate of depression, and depression-related symptoms such as fatigue, sleep disturbance, poor concentration and irritability in people with CFS, antidepressant therapies have received considerable attention. To date, there has been no evidence that patients respond in the way that would be expected if CFS were simply misdiagnosed or "masked" major depression. However, certain agents have been found to be beneficial for patients with CFS, particularly those with significant mood or sleep disturbances. Moclobemide (a reversible monoamine oxidase inhibitor) has been evaluated in a large double-blind, placebo-controlled trial.[450] Limited evidence of benefit was observed, with an improvement in the subjective sense of vigour and energy that was not associated with any alteration in mood. Similarly, selegiline (a specific monoamine oxidase inhibitor) has been reported to relieve tension and anxiety, and improve vigour and sexual relations.[456] All of these agents are somewhat "amphetamine-like" in their actions. While this may assist with key symptoms like fatigue, wakefulness and concentration, they should be used cautiously and closely monitored for side effects such as agitation and insomnia. Their most effective use may be in combination with an active sleep–wake cycle approach.[449]

While the new serotonergic agents are particularly popular for treating major depression, there has been little evidence of their overall usefulness in patients with CFS. In one of the first large trials, fluoxetine (a selective serotonin reuptake inhibitor [SSRI]) showed no more benefit than placebo.[457] However, SSRIs may have a place in patients with concurrent major depression or a strong personal or family vulnerability to anxiety or depression. SSRI therapy needs to be closely monitored for adverse side effects such as nausea, agitation and gastrointestinal disturbances in the early stages of treatment. As SSRIs may disturb sleep–wake architecture during the first few weeks of treatment, patients should also be closely monitored for any exacerbation of the CFS symptom complex. From this perspective, the older tricyclic agents and some of the new antidepressants with more sedative properties (eg, nefazodone) may be more suitable for some patients.

Studies of combination therapy with a low dose tricyclic antidepressant and an NSAID in people with fibromyalgia showed beneficial effects on muscle pain and sleep disturbance, but not on fatigue or mood.[458,459]

Corticosteroids: Two short-term, placebo-controlled trials of low-dose hydrocortisone therapy in patients with CFS showed a reduction in fatigue and improvement in "wellness", but this was associated with a significant depression of adrenal function.[460,461] Given the serious morbidity associated with long-term use,[462] corticosteroids cannot be recommended for CFS based on current evidence.

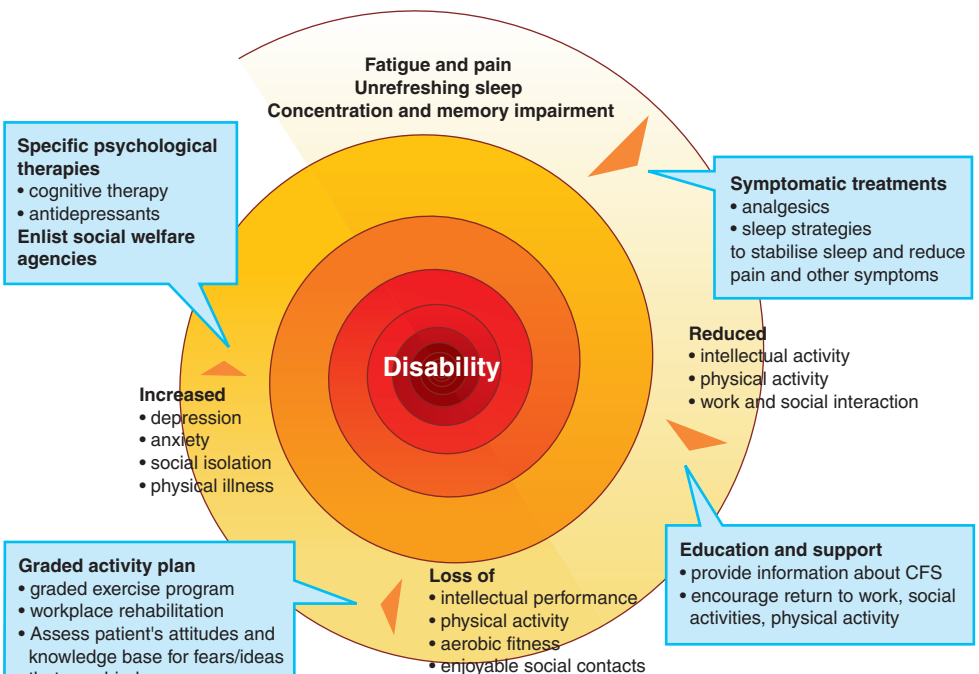
Mineralocorticoids: Although some patients have been found to have postural blood pressure changes consistent

Perspectives

"The doctor has the major responsibility for the care of people with CFS. However, many people do not have a supportive, well-informed medical practitioner. For them, the support of local community services is vital. The doctor and community services must work together to meet the needs of people with this disorder."

— a patient support group

3.1: Breaking vicious circles – a rationale for therapy



Perspectives

"My GP has the greatest role in helping me manage my illness on a day-to-day basis, although he refers me to a specialist when he thinks we could use help with a particular problem. For instance, when it was getting too hard for me even to manage my kitchen, he found an occupational therapist to help me redesign my domestic arrangements."

— a person with CFS

with neurally mediated hypotension (Box 1.5), mineralocorticoid therapy has not been found to be beneficial.[463,464]

The role of rehabilitation, behavioural and cognitive treatment approaches

Rehabilitation, behavioural and cognitive approaches link the principles of good clinical management with varying degrees of graded physical activity and psychological intervention.[153,465,466] They have been evaluated not only in patients with CFS, but in a wide variety of other closely related and often chronically debilitating medical and psychological disorders (eg, chronic pain, chronic daily headache, irritable bowel syndrome and chronic depression). Such treatments are not designed to achieve rapid symptomatic relief. Rather, they are aimed at maximising functional capacity over longer periods. For clinical trial purposes, a specific number of structured treatments are packaged over a set time period. In routine clinical practice, however, the initial treatment strategy is usually individualised according to the patient's level of disability and personal preferences, and subsequently modified according to the response. This is sometimes referred to as "pacing".[448]

The rationale for these approaches is outlined in Box 3.1.

The behavioural component encourages planned and supervised resumption of appropriate physical and mental tasks. A physical activity program is individually designed to take account of the patient's current level of disability.[467,468] After a prolonged period of illness and inactivity, new activities are introduced gradually and, most importantly, are "paced" (ie, scheduled to stop before they produce a significant exacerbation of symptoms). Over time the level of activity attempted is slowly increased at a rate determined by the patient's response.

The cognitive component aims to identify beliefs, attitudes and behaviours that may impair recovery.[469-471] Examples include a fear that *any* increased physical activity will cause harm or prolong illness; a belief that *all* treatment is futile and that only complete rest will help; a belief that *complete* withdrawal from work, school and social activities is necessary; a belief that occult chronic infection or chemical exposure has caused *permanent* injury. The existence of such beliefs is ascertained by exploring the person's causal attributions and his or her understanding of the illness.

As simplistic illness attributions may be associated with poor outcomes,[470] people with CFS should be encouraged to adopt the widest possible view of the medical, physical, and psychosocial management strategies to assist in coping with the illness.[472,473] The doctor and patient should work cooperatively to improve understanding, attitudes and behaviours that can help maximise long-term function.

In general, trials with more substantial differences between the intervention and the control treatment arms show the greatest benefits.[474] Active treatment programs that emphasise strong behavioural components (physical activity, rehabilitation) achieve good short-term results, but studies that incorporate a cognitive component produce more sustained long-term improvements. This may be because patients more readily adopt lifestyle changes that help maintain improved functional capacity beyond the formal treatment period.[465,475-477]

On balance, current evidence suggests that rehabilitative, behavioural and cognitive approaches should be an integral component of managing people with CFS.[478] This contrasts with previous beliefs that prolonged rest and social withdrawal should be advocated.[479] By the time patients present with established CFS, many have already experimented with prolonged rest and have found it unhelpful. In some, it may be associated with an exacerbation of sleep–wake difficulties and fatigue. Doctors should ensure that patients are informed of the dangers of prolonged rest[480] and the psychological risks of social isolation.

Applying management principles

In routine clinical practice these management principles can be applied within any of the following conceptual frameworks, depending on the preferences of the patient and the expertise of the doctor:

A *cognitive behaviour therapy* model: This tends to suit practitioners and patients who are comfortable working with an overtly behavioural approach to managing CFS.[466] Some patients find psychological terminology alienating, believing it to imply that their symptoms and disability are imaginary, contrived or "psychosomatic". Such beliefs are unfounded. Skilled practitioners who are able to explain the role of behavioural and psychological factors in a wide range of medical disorders can often overcome a patient's initial reservations and gain his or her confidence. When properly used, a cognitive behavioural management approach promotes active patient participation with self-monitoring, and takes account of previous experiences, both beneficial and adverse. Contrary to popular myths, this approach does not simplistically impose a psychological model of causation. Rather, it encourages patients to adopt a wider view of the range of medical and psychological approaches that can promote optimal long-term functioning.

A *disease education* model: This approach is used in other chronic and relapsing conditions such as diabetes or asthma, and therefore best suits patients and practitioners who are most comfortable with an overtly "medical" management model.[481] Within this framework (as with the cognitive behaviour approach) patients can be helped to gain a deeper understanding of their illness, adopt appropriate management strategies, avoid harmful treatments, and develop practical coping skills. As with many other chronic

medical disorders, it is better for patients with CFS to be empowered through appropriate self-management and self-monitoring techniques[482] rather than passively submitting to fruitless investigations and marginally effective medical interventions.

A *rehabilitation* model: This is akin to approaches used for disabling medical conditions such as brain or spinal injury, stroke, or chronic heart and lung diseases.[483] In the context of CFS, this model is best suited to doctors and patients who feel most comfortable focusing primarily on physical aspects of management.

Limitations of the evidence

There have now been a number of controlled or partially controlled studies of the various components of cognitive behavioural management approaches. Although most have shown significant short-term or longer-term benefit (or both), improvement has not been observed in all patients or in all studies,[484,485] and, when observed, may be modest.[486]

It is important to note that studies differ substantially in patient selection, intensity and duration of treatment provided, and suitability of the "control" interventions used for comparison. In most studies patients were only included if they were physically well enough to attend clinics for assessment, treatment and follow-up. It is therefore difficult to extrapolate the results to patients with more severe disability. Moreover, many studies have significant refusal and drop-out rates, which may reflect on the acceptability of the treatment regimens. These factors significantly limit the generalisability of the findings.[478]

What is the role of sleep management?

People with CFS experience a range of changes in sleep.[77,112,328-331,487-491] The most common features are reduced sleep efficiency, longer sleep onset, increased awakenings during sleep, increased total time in bed, and disturbance of circadian rhythm. There is a growing view that sleep disturbance in patients with CFS may be part of a wider abnormality of sleep–wake cycle function, and that restoration of the normal sleep–wake cycle, with consequent normalisation of circadian rhythm, should be an important goal of therapy.

In patients with CFS, behavioural approaches to sleep–wake cycle disturbance are likely to be more successful than pharmacological approaches, as the latter do not induce normal sleep. Cognitive and educational management approaches should be aimed at promoting an understanding of the role of disordered sleep, and dispelling any irrational fears or inappropriate beliefs about sleep. Relaxation training and stress management may be useful for some patients.

Sleeping for longer does not appear to improve physical or mental functioning in patients with CFS, and excessive periods of daytime sleep or frequent napping serve only to further disrupt circadian rhythm. The aim of sleep management is to establish a regular, normalised sleep–wake pattern:

- try to avoid excessive night-time sleep periods;
- avoid going to bed too early in the evening;
- avoid stimulants during the evening period;
- wake at a regular time in the morning (eg, 7 AM);
- get out of bed at a regular morning time (eg, by 8 AM);
- reduce (to less than 30 minutes) or abolish daytime naps; and
- engage in daytime physical and mental activities (within the limits of the individual's functional capacity).

While the recommendations above are generally considered helpful for promoting good sleep in a range of sleep disorders, direct evidence for their benefit in CFS is currently lacking. If a patient with CFS has a concurrent *primary* sleep disorder (eg, sleep apnoea, restless leg syndrome, narcolepsy), this requires specific intervention.

Perspectives

"Each new proposed treatment might just be the one to set things moving in the right direction. They stretch from the sublime to the ridiculous, but you must try them all lest you risk the 'Don't you want to recover?' question. These treatments aren't always benign, often leaving you physically worse off than when you started, not to mention emotionally and financially."

— a person with CFS

3.2: Treatments for chronic fatigue syndrome for which scientific evidence is lacking*

Vitamin and mineral supplements
- Vitamin C
- Vitamin E
- Vitamin B_6
- Vitamin B_{12}
- Coenzyme Q_{10}
- L-Glutamine
- Magnesium
- Zinc

Acupuncture

Homoeopathy

Naturopathy

Chiropractic

Tai chi

Meditation

Physical therapies
- Massage
- Colonic irrigation
- Cold baths
- Feldenkreis
- Aromatherapy
- Oxygen therapy
- Hydrogen peroxide

Herbal treatments
- Echinacea
- Garlic

Dietary restrictions
- "Hypoglycaemic" diet
- "Anti-candida" diet
- Low salicylate, low preservative diet

* Not an exhaustive list.

Unproven therapies in CFS

Given the variable clinical course of CFS, the likelihood of spontaneous improvement and the possibility of non-specific (placebo) responses, properly controlled clinical trials are essential for the evaluation of all proposed new treatments[153] (see Box 3.2). Any claim that a particular treatment can "cure" most people with CFS should be

regarded with a high degree of scepticism, not least because patient cohorts in CFS treatment trials are generally heterogeneous[16,113] and hence unlikely to respond in a uniform fashion. It should be borne in mind that in some controlled trials over 30% of people with CFS may show improvement in the non-specific (placebo) treatment arm.[153,450]

In general, evaluation of proposed new treatments for people with CFS requires:

- a plausible scientific rationale for the agent or treatment method to be tested, and preliminary findings showing safety and potential efficacy (phase I data); and
- extension of clinical studies beyond short-term, anecdotal or case-series approaches to randomised controlled trials that evaluate long-term treatment outcomes.[490,491]

The validity of the results of clinical trials is highly dependent on the quality of study design and analysis.[492,493]

Critical methodological requirements are:

- use of an internationally accepted case definition;[6,32]
- random assignment to test or comparison groups;
- adequate sample size;
- use of well-characterised outcome measures[494] and standardised self-report instruments for measuring fatigue, mood and other key symptoms;[32]
- independent, blinded assessments of functional status at onset, completion of treatment, and three to six months later (to ensure durability of the treatment effect); and
- reporting of refusal and drop-out rates, and of the type and frequency of adverse side effects.

Even with well-designed trials, positive results should be independently replicated[495] before a new treatment is widely promoted to the general public. The use of essential fatty acids for CFS is a case in point.[496] Doctors are encouraged to discuss frankly issues about evidence — including what is known and what is not known — to ensure that patients are able to make informed decisions about treatment.

Perspectives

"So far none of the alternative medicines have any scientifically proven benefit for people with CFS, although some individuals do seem to benefit from particular treatments they try. We also know that people who are desperate to get well may be exploited by practitioners offering unproven treatments. If a practitioner is offering alternative treatments to people with CFS, we believe that it is essential that they are informed of the cost and risks of the treatment, as well as whether there is any published scientific evidence to support its use."

— a patient support group

4: CFS in children and adolescents

Prevalence

The prevalence of CFS in adolescents in Australia is not known, although in a prevalence study by Lloyd et al[30] 20% of those diagnosed with CFS were in the 10–19-years age range. In the United States, prevalence estimates among adolescents reported by Marshall[160] depended on the method of case acquisition. These ranged from 116 per 100 000 (telephone interview of CFS-like illness in San Francisco) to 22–26 per 100 000 (school nurses reporting diagnosis, Wichita, Reno) and 3 per 100 000 (physician surveillance: referred cases in four centres).[497] All socioeconomic groups are represented and females comprise 71%–74% of the total.[160,162,454,498]

Onset

The onset of the illness in children is typically reported to be abrupt, following a suspected or confirmed viral illness in 85%.[498] A seasonal variation with peak onset in autumn and winter has been reported in Australia, suggesting an infectious contribution.[498] Epstein–Barr virus (EBV) was the most common infection to be documented serologically at the onset of fatigue symptoms (12% of 290 cases); others were cytomegalovirus, Ross River virus, toxoplasmosis, chickenpox and *Mycoplasma*. Findings are similar in the US, with most adolescents reporting fatigue following a viral illness, most commonly EBV.[160,499]

Symptoms

An Australian series of 290 adolescents with CFS from a tertiary referral practice showed a clinical picture highly consistent with that characterised in adults. Prolonged fatigue after physical activity was present in all individuals. Headache, loss of ability to concentrate, the excessive need for sleep, excessive fatigue and myalgia following minor activity, nausea, abdominal pain, sore throat without coryza, and a feeling of disturbed balance were present in 87%, with symptoms rated as severe or moderately severe in over 50%. Feelings of depression and sadness were present in more than 50%. Twenty per cent of individuals met diagnostic criteria for fibromyalgia, a similar figure to that reported in other series.[157,158,500-502] The course of the illness also varies. About two-thirds of individuals report continuous symptoms with fluctuating levels of severity, and 15% have a relapsing-and-remitting course.[159]

Perspectives

"So often I am told I don't look sick. Most of the time now I don't tell people I'm sick when I go out. When you're in a support group; however, it's good not having to continually justify yourself. I've formed many strong friendships through my support group which I think will far outlive my battle with CFS."

— a young person with CFS

CFS in young people

- CFS can occur in children and adolescents (Level I).
- Clinical improvement is reported frequently in adolescents with CFS, with return to normal functioning over time in a significant proportion (Level III-2).
- An individualised management plan should be developed in partnership with the young person and their family (Level IV).
- The special needs of young people — social, educational and emotional — should be given high priority (Level IV).

Differential diagnosis in young people

The range of conditions that need to be excluded is less extensive than for adults. Recommended investigations are identical to those in adults, including a urinalysis, a full blood count, erythrocyte sedimentation rate, biochemical tests of kidney and liver function, and thyroid function tests.

Systemic lupus erythematosus (SLE) and other connective tissue disorders may present with lethargy and musculoskeletal symptoms. Inflammatory bowel disease, coeliac disease, and gastrointestinal infection (eg, giardiasis) should be considered if there is abdominal pain, altered bowel habit or weight loss. A diet history should form part of the routine assessment. Occasionally, restrictive diets that are implemented in a search for alternative therapies have resulted in significant weight loss. Significant weight fluctuations, cessation of menses, altered body image and abnormal eating behaviour should raise the question of an eating disorder.

Adolescents with CFS often feel miserable, frustrated and angry, particularly after several months of illness. However, young people readily differentiate between feeling miserable meaning "fed-up" from miserable meaning "life is not worth living". Some groups report a higher rate of depression in young people with CFS compared with other chronic illnesses,[160] but the sample sizes were small and such series are susceptible to selection bias. When somatic symptoms characteristic of CFS are excluded from the commonly used depression scales, only a small proportion have major depression with anhedonia (7%). The rate is higher in adolescents with more severe CFS, particularly when there is a gradual onset and delay in diagnosis.

Anxiety about returning to the school situation is common in children and adolescents with CFS.[503] If extreme, however, other conditions that can mimic or complicate CFS should be considered (eg, depression, eating disorders, school refusal syndromes and, rarely, child abuse).[448]

Prognosis

Clinical improvement with return to normal functioning is frequently reported in adolescents with CFS, although the longest follow-up studies indicate that a small proportion remain unwell. The average duration of illness is 2–4 years

with a range of 1–9 years until well.[159-163] Illness pattern varies — about two-thirds have continuous symptoms with fluctuating levels of severity, and 15% have a relapsing-and-remitting course.[159]

One follow-up study reported that improved functioning rather than return to completely normal health was a relatively common outcome after implementation of a structured management program.[162] This program consisted of educational support, graduated exercise, symptom relief, social contact and guidance on planned energy use. After an average of three years (range, 1–6 years) 30% were back to normal, and an additional 20% had mild symptoms following vigorous exercise, but with an otherwise normal activity level. Another 20% were functioning at less than 50% of their previous level of activity, including participation in school or work. Greater morbidity was linked with delay in diagnosis and in receiving assistance.

Management

For young people, CFS often poses special problems that relate to their development.[504,505] Some problems are specific to CFS, while others relate to the effect of chronic illness on the emotional and social aspects of adolescent development, examples of which are:

- learning to become autonomous;
- developing a sense of body image;
- understanding and developing relationships;
- making career plans;
- dealing with sexual drives; and
- developing value systems.

Loss of time from school, reduced stamina for writing, and difficulty concentrating (being slower to do things and being only able to concentrate for short periods of time) all contribute to significant educational disruption. Perhaps the most significant effect on schooling, however, relates to the loss of social contacts and access to social learning that plays such a large part in school life.

A management plan should be developed in partnership with the young person and his or her family.[448] The individual's illness pattern and severity should be taken into account when designing an individualised program. Although few randomised treatment studies have been performed in children, several strategies have been proposed as helpful.[161-163,503,506,507]

Perspectives

"Support groups for adolescents and young adults with CFS have proved to be a great success wherever they have been established. They demonstrate the value of, and need for, social interaction with others in the same situation. People with CFS are no different from people with other chronic illnesses in this respect."

— a patient support group

Perspectives

"One consequence of being chronically ill for years at a time is the isolation. As much as you try, it is very hard to keep up the old friendships from school, work and uni. People move on, but I have not been able to go out and socialise like before."

— a person with CFS

- Symptom management should include treatment of headache, sleep disturbance, nausea, abdominal pain and dysmenorrhea, and muscle aches and pains.
- Depression and anxiety symptoms should be recognised and treated.
- Activities should be undertaken in a "paced" fashion and planned over a weekly period. The young person with CFS should be encouraged to balance social, physical and intellectual activities, and to make a commitment to undertake segments of each component regularly. This allows the individual to regain some control over their life. A gradual increase in physical activity with school attendance, or a graduated exercise program at home, can be incorporated into an overall weekly plan.
- Maintaining social contact should also be given high priority. This may be through school or via extracurricular activities. Contact with support groups can also be helpful.
- Liaison with the school is essential in order to design an education program involving attendance for particular subjects, or organising some school work by distance education with incorporation of social contact. Early planning and implementation of an educational program is desirable (ie, within 4–6 weeks of onset).

Once clinical improvement occurs, a "tailor-made" program for returning to school can be instituted. Returning to school can be anxiety provoking and stressful for young people with CFS because of remarks made by peers or teachers, as well as the resumption of physical, intellectual and social activities. A loss of confidence in social skills and intellectual ability is commonly reported.

Is referral to a specialist paediatrician necessary?

In a survey of adolescents with CFS, general practitioners were considered to be most helpful when they recognised the illness, acknowledged its effects, provided ongoing support, and monitored progress.[161,162] Specialist paediatricians were found to be helpful in:

- confirming the diagnosis;
- formulating and coordinating a plan of management;
- providing suggestions for symptom management; and
- providing documentation for and referral to education authorities (to arrange distance education, special consideration and special provision for Year 12 assessments, etc).

5: Social and legal issues

Diagnostic labelling of patients with fatigue

In the general population, fatigue states form a continuum in terms of severity and duration, and it is only in those with the most severe and persistent symptoms that a diagnosis of 'CFS' may be appropriate. Although the internationally accepted CFS case definition remains the "gold standard" for diagnosis, it is necessarily arbitrary, having been developed for the purpose of making valid comparisons between research studies carried out in different settings. As such, it creates an artificial boundary within the clinical continuum of fatigue states, giving the false impression that a specific clinical "entity" has thereby been delineated.[18,29,46,508]

In the absence of a clear understanding of aetiology and pathogenesis, the term CFS should be regarded as a *descriptive* label only.[46,508] Diagnostic boundaries are further blurred by the clinical overlap with other conditions such as fibromyalgia, irritable bowel syndrome, neurasthenia, anxiety and depression, in each of which fatigue can occur as a major symptom.[508] In each person with chronic fatigue the doctor must exercise clinical judgement in deciding whether CFS is an appropriate diagnostic label.[46]

What are the benefits of making a diagnosis of CFS?

A formal diagnosis of CFS can have positive implications for both the patient and the doctor. It allows the doctor to approach the patient with a greater degree of confidence, to explain the nature of the problem, to outline what treatments are appropriate, and to give a considered opinion as to what the outcome might be. Making a diagnosis of CFS should also mark the end of investigations to exclude other causes of illness (except at annual review — see Box 2.2).

From the patient's perspective, having a definitive diagnosis can go a long way towards relieving unwarranted fears and anxieties about the cause of symptoms.[510,511] Importantly, also, it validates the patient's experience of illness and suffering, making it easier to inform others of the nature of the illness, and legitimising the patient's entry into medical care. Once a patient has engaged with the doctor in this process, a series of personal, social and legal obligations result.[512,513] Family members, friends and employers can be expected to make appropriate allowances, and all concerned can be encouraged to make constructive contributions to the management plan. In the long term, this can help minimise morbidity.[451]

Perspectives

"Health professionals find it easier to label patients with depression, rather than recognise and acknowledge the natural grief reaction to the profound losses which occur with CFS — loss of health, disrupted family life, interrupted education and career, low self-esteem, etcetera. You can't dispense antigrief pills."

— a person with CFS

Implications of diagnosis

- Making a diagnosis of CFS encourages appropriate treatment planning (Level IV).
- A diagnosis of CFS does not establish a specific aetiology (Level I).

What are the disadvantages of a diagnosis of CFS?

As with many other chronic disorders, media reports, popular books and fundraising campaigns generally focus on the more extreme and dramatic end of the severity spectrum in CFS. In consequence, for the majority who are not so severely affected a diagnosis of CFS may conjure up alarming images of being confined to bed or a wheel chair, and life-long invalidism. In most cases, careful discussion with a knowledgeable practitioner can dispel such illusions, but some patients still harbour gloomy thoughts of a bleak future, with shattered dreams of family and career prospects.

The concern of some that "medicalisation" associated with providing a diagnostic label of CFS may create a self-fulfilling prophecy[514] is not usually borne out by experience.[510,511] In certain patients, however, the practitioner may consider it prudent to refrain from making a definitive diagnosis of CFS, or at least to be much more circumspect in applying the label. Thus, when the prognostic features are favourable (ie, younger age, less severe symptoms, shorter duration of illness) a more non-committal diagnosis, such as "post-infectious fatigue state", may be appropriate.

Importance of the doctor–patient relationship

Doctors who display the essential therapeutic characteristics of empathy, acceptance of their patient's suffering, non-judgemental style and a commitment to continued care are more likely to make an appropriate diagnosis[515] and to minimise the adverse effects of the illness experience.[452,513] Conversely, those who reject the patient's illness experience are likely to promote feelings of alienation and perpetuate ill health.[516] A qualitative study of people with CFS found that lack of perceived medical support and understanding was associated with increased seeking of alternative medicine.[517] Rejection by family, friends, peers and doctors leads many to experience CFS as a "delegitimising" illness.[518] Dismissing a patient's suffering as non-existent or imaginary is antitherapeutic.[28]

Broaching the issue of psychological factors in causation should be done with caution and sensitivity, avoiding stereotypic value judgements. The hypothesised role of "somatisation"[110] is particularly problematic.[111] Outdated and simplistic notions of "psychogenesis", with their implications of "imaginary" illness and "unconscious malingering", leave patients feeling stigmatised, guilty and resentful. Pejorative terms reflecting a false dichotomy between "organic" and "functional" disease[519,520] are best avoided.

Unwarranted speculation about psychogenesis, based on the outcome of trials of cognitive behavioural therapy in

Perspectives

"Currently, community services in Australia serve people with CFS, their families and carers very poorly. Services and support for people with other chronic and serious illness are generally provided without the ambivalence, relative ignorance and generally negative attitudes with which the support is provided to people with CFS, their families and carers."

— a patient support group

CFS, should also be avoided. This is only likely to further alienate patients and cause resistance to potentially beneficial management strategies. If an effective therapeutic relationship is to develop, doctors must acknowledge that, despite the current lack of understanding of the underlying cause and mechanisms of chronic fatigue, the symptoms are real and the suffering and associated disability is genuine.[448]

The role of patient support groups

Support groups have gained prominence in many areas of medicine, including in CFS, and they fill an important gap in areas that have traditionally been poorly catered for within the healthcare system. For individuals and families, they provide an opportunity to share experiences and exchange ideas on coping with practical day-to-day difficulties; they disseminate information on availability and quality of medical and government services, and news of research and treatment advances; and they can offer welcome relief from the sense of isolation that some patients feel. Support groups also have a more general advocacy role, for example in lobbying government agencies to improve funding for patient services, in fund-raising for ancillary services and research, and in promoting community awareness of the plight of sufferers (Box C, *page S26*).

Not all aspects of CFS support groups are necessarily positive. Inevitably, they tend to attract patients with the greatest functional impairment,[146] and this may inadvertently reinforce stereotypes of chronicity, disability and dependency. Moreover, the quality of advice can vary within and between groups, so it is important for practitioners to have ongoing knowledge of the activities and attitudes of local support groups.

Whenever possible, doctors should seek to work cooperatively with support groups. If effective dialogue is to be established and maintained, professionals must be sensitive to the concerns of patient groups, particularly in relation to the inappropriate use of pejorative and stigmatising terms.[521] Arrogant and dismissive professional attitudes, amplified by polarised press coverage, can contribute to the alienation of patients from traditional medicine.[517,522] Poor communication can also perpetuate misconceptions about aetiology, natural history and treatment rationales, which may themselves contribute to disability.[48,110,514,523]

Perspectives

"People with CFS seeking financial support from superannuation funds often experience drawn out applications, ill-informed and hostile review panels, further medical tests, lack of consultation with the treating doctor and the need to resort to legal action in an effort to obtain some financial support. This puts people with CFS under significant stress and may impede recovery."

— a patient support group

Occupational issues

Many people with CFS struggle to continue working, despite their chronic illness, for reasons such as self-fulfilment, social identity, or economic necessity. The doctor can provide support by appreciating the specific difficulties experienced by CFS sufferers, and suggesting appropriate coping strategies. Limited energy, cognitive impairment, and memory lapses can impair work effectiveness, placing jobs in jeopardy. Arranging flexibility, prioritising work and compensating for deficits are commonly adopted mitigating strategies.[524]

Unpredictability resulting from the fluctuating nature of fatigue symptoms[525] is a significant problem in conforming to a work routine. Flexibility can often be negotiated in the form of shorter hours or a shorter working week, a variable work schedule with breaks for rest as needed, or discretionary task selection to match variations in capacity.[524]

Many patients choose to stop working, or are unable to continue, either temporarily or permanently. Practitioners should be supportive in helping patients make the most appropriate choices in relation to their own personal priorities. Those for whom "life is career", and whose struggle to keep working is proving unsuccessful, may become deeply depressed, whereas those who see the maintenance of family and social life as a higher priority may find giving up work a more rational and satisfying choice.[524]

Medicolegal issues

Assessing a person with CFS for medicolegal purposes can be highly complex, and should be performed by a suitably qualified and experienced specialist. The role of the general practitioner is to provide factual information, such as details of consultations and referrals, investigations performed and treatment recommended.

In verifying a diagnosis of CFS, the current international diagnostic criteria (Box A) should be applied, including documentation of the characteristic symptoms, the lack of abnormalities on physical examination and results of the recommended laboratory investigations. A psychiatric evaluation may be indicated to document any psychological comorbidity.

Forming an opinion about the level of disability is a usual requirement in medicolegal assessment. Since CFS is a subjective illness, initial evaluation relies on a systematic review of the patient's self-reported functional capacity and an assessment of whether this is accurate. Corroborating information may be obtained from a partner or other family

member, and from other practitioners with detailed knowledge of the patient.

A doctor acting as an assessor or expert witness may be asked to provide an opinion on causation. Uncertainties regarding the aetiology and pathogenesis of CFS should be acknowledged, and conclusions about the role of infection, chemical exposure or the emotional demands of the workplace should be appropriately tentative unless the clinical evidence is clear-cut and compelling.

Opinions about prognosis should be based on the known natural history, taking account of the duration, clinical course and severity of the individual's illness to date, and his or her progress in response to appropriate symptomatic and behavioural management measures. The notion of "permanent" disability is problematic, as most people with CFS improve gradually, and some eventually recover. In people who have been severely disabled and unable to work for more than five years, the probability of substantial improvement within 10 years is less than 10%–20%. This may be regarded as "permanent disability" for medicolegal purposes.

In the absence of evidence of malingering, speculative judgements about unconscious motivation should be avoided. The psychoanalytic concept of "secondary gain" has been misused in medicolegal settings and does not rest on a solid empirical base.[526,527] In evaluating patients with CFS, hypothesised secondary gains should be weighed against manifest secondary losses. The notion of "abnormal illness behaviour" is contentious,[528] and the term should not be used as a diagnostic label.

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