

Chronic fatigue syndrome

**Draft Clinical Practice Guidelines on
the evaluation of prolonged fatigue and
the diagnosis and management of chronic fatigue syndrome**

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

Version 1
December 1997

This draft is also available on the world wide web:

<http://www.mja.com.au/public/guides/cfs/cfs1.html>

Published by The Medical Journal of Australia

MJA

Membership of the Working Group

Convenors

Dr Robert Loblay Royal Australasian College of Physicians

Associate Professor Graeme Stewart Royal Australasian College of Physicians;
Former member, Ministerial CFS Review Committee

Members

Dr James Bertouch Australian Rheumatology Association

Dr Peter Cistulli Australasian Sleep Association

Dr Paul Darveniza Australian Association of Neurologists

Mr Craig Ellis Consumers Health Forum of Australia; Member, ME/CFS Society of Victoria

Professor Paul Gatenby Royal Australasian College of Physicians

Dr David Gillis Australasian Society of Clinical Immunology and Allergy

Professor Ian Hickie Royal Australian and New Zealand College of Psychiatrists

Associate Professor Andrew Lloyd Australasian Society for Infectious Diseases

Dr Bryce Phillips General practitioner; Former member, Ministerial CFS Review Committee

Professor Wai-On Phoon Australasian Faculty of Occupational Medicine

Dr Katherine Rowe Australian College of Paediatrics

Dr Ian Steven Royal Australian College of General Practitioners

Professor Denis Wakefield Royal College of Pathologists of Australia

Dr David Watson Consultant Physician; Former Chairman, Ministerial CFS Review Committee

Project Officer

Ms Victoria Toulkidis Royal Australasian College of Physicians

Research assistant

Ms Cristina Ricci School of Psychiatry, University of New South Wales

Acknowledgments

We thank the following individuals: Andrew Lloyd, Ian Hickie and Cristina Ricci for their comprehensive review of the published literature and preparation of preliminary drafts; Helen Lapsley (former chair of the Quality of Care and Health Outcomes Standing Committee of the National Health and Medical Research Council) for advice on guideline development and assessment of levels of evidence; Craig Ellis and Joan Rothery for compiling and summarising the submissions from individual patients and health consumer organisations; Martin van der Weyden (Editor, *Medical Journal of Australia*) for advice on the format and presentation of the guidelines; Craig Bingham for editing, preparation of the figures, and HTML formatting; Peter Schlesinger (Department of Health and Family Services) for administration of the Commonwealth Grant; and Victoria Toulkidis for managing the project.

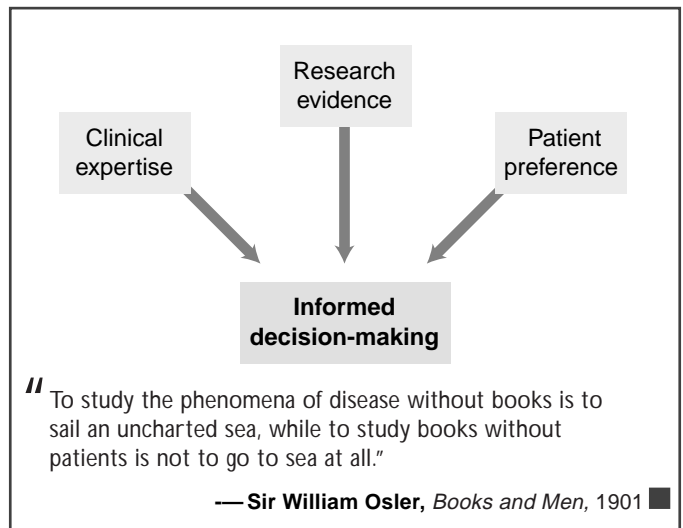
Preface

These guidelines are primarily aimed at assisting general practitioners, but they will also be useful to specialist physicians and other health care professionals involved in managing people with fatigue states, including physiotherapists, occupational therapists, psychologists and social workers. They are based on the best information available at the date of publication, and are intended to provide a general guide to appropriate 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 Commonwealth Minister for Health established a CFS Review Committee 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 was circulated to all physicians in *Fellowship Affairs*, together with a questionnaire, and the paper and 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. Meanwhile, representatives of the Review Committee, the RACP and ASCIA met and agreed to develop an expert consensus position regarding the diagnosis and management of CFS. Fortunately, in October 1995, the National Health and Medical Research Council (NHMRC) published *Guidelines for the development and implementation of clinical practice guidelines*, which provided an ideal framework for this purpose. Consequently, in 1996, a multidisciplinary Working Group (including a consumer representative) was established under the auspices of the RACP to develop and disseminate evidence-based guidelines, following the procedures recommended by the NHMRC. The Com-



monwealth Department of Health and Family Services provided funding.

Guideline development

The Working Group conducted an exhaustive 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 (see part 6, page 26). In addition, the Ministerial Review Committee report and a variety of other local and international public domain documents were examined.

Submissions were also invited from interested practitioners, consumers and patient support groups. Eighty submissions were received from people with CFS, carers, concerned individuals and CFS Societies, and these were compiled and summarised for the Working Group by the consumer representative. A copy of the consumer perspective summary document is available on the world wide web at <http://www.racp.edu.au/consumer.htm>.

The Working Group prepared an exposure draft of the guidelines which was disseminated widely to relevant specialist societies, Royal Colleges, the NHMRC, complementary practitioner associations, patient support groups, and interested individual practitioners and consumers. The exposure draft was also produced on the world wide web site of the *Medical Journal of Australia* at <http://www.mja.com.au/public/guides/cfs/cfs1.html>. The final document was then revised in the light of the comments received.

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Clinical overview

Prolonged fatigue is a common complaint in the community and is usually transitory. If fatigue continues for more than six months, is disabling, and is accompanied by other constitutional and neuropsychiatric symptoms, then a diagnosis of chronic fatigue syndrome (CFS) should be considered.

Although the symptoms of CFS are currently hypothesised to be due to abnormal brain function, the underlying pathophysiology is not known at present. Therefore, CFS cannot currently be defined as a specific “disease” entity. Indeed, there is growing evidence that the disorder is heterogeneous, and it will probably prove to have no single or simple aetiology.

Nevertheless, the suffering and disability—physical, psychological and social—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 convey to people with CFS their recognition of the reality and seriousness of the suffering and associated disability, even though an underlying disease process cannot presently be defined.

Diagnosis of CFS

A diagnosis of CFS is made on clinical grounds. It relies on the presence of characteristic symptoms (see Box 1), 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 be considered an alternative primary diagnosis.

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

Clinical history

The history should closely examine 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 even days. The fatigue should be differentiated specifically from weakness (neuromuscular disease), dyspnoea and effort intolerance (cardiac or respiratory disease), somnolence (primary

1: Diagnostic criteria for chronic fatigue syndrome (Fukuda, et al. 1994)

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

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 intolerance (hypothyroidism); snoring and daytime somnolence (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 abuse. A history of altered bowel habit may indicate an underlying gastrointestinal infection (e.g., 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 ESR
- serum levels of electrolytes, calcium and creatinine
- biochemical liver function tests
- thyroid function tests (TSH)
- urinalysis for blood, protein and sugar.

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

Specialist referral

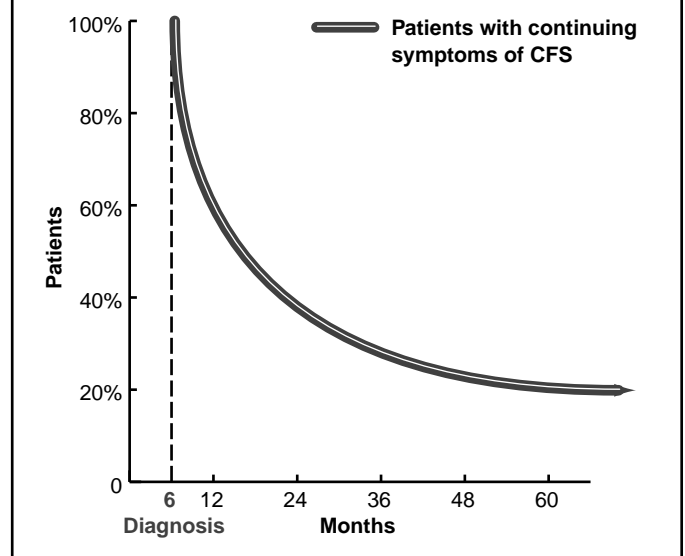
In most cases, a general practitioner should be able to make a confident diagnosis of CFS. However, if, after a careful history, examination and screening investigations, the diagnosis remains in doubt, the opinion of a specialist physician should be sought. Referral to a psychiatrist may also be useful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

Management

As most prolonged fatigue syndromes will resolve spontaneously, reassurance and supportive care is generally all that is required for early management. In people with established CFS, providing a definite diagnosis along with general information about the nature of the illness and its prognosis are important starting points for good clinical care.

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 the patient's illness

2: Model of natural history of chronic fatigue syndrome



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 social withdrawal
- maintain regular contact
- evaluate the basis of any new symptom or deterioration in function
- provide support for the person and his or her family, including access to social security, educational assistance and disability services where appropriate.

Understanding the illness

Helping the person with CFS to have a clear understanding of the nature of the illness is an important element of management. For example, some people harbour fears that they may be "going mad", or that minute amounts of environmental toxins may be causing irreversible immunological or neurological damage. Unwarranted concerns of this kind may lead to maladaptive attitudes and behaviours which may themselves increase disability and retard recovery.

Both the doctor and the patient should avoid simplistic attributions of CFS to "a virus", "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 of the individual's disability is more appropriate.

No pharmacological agent has been reliably shown to be effective treatment for CFS. Management strategies are therefore directed at minimising impediments to recovery, notably,

loss of aerobic fitness, disruption of the sleep–wake cycle, intercurrent depression and social isolation. These strategies, together with promotion of a clear understanding of the illness, are sometimes termed *cognitive behavioural therapy* (see Box 4.4, page 21).

Physical activity

In the early stages of the illness, many people with CFS make the mistake of putting off chores or social engagements until they feel better, then pushing themselves too hard 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.

It is also important to discuss with the person with CFS the vicious circle whereby initial avoidance of physical activity may lead to longer-term avoidance of all activity.

In general, people with CFS should begin by undertaking physical and intellectual tasks in divided sessions of relatively short duration, rather than engaging in extended periods of activity. As exercise tolerance improves, activity can be gradually increased. Graded exercise programs have been shown to be safe for people with CFS, and can improve both aerobic capacity and functional status.

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

- commencing at a level of activity which can be achieved without exacerbation of symptoms
- undertaking activity on a regular basis in sessions of limited duration
- planning for regular reviews to achieve feasible increases in activity over a realistic time-frame (e.g., several months).

Sleep

Unrefreshing sleep is extremely common in people with CFS. Although they usually report an increased total sleep time, typically it has a broken and restless pattern. A shift from regular night-time sleep to day-time naps and a late-night to late-morning sleep cycle is also common.

It is known that this type of disruption to a healthy sleep pattern can induce prolonged symptoms in healthy volunteers, including prominent fatigue, musculoskeletal pain, irritability and concentration impairment.

Restoration of a regular, unbroken, night-time sleep of about eight hours duration should be a goal of management of people with CFS. This goal may be achieved by:

- avoiding day-time naps
- gentle exercise late in the day or early evening
- establishing a regular bed-time routine
- analgesics and/or non-steroidal anti-inflammatory drugs (NSAIDs) for relief of musculoskeletal pain or headache and, if necessary
- sedative–hypnotic medication to achieve sleep.

Some people develop habituated patterns of “phase-shifted” sleep (typically midnight to midday), or of initial insomnia

(spending several hours in bed before falling asleep). These patterns may require a structured sleep hygiene program to restore a more normal regimen. In general, such sleep interventions in people with CFS can significantly reduce symptoms and improve functional capacity. Where appropriate, the advice of a specialist sleep physician should be sought.

Symptomatic drug treatment

No medication has yet been demonstrated 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 treatment offers more symptomatic benefits than harmful side effects.

People with CFS may have increased susceptibility to drug side effects, and it is generally wise to begin with small doses when introducing potent agents to a patient whose response cannot be predicted.

Although depression is a common symptom in people with CFS, the illness as a whole cannot be attributed simply to major depression. Hence, antidepressant drugs do not provide a panacea for CFS. At least one agent (fluoxetine) has been specifically shown to be ineffective.

However, the antidepressant group of drugs includes several different classes of pharmacological agents, each of which may have particular activity in relation to one or more symptoms of CFS, such as subjective energy (moclobemide), sleep disturbance (amitriptyline, nefazodone), muscle and joint pain (amitriptyline), concentration (moclobemide), and depressed mood (sertraline, paroxetine, nefazodone).

A reasonable approach is to consider undertaking a therapeutic trial of a selected drug based upon 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 improving sleep and reducing pain.

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.

A successful return to work or school after a prolonged illness with CFS often requires a rehabilitation program incorporating medical treatments, psychological support and occupational therapy, and the doctor may need to coordinate the help of other health care and educational professionals to implement this where appropriate.

Consideration should also be given to the impact of the ill-

ness on the person's family. 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 arranging, 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 regarding access to social welfare agencies. Support groups also provide an opportunity for individuals to exchange information on how to cope with the many practical day-to-day difficulties which arise for those living with this debilitating condition.*

*A list of the contact details for Australian CFS support groups is provided at the back of this book.

FAQs: Questions frequently asked of doctors by people with CFS

- **What causes CFS?**

No single cause of the illness has been identified. Infections, psychological factors, as well as genetic influences, are likely to contribute.

- **Is there a diagnostic test for CFS?**

No, there is no blood, urine, or imaging investigation to diagnose CFS. The keys to diagnosis are recognition of the characteristic symptoms and exclusion of other possible causes.

- **Is CFS a psychological disorder?**

All chronic illnesses have significant medical, psychological and social components. CFS is not simply a form of depression or anxiety.

- **How long will it take to recover?**

It is not possible to predict for any individual person when the disorder will resolve. However, people with CFS who have been ill for less than two years have a high likelihood of recovery within the following two to three years.

- **Will bed rest cure the illness?**

No, bed rest may temporarily ease symptoms, but will not improve the chance of recovery. If continued, bedrest may worsen and perpetuate the illness.

- **Is there a cure for CFS?**

No, there is no single curative treatment for CFS. However, there are a range of symptomatic and supportive treatments which are beneficial.

- **Will exercise cure the illness?**

No, although a regular but gentle exercise program that is individually designed for each person is beneficial. Excessive physical activity may worsen symptoms in the short term.

- **Does a modified diet help?**

There is no evidence to suggest that dietary treatment or "megavitamin" therapy is effective in treating CFS. Some diets proposed for people with CFS are nutritionally deficient and may cause harm.

- **Are there complementary medical approaches which help?**

There is no evidence that such treatments are effective, but little or no research has been undertaken. It is reasonable to evaluate unproven treatments on an individual patient basis (trial the treatment in comparison with placebo) provided there is no likelihood of harm from the treatment.

- **Can people with CFS continue working?**

Yes. CFS is associated with a spectrum of disability ranging from people who are housebound to those who experience more mild symptoms. Whenever possible people should be encouraged to continue working.

- **Are people with CFS eligible for Sickness Benefits?**

Yes. Like any other medically certified illness, sickness benefits or disability allowances are an important part of ensuring the financial stability of people with CFS.

- **When recovery occurs does it happen overnight?**

Recovery typically occurs gradually over weeks to months.

- **Are there long term problems following CFS?**

There are no long term problems after recovery from CFS. This condition is not associated with an increased risk of infection or cancer.

1: What is chronic fatigue syndrome?

The spectrum of fatigue states

Prolonged and disabling fatigue is present in 10%–25% of patients presenting to general practitioners (Kroenke et al. 1988; David et al. 1990; Cathebras et al. 1992; Katerndahl, 1993; Walker et al. 1993; Fuhrer and Wessely, 1995; Hickie et al. 1996a). Fatigue syndromes lie along a continuum of severity (David et al. 1990; Lewis and Wessely, 1992; Pawlikowska et al. 1994; Hickie et al. 1995) from the ubiquitous transient and mild states to the more severe and prolonged fatigue disorders, including CFS. As with other problems in clinical medicine (such as hypertension or obesity) there is a continuum from health to severe illness, and the challenge is to identify the point at which the state (of blood pressure, bodyweight, or fatigue) becomes a source of ill health. In relation to fatigue states, it is important to identify those people in whom the disorder is associated with ongoing disability (Komaroff et al. 1996a; Buchwald et al. 1996) and significant personal or economic cost (Lloyd and Pender, 1992).

Syndromal diagnoses like CFS are widely used in clinical medicine (e.g. migraine headache, systemic lupus erythematosus, major depression). CFS is not a “disease”, as this concept refers to a disorder classified according to its underlying cause or pathophysiology (Jennings 1986). By contrast, CFS is an “illness”, which is a subjective state, and can only be defined by reference to the sick individual (Cassell 1991). “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 the underlying *disease* process has not been identified. Our goal as physicians is not only to identify and treat disease, but also to help relieve suffering and disability, whatever the cause.

What is CFS?

In 1988, the US 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 (Holmes et al. 1988). Current diagnostic criteria (see Box 1 on page 1) describe CFS as a syndrome of physical and mental fatigue, usually of acute onset, which is markedly exacerbated by physical activity. The other common symptoms include general malaise, headaches, poor memory and concentration, unrefreshing sleep, myalgia, arthralgia, and irritable mood (Lloyd et al. 1988; Hickie et al. 1990; Komaroff and Buchwald, 1991; Hickie et al. 1995; Komaroff et al. 1996b). The diagnostic cri-

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%–0.5% (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 socio-economic groups (Level I)

For an explanation of the rating of levels of evidence, see part 6, page 26

Perspectives

“CFS is like living in a fog of fatigue and pain that affects all my body, even after limited activities — the way I move, the way I think and the way I live. Rest is bliss to ease the awful pain — but with 70% less active hours in my day my patience is tested to the limits. I feel I must keep going hoping the ‘fog’ will lift — but how long?”

— a person with CFS ■

teria also emphasise that the person must have been unwell for more than six months and that the symptom complex is associated with substantial disability.

In primary care, about two-thirds of people with chronic fatigue will have another medical or psychiatric disorder that accounts for it (Manu et al. 1988a, 1988b, 1989; Buchwald et al. 1995; Lawrie et al. 1997).

CFS is not simply a diagnosis of exclusion, although the careful assessment of other possible medical and psychological causes is a fundamental step (Fukuda et al. 1994). Some people with severe fatigue syndromes will fail to meet the research diagnostic criteria for CFS but may still benefit from the assessment and intervention strategies described in these guidelines.

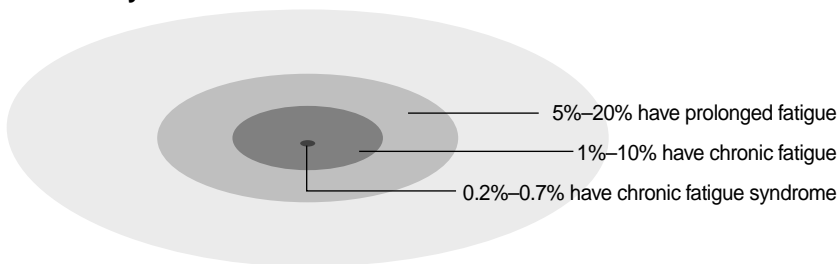
Delineating a clinical syndrome facilitates research that tests

1.1: The prevalence of fatigue states

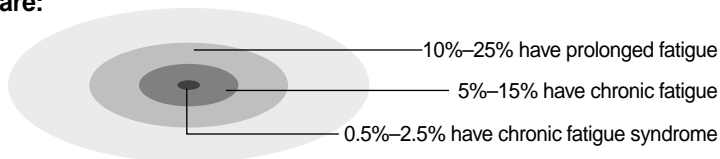
Definitions:

- ◆ **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 (see also Box 1 on page 1) (Defined by Fukuda et al. 1994)

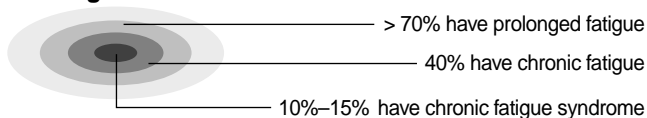
Community:



Primary care:



Tertiary referrals for fatigue:



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

Study	PF	CF	CFS
Buchwald 1987, USA	—	21%	—
Kroenke 1988, USA	23.8%	—	—
David 1990, UK	10.5%	—	0.16%
Cathebras 1992, Canada	13.6%	5.7%	—
Bates 1993, USA	—	27%	0.3%–1.0%
Katerndahl 1993, USA	6.9%	—	—
McDonald 1993, UK	—	11.2%	2.5%
Walker 1993, USA	6.7%	—	—
Pawlikowska 1994, UK	—	18.3%	—
Buchwald 1995, USA	—	19%	0.1%–0.3%
Wessely 1997, UK	—	11.3%	0.5%–2.6%
Hickie 1996, Australia	25%	—	0.3%–1.3%

the validity of the concept by clinical description, laboratory and epidemiological studies. It also encourages pathophysiological and treatment research before the pathogenic process has been clearly elucidated.

Although a variety of clinical and research definitions have been proposed (Lloyd et al. 1988; Holmes et al. 1988; Lloyd et al. 1990; Sharpe et al. 1991; Schluederberg et al. 1992; Fukuda et al. 1994; Komaroff et al. 1996b), the current international consensus criteria for CFS (Fukuda et al. 1994) are generally accepted within the scientific literature. Box 1.1 outlines the criteria for CFS and also for prolonged fatigue and chronic fatigue.

What other names are commonly used for CFS?

In the British medical and patient literature “**myalgic encephalomyelitis**” (Lancet 1956), and in the more recent American patient literature “**chronic fatigue and immune dysfunction syndrome**” (CFIDS) have been used to describe the disorder. Both names inappropriately suggest that the cause is already understood (inflammation of the brain and muscles, or immune deficiency). Most research groups prefer the term “CFS” as it leaves open the question of aetiology (Holmes et al. 1988; Fukuda et al. 1994).

Neurasthenia (literally meaning “nervous exhaustion”) is a diagnosis included in the International Classification of Diseases (10th Edition) to describe a syndrome of mental and physical fatigue of at least three months’ duration (ICD-10). The term has a long tradition in psychiatric classification (Wessely, 1990; Hickie et al. 1997), although its specific relationships with CFS, and common psychological disorders (anxiety and depression), are not resolved. Neurasthenia has a prevalence of 5.4% (range, 2%–10%) in primary care settings worldwide (Goldberg and Lecrubier, 1995).

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% (Lloyd et al. 1990; Price et al. 1992; Gunn et al. 1993). 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. To date, three studies have provided a more realistic estimate of 0.2% to 0.7% (that is, 200–700 cases per 100,000 persons: Jason et al. 1995; Buchwald et al. 1995; Lawrie et al. 1997). Further studies are now required.

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). While physicians working in tertiary referral centres may encounter patients with CFS quite commonly, primary care doctors will not (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% (Wessely 1995; Hickie et al. 1996*b*; Lawrie et al. 1997), whereas the incidence of CFS is about 0.4% (Lawrie et al. 1997).

Who is at risk of CFS?

CFS predominantly affects young adults, with a peak age of onset between 20 and 40 years (Lloyd et al. 1990; Jason et al. 1995; Lawrie et al. 1997). In study samples from treatment centres CFS appears to be more common in women (typically in a ratio of 2–3:1 — Lloyd et al. 1989; Komaroff 1994), but

this may be because women attend all levels of medical care more frequently than men (Henderson 1974). CFS does not preferentially affect individuals from upper socioeconomic groups (contrary to the notion of “yuppie flu” — Lloyd et al. 1990), rather, some studies suggest that fatigue syndromes may be more common in people from more socially disadvantaged groups (Hickie et al. 1996*a*; Lawrie et al. 1997).

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 (Wessely et al. 1995) 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 (White et al. 1995). In the Australian context it appears that infections such as Q fever and Ross River virus infection may also trigger CFS (Marmion et al. 1996; Eltumi et al. 1996; Selden and Cameron, 1996; reviewed in Hickie et al. 1996*c*).

What is the cost of CFS to the community?

The financial impact of CFS on people with CFS and the community has been evaluated (Lloyd and Pender 1992). 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 (those related to lost productivity associated with the disorder) the aggregate annual cost of CFS was \$9436 per case (1988/89 dollars). Converting these costs to 1997 dollars gives a direct cost of \$2509 per case and an annual aggregate cost of \$12 228 to the community. Based upon 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 \$416 million dollars.

2: How should people with fatigue be evaluated?

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 (Wessely and Powell 1989; Merikangas and Angst 1994).

To differentiate the various causes of mental and physical fatigue, the doctor 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 as it is not relieved by sleep, and from neuromuscular weakness as people with CFS can generate muscle strength and endurance when circumstances demand a response (Lloyd et al. 1988, 1991). Fatigue should be differentiated from a lack of motivation and loss of pleasure from usual daily activities, which suggest a depressive illness.

How should a doctor evaluate fatigue?

The evaluation of prolonged fatigue is outlined in Box 2.2.

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

- unrefreshing sleep
- myalgia
- arthralgia
- concentration loss
- memory impairment
- irritable mood

— all of which may be exacerbated by minor physical activity.

Diagnosis

Clinical diagnosis

- ◆ A diagnosis of CFS is made on clinical grounds (Level IV)
- ◆ Diagnosis relies upon 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 (e.g., 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 confident 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 part 6, page 26

Although these symptoms are common in people with CFS, they are not specific. They may also occur in a range of other medical and neuropsychiatric disorders (e.g., sleep apnoea, hypothyroidism, major depression, somatoform disorders — Katon and Russo 1992; Hickie et al. 1995; Komaroff et al. 1996).

When taking a medical history, the questions should focus on key symptoms that might suggest alternative explanations for the fatigue state (see Boxes 2.1 and 2.3). Fatigue accom-

panied 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 (e.g., multiple sclerosis). Many commonly prescribed medications (e.g., antihistamines, sedatives), and other substances (e.g., alcohol, marijuana, amphetamines) cause fatigue directly, or indirectly via a disturbance of the sleep-wake cycle.

Similarly, the physical examination should be directed towards elucidating alternative diagnoses. The physical examination of people with CFS is normal (Fukuda et al. 1994), so evidence of objective muscle weakness, neurological signs, evidence of cardio-respiratory disease or fever all indicate diagnoses other than CFS (see Box 2.3). Although people with CFS often complain of tender cervical lymph nodes, demonstrable lymphadenopathy is rarely present (Fukuda et al. 1994).

When adults present for medical assessment with fatigue states the most common alternative diagnosis to consider is major depression (Taerk et al. 1987; Manu et al. 1988a; Kruesi et al. 1989; Wessely and Powell 1989; Gold et al. 1990; Hickie et al. 1990; Katon et al. 1991; Wood et al. 1991; Buchwald et al. 1995, 1997; Wessely et al. 1995; Lawrie et al. 1997). Other commonly detected disorders (Box 2.3) are sleep apnoea, hypothyroidism, anaemia, chronic hepatitis, panic disorder, generalised anxiety, and somatoform disorders (Lane et al. 1991; Buchwald et al. 1995; Hickie et al. 1995; Fischler et al. 1997; Lawrie et al. 1997).

When patients are being treated for an alternative medical disorder (e.g., hypothyroidism and receiving thyroxine replacement) or a psychiatric condition (e.g., manic-depressive illness and receiving lithium carbonate), a separate diagnosis of CFS is not justified.

What psychological evaluation is required?

A formal diagnosis of CFS cannot be made without appropriate psychological evaluation of the patient (Fukuda et al. 1994). This need not be done by a spe-

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, *JAMA* 1991; 8: 265

“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

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

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

Person describes:	Interpretation
<ul style="list-style-type: none"> Reduced muscle power at rest Difficulty walking or lifting weights 	➤ Muscle weakness (e.g., myopathy; polymyositis)
<ul style="list-style-type: none"> Loss of muscle power over time with activity 	➤ Neuromuscular fatigability (e.g., myasthenia gravis)
<ul style="list-style-type: none"> Physical and mental fatigue at rest 	➤ Central fatigue (e.g., multiple sclerosis)
<ul style="list-style-type: none"> Lack of motivation to commence tasks Lack of pleasure from tasks undertaken 	➤ Anhedonia (e.g., major depression)
<ul style="list-style-type: none"> Daytime sleepiness Short sleep latency 	➤ Somnolence (e.g., sleep apnoea, narcolepsy)
<ul style="list-style-type: none"> Breathlessness at rest or on exercise 	➤ Dyspnoea ➤ Weakness (e.g., airflow limitation; cardiac failure; anaemia)
<ul style="list-style-type: none"> Muscle pain, joint pain Fever, malaise 	➤ Inflammation (e.g., systemic lupus erythematosus) ➤ Infection (e.g., influenza)

cialist psychiatrist or psychologist, although that may be useful 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 (Ellen et al. 1997). These include self-report questionnaires such as the GHQ-30 (Goldberg and Williams 1988) and SPHERE (Hickie et al. 1996*d*), or structured interview schedules such as PRIME-MD (Spitzer et al. 1994).

History

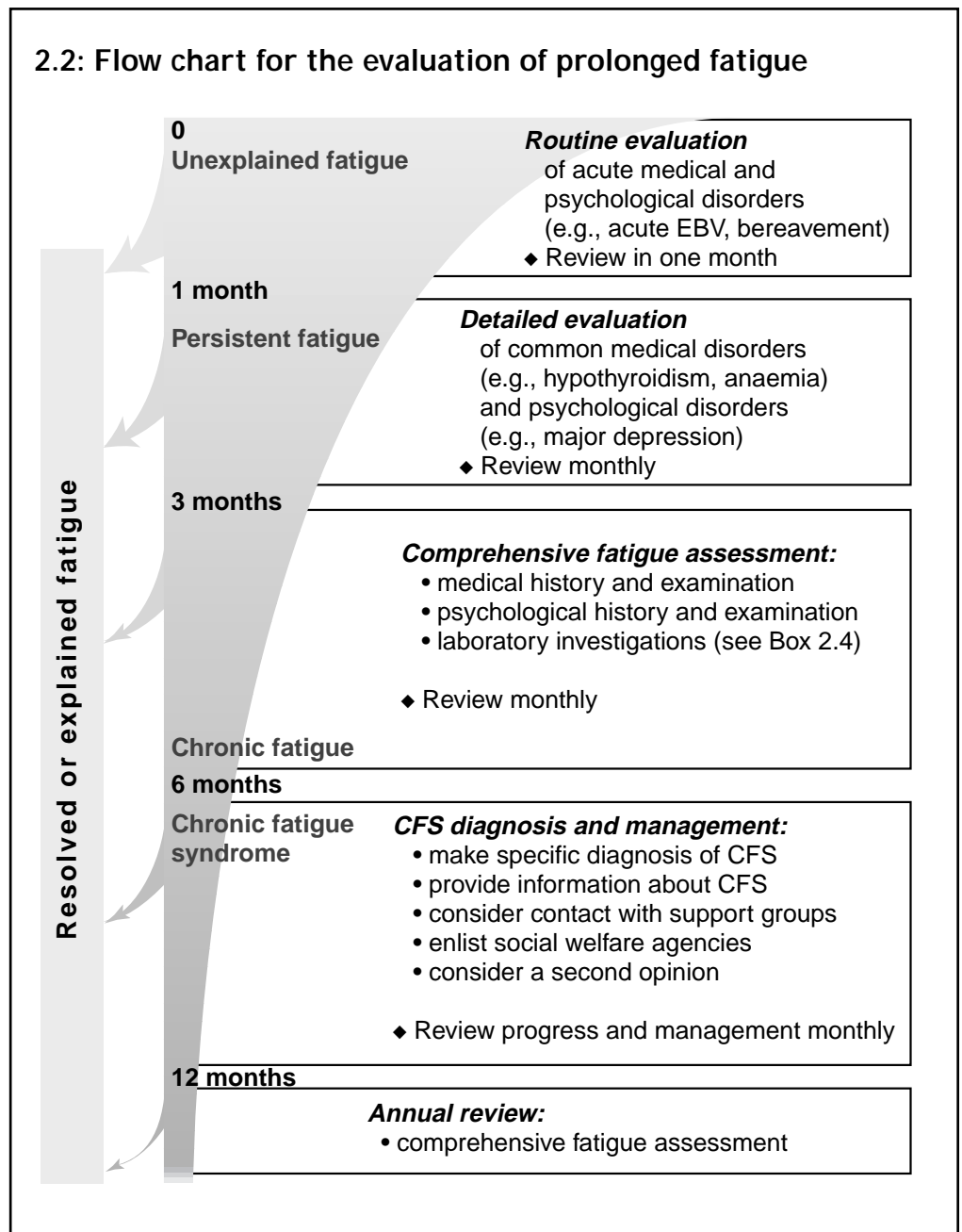
Important historical features include:

- prior episodes of anxiety or depression
- a past history of multiple, unexplained physical symptoms
- prior alcohol or other substance abuse.

Most people with depressive disorders present to primary care complaining 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 abuse. 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 typical depression, who report severe anorexia, weight loss, self-reproach and guilt, suicidal plans, persistent

2.2: Flow chart for the evaluation of prolonged fatigue



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

“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

■ 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 ■

loss of motivation or a pervasive loss of pleasure (DSM-IV; ICD-10; Hickie et al. 1990; Johnson et al. 1996).

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 (DSM-IV; ICD-10).

Mental state

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, Parker et al. 1990, 1994), 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 health care agency, although they typically complain of non-specific symptoms such as poor sleep, poor appetite and tiredness rather than depressed mood (Power et al. 1997; Appleby et al. 1996; Rutz et al. 1989). Other risk factors for suicide include being male, social isolation, concurrent drug and alcohol use and access to lethal means (Moscicki 1997; Maris 1997).

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. Common issues to be addressed include:

- the consequences of the illness for the person's ability to participate in work or school
- the effects of the illness on key relationships with spouse, partner, or parents
- 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 (e.g., rheumatoid arthritis) and psychological conditions (e.g., major depression) (Vercoulen et al. 1996; Buchwald et al. 1996; Komaroff et al. 1996). Accordingly, the 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.

2.3: Alternative causes of chronic fatigue*

Physiological

- Sedentary lifestyle
- Sleep deprivation

Drugs

- Medication (e.g., 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

Psychological

- Depression
- Anxiety disorder
- Somatisation disorder
- School phobia

Occult malignancy

Occupational and environmental factors

- e.g., organic solvents, heavy metals

*Not an exhaustive list.

The 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 as a result of the accumulated time lost due to 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 doctor should specifically evaluate the effect of the illness upon the patient's key interpersonal relationships. This is preliminary to education and advocacy on behalf of the patient with these individuals and institutions.

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 Box 5.1–5.4), no specific diagnostic test for the disorder has emerged (Fukuda et al. 1994). For any laboratory test to be accepted as having diagnostic validity, it would need to demonstrate both high sensitivity (i.e., almost all people with CFS return a positive result) and high specificity (i.e., almost all healthy persons, and people with fatigue who do not have CFS, return a negative result). In fact, as the diagnosis of CFS currently identifies a heterogeneous group of people (Hickie et al. 1995), it is unlikely that any one diagnostic test will emerge.

The only laboratory tests recommended for the standard evaluation of people with fatigue states (Box 2.4) are intended for the detection of alternative medical conditions.

The diagnostic yield of investigations beyond this restricted list is very low (Valdini et al. 1989; Lane et al. 1990; Buchwald and Komaroff 1991). If specific alternative diagnoses are suggested by the clinical history or examination (e.g., 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 scientific standards of evaluation. Consequently, these “tests” (e.g., dark field blood testing for red cell morphology or “candida” identification; environmental sensitivity testing) are not recommended.

Does chronic fatigue overlap with other illnesses?

Fatigue is a central feature of many clinical syndromes (see Box 2.5), including CFS, fibromyalgia, irritable bowel syndrome, major depression, anxiety and somatoform disorders (Goldenberg 1989, 1996; Wessely and Powell 1989; Goldenberg et al. 1990; Kirmayer and Robbins 1991; Moldofsky 1993; Hickie et al. 1995; Gomborone et al. 1996; Buchwald et al. 1996; Fischler et al. 1997). These syndromes also share other non-specific symptoms, including musculoskeletal pain, sleep disturbance, neurocognitive impairment and irritable mood (Box 2.5).

Fibromyalgia, in particular, is a closely related syndrome, differing mainly in its relative emphasis on musculoskeletal pain rather than fatigue (Goldenberg 1996; Wolfe et al. 1990). However, treatment approaches may vary (see Part 4).

The number of non-specific medical symptoms reported by a person with CFS is strongly correlated with the presence of psychological symptoms (Katon and Russo 1992; Hickie et al. 1995). Up to two-thirds of adults with CFS have either a prior, or concurrent, diagnosis of major depression (Katon and Walker 1993; Taerk et al. 1987; Manu et al. 1988a; Kruesi et

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

Recommended

- Full blood count and film
- Erythrocyte sedimentation rate
- Urea, electrolytes and creatinine
- Serum calcium and phosphate
- Liver function tests
- Thyroid stimulating hormone
- 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)
- 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.

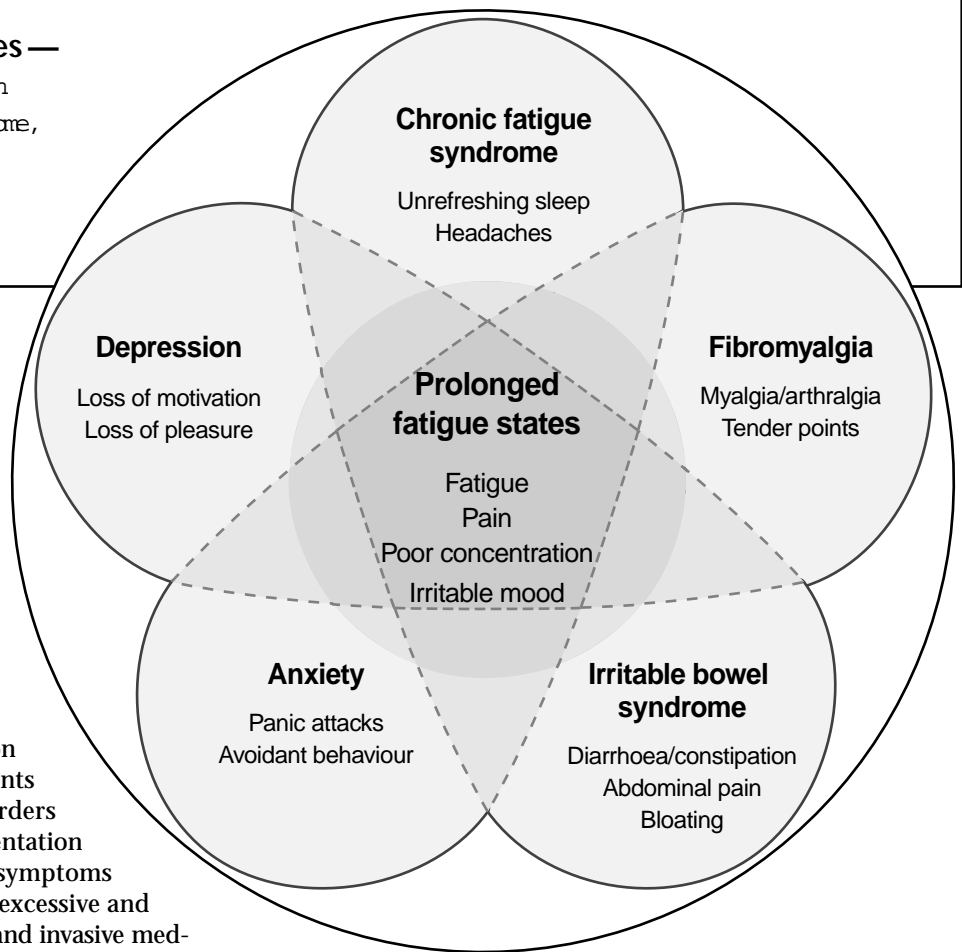
al. 1989; Wessely and Powell 1989; Gold et al. 1990; Hickie et al. 1990; Katon et al. 1991; Wood et al. 1991; Buchwald et al. 1995; Wessely et al. 1995; Lawrie et al. 1997), as do people with fibromyalgia (Hudson and Pope 1996) and irritable bowel syndrome (Langeluddecke 1985; Walker et al. 1995). By comparison, the lifetime rate of comparable depressive disorders in the general community is 15%–25% (Reiger et al. 1988; Wells 1989; Kessler et al. 1994; Blazer et al. 1994; Mason and Wilkinson 1996).

The high rate of comorbidity is not surprising as diagnostic criteria for both CFS and major depression (DSM-IV; ICD-10) include fatigue, sleep disturbance, cognitive impairment and mood alteration.

2.5: Overlapping diagnoses —

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

Perhaps the most difficult diagnostic uncertainty between CFS and psychological illness is in relation to somatoform disorders. In these disorders, people present with medically inexplicable physical symptoms that are assumed to be due to underlying psychological processes. As the causes of CFS are “unexplained”, there is obvious overlap between the diagnostic criteria for the somatoform disorders and CFS (Lane et al. 1991; Katon and Russo 1992; Abbey 1993; Hickie et al. 1995; Johnson et al. 1996; Fischler et al. 1997). Patients with the most severe somatoform disorders typically have a lifelong pattern of presentation to medical practice with unexplained symptoms and chronic disability, and a pattern of excessive and poorly justified laboratory investigation and invasive medical treatments (DSM-IV; ICD-10).



When should a doctor seek another opinion?

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.

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.

■ 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 ■

What are the expectations in medicolegal assessments of people with CFS?

Any practitioner who is going to act as an expert witness should be qualified as a specialist and have extensive experience with people with CFS. In verifying a diagnosis of CFS, the current international diagnostic criteria (Box 1 on page 1) should be applied, including documentation of the charac-

teristic symptoms, the lack of abnormalities on physical examination and the results of the recommended laboratory investigations. A psychiatric evaluation may be indicated to document any psychological co-morbidity. It is sensible to obtain an independent history of the illness from the spouse, partner or parent, including an evaluation of the level of associated disability. The courts can reasonably expect the doctor to understand and acknowledge the uncertainties and the controversies surrounding CFS.

Expert witnesses are frequently asked to comment on the likelihood that CFS arose as a consequence of a risk factor in the occupational setting (e.g., infection, chemical exposure, or the emotional demands of the workplace). Given that the pathophysiological basis of CFS is unknown (see Part 5), definitive statements about occupational risk factors are unwise. The legal system also frequently requests an assessment of the current level of disability. As CFS is a subjective illness, the evaluation of disability includes two components: first, a systematic review of the patient's report of his/her functional capacity (with corroborating reports of the spouse, partner or parent), and, second, an assessment of whether the patient is an accurate and reliable historian.

■ 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 ■

Another key expectation of the medicolegal evaluation is the prognosis for recovery. Statements about prognosis should be expressed in terms of probabilities, based on the existing data regarding natural history (see Part 3). These judgements are best made after adequate symptomatic and behavioural treatment (see Part 4). The likelihood of spontaneous resolution of CFS of short duration (i.e., 6–12 months) is about 50% over the following year, but when the illness has been present for several years the remission rate is lower (Box 3.2).

The notion of “permanent” disability is problematic, as the great majority of people with CFS improve gradually or eventually recover. However, a reasonable approach is to suggest that, when the likelihood of substantial improvement is less than 10%–20% over the following decade (as is the case in people with more than five years of disability) and the person is incapable of gainful employment, this should be regarded as “permanent disability” for medicolegal purposes.

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 benefits of a diagnosis of CFS?

A formal diagnosis of CFS may have positive implications for both the patient and the doctor. It permits the doctor to say with some confidence what is wrong with the patient, what treatments are appropriate and what is likely to happen in the future. Giving people this information may go a long way towards relieving their anxiety about the nature of their illness. It validates their experience of ill-health and makes it clear to others that the patient has legitimately entered medical care (Woodward 1993). This can improve patients' relations with their families and encourage everybody to participate actively in the treatment process. This helps to minimise long-term morbidity (Cope et al. 1994).

A formal diagnosis is essential for the transfer of information between those involved directly or indirectly in patient care. Once patients have engaged with their doctors in this process, a series of personal, social and legal obligations result (Mechanic 1986, 1993). All persons, including relevant third parties, are then expected to behave in ways that provide support during the illness and facilitate recovery (Mechanic 1986).

Making the diagnosis should mark the end of investigations to exclude alternative diagnoses.

What drawbacks can occur as a consequence of a diagnosis of CFS?

Unless medical diagnoses such as CFS are based on sound empirical data, they may create or perpetuate myths about aetiology, natural history and treatment rationales which can themselves increase disability (Wessely 1990; Abbey 1993; Shorter 1993; Finestone 1997). Inappropriately linking simple biomedical notions of disease (e.g., infection or poisoning) with complex forms of ill-health (notably chronic fatigue) may create artificial concepts such as a “chronic viral infection” and “chronic immune deficiency”. Such concepts may then actively promote chronic ill-health, life-time disability or third party responsibility, as may have occurred previously with upper limb repetitive strain injuries in Australia (Lucire 1986; Littlejohn 1986). Such overly simplistic notions tend to minimise the important roles of social and psychological factors in determining the course of chronic ill-health (Kleinman 1986; Mechanic 1993; Ware 1993).

3: What is the natural history of prolonged fatigue and chronic fatigue syndrome?

What is the outcome of fatigue states?

Spontaneous recovery in cases of prolonged fatigue is high (Box 3.1; Joyce et al. 1997). Similarly, prolonged fatigue after infectious mononucleosis has a high rate of spontaneous resolution (White et al. 1995a). In the cohort studied by White et al., 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.

The long term outcome of CFS has been evaluated mostly in people treated within tertiary referral settings (Box 3.2). Such patient samples are biased towards chronic illness and limited patterns of recovery (Katon and Walker 1993; Wessely et al. 1995; Joyce et al. 1997). Patient reports drawn from self-help group populations show similar biases (Sharpe et al. 1992). In an Australian study conducted within a specialist setting (Wilson et al. 1994b), 65 out of 103 patients (63%) who had been symptomatic for about five years reported improvement in symptoms and 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 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.

Up to 20% of cases of CFS may occur in children aged 10–19 years (Lloyd et al. 1990). Children with prolonged fatigue or CFS do significantly better than adults, with 77%–94% reporting improvement or recovery in the two published studies specifically evaluating children (Feder et al. 1994; Carter et al. 1995).

One death by suicide and two unrelated deaths occurred in 2075 people followed up in 19 published studies of the outcome of prolonged fatigue and CFS (Joyce et al. 1997). These studies included mean follow-up periods ranging from six months to four years, thus suggesting that suicide rates and overall mortality are not increased in people with CFS.

What factors may delay recovery?

The factors associated with a poorer outcome include older age, concurrent psychiatric disorder, and the person's belief that the illness is purely physical in origin (see Box 3.2; reviewed in Joyce et al. 1997). Outcome has not been found to be associated with gender, marital status or life stress events (Sharpe et al. 1992; Bruce-Jones et al. 1994), or with laboratory parameters, such as viral antibody titres and immunological measures (including T cell subset measurements) (Wilson et al. 1994a). In a study of the relationship of non-specific viral illness and the development of prolonged fatigue in general practice, the person's view of the illness and the doctor's behaviour, rather than the viral infection, were predictive of the development of prolonged fatigue (Cope et al. 1994).

Natural history

- ◆ Most fatigue syndromes are of short duration and the person spontaneously recovers (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)
- ◆ Older age, psychological disorder, and belief in a purely physical cause of CFS are associated with poorer outcomes (Level II)
- ◆ A supportive doctor–patient relationship is an important component of management of people with CFS (Level III-3)

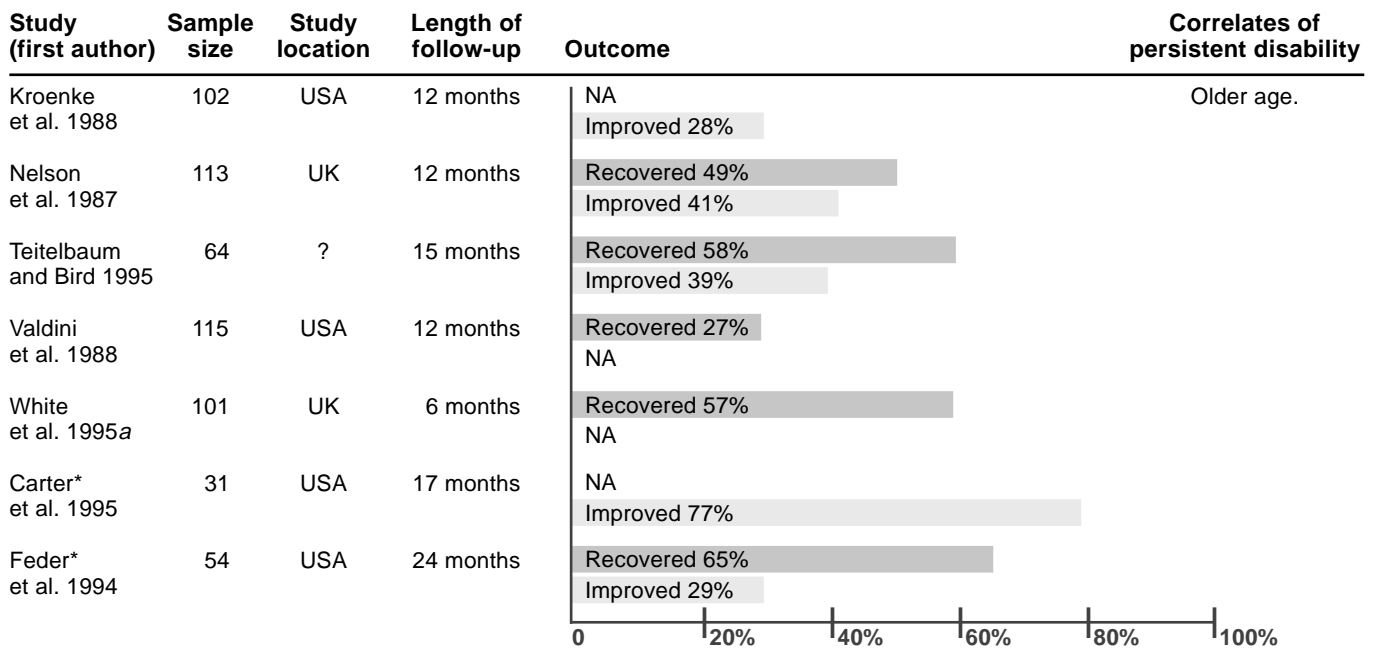
For an explanation of the rating of levels of evidence, see part 6, page 26

Does the doctor–patient relationship affect the outcome of CFS?

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 accurate diagnosis (Goldberg et al. 1993) and minimise the adverse effects of the illness experience (Frank 1983; Mechanic 1993).

Conversely, doctors who reject the patient's illness experience are likely to promote feelings of alienation and perpetuate ill health (Twemlow et al. 1997). Simplistic notions offered by doctors, with unjustified medical labels such as "chronic viral infection" or pseudomedical diagnoses such as "hypoglycaemia", are inappropriate and unhelpful (Ernst 1996). If these labels lead to inappropriate pharmacological interventions, not only are they likely to be unsuccessful, but they will often result in increased hostility towards the medical profession and conventional medical treatments.

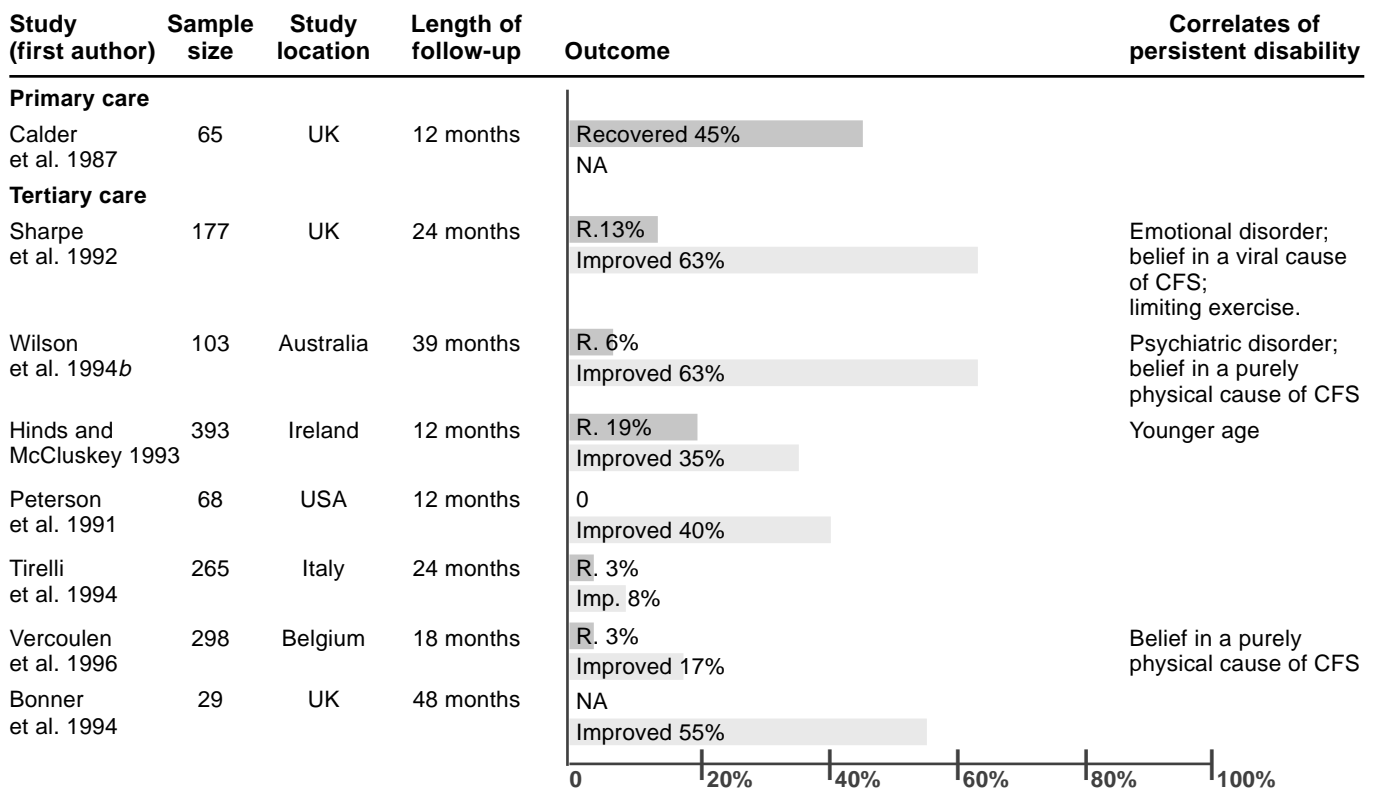
3.1: Natural history of prolonged fatigue in primary care



* Paediatric patient group

NA = Not available.

3.2: Natural history of chronic fatigue syndrome



NA = Not available.

4: How should people with CFS be managed?

What are the principles of managing people with CFS?

Once the diagnosis of CFS is made, the doctor should aim to establish a management plan with the patient. The plan should outline the available pharmacological and non-pharmacological approaches, the role of continuing medical care and the place for physical, social and workplace rehabilitation programs. While no single treatment is “curative”, a combination of treatments can significantly reduce disability.

Appropriate symptomatic treatments (e.g., analgesia for pain, antidepressants for depressed mood, sedatives for sleep disturbance) need to be considered on an individual basis and reviewed regularly. As with other chronic medical and psychological disorders, the relationship between doctor and patient may influence the long-term course of the disorder (Cope et al. 1994). In part, the significant non-specific (placebo) response rate in controlled treatment trials for people with CFS is likely to reflect this important component of good clinical practice (Frank, 1983; Elkin et al. 1989).

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.

What are the expectations of a treatment trial for CFS?

Given the likelihood of spontaneous improvement and the variable clinical course of CFS, controlled treatment trials are essential for all proposed (immunological, psychological, antiviral and metabolic) treatments (Wilson et al. 1994a). Patient cohorts in CFS treatment trials are likely to be heterogeneous because of the relatively subjective and non-specific criteria used to make the diagnosis (Hickie et al. 1995a). Consequently, any claim that a particular treatment can cure most people with CFS is likely to be spurious, or the treatment will be acting via a non-specific mechanism (Hickie et al. 1995b). At least 30%–50% of people with CFS typically demonstrate improvement in the non-specific (or “placebo”) treatment arm of controlled trials (Wilson et al. 1994a; Hickie et al. 1995b).

In general, evaluating proposed treatments for people with CFS requires:

- a reasonable scientific rationale for the agent to be tested, and preliminary findings showing safety and potential efficacy (phase I data)
- randomised, double-blinded and placebo-controlled trials (Standards of Reporting Trials Group, 1994; Begg et al. 1996).

Management

- ◆ No single pharmacological treatment has been shown to be effective for people with CFS (Level I)
- ◆ Cognitive–behaviour therapy is effective for people with CFS (Level I)
- ◆ Graded aerobic exercise is safe and effective for 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 part 6, page 26

■ 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 ■

The validity of the results of trials is highly dependent upon the quality of study design and analysis. Critical requirements are the use of an accepted case definition, an adequate sample size and the use of well-characterised outcome measures (Freiman et al. 1978; Sacks et al. 1982; Moher et al. 1994). For CFS treatment trials, this specifically implies the use of:

- internationally accepted diagnostic criteria (Schluederberg et al. 1992; Fukuda et al. 1994)
- recognised self-report measures of fatigue, mood and other key symptoms (Schluederberg et al. 1992)
- independent assessments of functional status at onset, completion of treatment, and three to six months later (to ensure durability of the treatment effect).

Finally, positive results require replication in at least one comparable study, conducted by an independent research group (Sackett 1994).

4.1: Controlled trials of treatments for chronic fatigue syndrome

Intervention	First author; sample size	Quality of study design and analysis*	Beneficial effect reported?
Immunological/virological treatments			
Intravenous immunoglobulin G	(Peterson et al. 1990, <i>n</i> = 30)	1,3,4,6	No
	(Vollmer-Conna et al. 1997, <i>n</i> =96; dose-ranging study)	1,2,3,4,5,6,7	No
	(Lloyd et al. 1990, <i>n</i> =49)	1,2,4,5,6,7	Yes
	(Rowe et al. 1997, <i>n</i> =71; children)	1,2,3,4,5,6,7	Yes
	(Strayer et al. 1994, <i>n</i> =92)	1,2,3	Yes
Poly(I).poly(C ₁₂ U) (<i>Ampligen</i>)	(Straus et al. 1988a, <i>n</i> =27)	1,2,3,6	No
Acyclovir	(Lloyd et al. 1990, <i>n</i> =90)	1,2,3,4,5,6	No
Transfer factor	(See and Tilles 1996, <i>n</i> =30; crossover design)	1,2,4,5,6	No
Interferon alfa			
Behavioural treatments			
Cognitive behaviour therapy	(Sharpe et al. 1996, <i>n</i> =60)	1,2,3,4,5,6,7	Yes
	(Deale et al. 1997, <i>n</i> =60)	1,2,3,4,5,6,7	Yes
	(Lloyd et al. 1990, <i>n</i> =90)	1,2,3,4,5,6	No
	(Friedberg and Krupp 1994, <i>n</i> =42)	3,5	No
Graded exercise	(Fulcher and White 1997, <i>n</i> =66)	1,2,3,4,5,6,7	Yes
CNS active agents			
Galanthamine hydrobromide (acetylcholinesterase inhibitor)	(Snorrason et al. 1996, <i>n</i> =49)	1,5	Yes
	L-Carnitine (Plioplys and Plioplys 1997, <i>n</i> =30, crossover)	3,5	Yes
Amantidine	(Plioplys and Plioplys 1997, <i>n</i> =30, crossover)	5	No
Moclobemide	(Wilson et al. 1994, <i>n</i> =90)	1,2,4,5,6,7	Yes
Fluoxetine	(Vercoulen et al. 1996, <i>n</i> =96)	1,2,3,5	No
Phenelzine	(Natelson et al. 1996, <i>n</i> =18)	1	Yes
Metabolic/other treatments			
Essential fatty acids	(Behan et al. 1990, <i>n</i> =63)	1,2,3,6	Yes
Magnesium sulfate	(Cox et al. 1991, <i>n</i> =32)	1,6	Yes
Liver extract—folic acid—vitamin B ₁₂	(Kaslow et al. 1989, <i>n</i> =15; crossover design)	1,2,3,5,6	No
Terfenadine	(Steinberg et al. 1996, <i>n</i> =30)	1,3,5	No
Hydrocortisone	(Straus, <i>n</i> =70)	1,2,3,4,5,6,7	No

*Comments code

Indicates the level of confidence in the findings of the study based upon study design, the representative nature and size of the patient sample, outcome measures used, and statistical analysis:

- 1 Randomised, double-blind, placebo-controlled study.
- 2 Sample size adequate to eliminate type II statistical error.
- 3 Response patterns demonstrated consistently in all outcome measures.
- 4 Outcome measured at a follow-up point three months or more after end of treatment.
- 5 Subject group enrolled likely to be representative of the general CFS patient population.
- 6 Response rate to placebo therapy consistent with standard clinical care (i.e., 15%–40%).
- 7 Analysis performed on an intention-to-treat basis.

What drug treatments for CFS have been evaluated?

A range of antiviral, immunoregulatory and metabolic drug regimens for people with CFS have been evaluated in double-blind placebo-controlled trials (see Boxes 4.1–4.3). Although limited positive responses have been reported, no agent has consistently demonstrated efficacy in well-designed studies.

Intravenous immunoglobulin: Four double-blind, placebo-controlled trials of therapy with intravenous immunoglobulin (based upon a rationale of disturbed immunity in people with CFS) have been published (Lloyd et al. 1990; Peterson et al. 1990; Rowe 1997; Vollmer-Conna et al. 1997). Two of these trials conducted by one research group in Australia produced conflicting results, with the larger dose-ranging study demonstrating no significant benefit (Lloyd et al. 1990; Vollmer-Conna et al. 1997).

Antidepressants: Because of the high rate of depression in people with CFS, antidepressant therapies have received considerable attention, but empirical evidence from trials is limited. Moclobemide (a reversible monoamine oxidase inhibitor) has been evaluated in a large double-blind, placebo-controlled trial (Hickie et al. 1998). Limited evidence of benefit was observed, with an improvement in the subjective sense of energy, which was not associated with any alteration in mood.

Treatment with fluoxetine (a selective serotonin reuptake inhibitor [SSRI]) showed no more benefit than placebo (Vercoulen et al. 1996).

Studies of combination therapy with a low dose tricyclic antidepressant and a non-steroidal anti-inflammatory agent in people with fibromyalgia found beneficial effects on muscle pain and sleep disturbance, but not fatigue or mood (Goldenberg et al. 1986; Jaeschke et al. 1991). A range of other agents which act primarily on CNS function have been examined in preliminary trials only (phenelzine, amantidine, galanthamine, L-carnitine — see Box 4.1).

4.2: Evaluation of treatment trials reporting benefit for people with chronic fatigue syndrome

Treatment	Level of evidence	Recommendation for treatment use*	Comments
Cognitive behaviour therapy	II	Recommended	<ul style="list-style-type: none"> Beneficial effect in three of five studies “Placebo” treatment often includes active behavioural therapy Replicated studies show benefit of graded exercise component
Poly(I).poly(C ₁₂ U) (Ampligen)	III-3	Not recommended. Further studies indicated	<ul style="list-style-type: none"> Unrepresentative patient group Limited treatment benefit No replication study
Moclobemide	III-3	Not recommended. Further studies indicated	<ul style="list-style-type: none"> Limited treatment benefit Response inconsistent across outcome measures No replication study
Intravenous immunoglobulin G	III-4	Not recommended. Further studies indicated	<ul style="list-style-type: none"> Two of four studies reported benefit Beneficial effect transient Possible benefit in children
Essential fatty acids	III-3	Not recommended	<ul style="list-style-type: none"> No sustained benefit shown No replication study
Magnesium sulphate	III-3	Not recommended	<ul style="list-style-type: none"> Small sample size No sustained benefit shown No replication study
Phenelzine	III-3	Not recommended	<ul style="list-style-type: none"> Small sample size Limited treatment benefit No sustained benefit shown No replication study
L-carnitine	III-3	Not recommended	<ul style="list-style-type: none"> Small sample size No sustained benefit shown No replication study
Galanthamine	III-3	Not recommended	<ul style="list-style-type: none"> Inadequate placebo control Limited treatment benefit No sustained benefit shown No replication study

*Level I or II evidence is regarded as adequate to guide routine clinical practice.

Is there a role for behavioural treatment approaches?

Cognitive-behavioural therapies for people with CFS link the principles of good clinical management with varying degrees of graded physical activity and psychological intervention (Wilson et al. 1994a; Sharpe et al. 1996).

The rationale for this approach is outlined in Box 4.4. It has two objectives:

- The behavioural component encourages planned resumption of physical and mental tasks. Tasks are stopped before they produce an exacerbation of symptoms, but the level of activity is gradually increased. The physical activity programs are individually designed to take account of the patient's current level of disability and avoid immediate worsening of symptoms.
- The cognitive treatment aims to overcome attitudes that may reduce the likelihood of recovery, such as fear of physical activity, social withdrawal, depressed mood, or a fixed belief that a viral illness has caused permanent injury so that recovery is impossible. These are identified in a systematic review of the person's attitudes to the cause of the illness, exacerbating factors and prognosis. The doctor works with the patient to improve the knowledge base and mental attitudes required for overcoming the illness.

The first (uncontrolled) study of cognitive behaviour therapy found a benefit in conjunction with antidepressant therapy (Butler et al. 1991). This benefit has been confirmed in some (Sharpe et al. 1996; Deale et al. 1997; Fulcher and White 1997), but not all (Lloyd et al. 1993; Friedberg and Krupp 1994) subsequent controlled studies. The discrepant results may relate to the intensity and duration of the cognitive-behavioural intervention and to variations in the standard clinical management provided to people in the control arm of each study (Hickie et al. 1995c).

The positive studies show a continuing benefit for cognitive behaviour therapy at long-term follow-up (Sharpe et al. 1996; Deale et al. 1997; Fulcher and White 1997). The exercise portion of the cognitive behaviour therapy approach has been shown to be more effective at improving aerobic capacity, symptomatic status and functional performance than relaxation and flexibility therapy (Fulcher and White 1997). Only one of the 66 people with CFS in this exercise study reported worsening of symptoms over the 12 months of the program.

On balance, the evidence strongly suggests that cognitive-behavioural treatment incorporating graded physical activity should be a cornerstone of management of people with CFS:

- Given that simplistic attributions of a purely physical basis for the illness are associated with poor outcome, people with CFS should be encouraged to adopt the widest possible view of the psychosocial, medical and rehabilitative strategies to promote recovery.
- Secondary medical and psychological morbidity caused by prolonged inactivity can be prevented by graded exercise programs with an individualised approach to the initial exercise level and a prolonged and realistic time frame for improvement.
- Concurrent depression or anxiety is associated with poor outcome and should be actively treated.

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 ■

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

Vitamin and mineral supplements

Vitamin C
Vitamin E
Vitamin B₆
Vitamin B₁₂
Coenzyme Q10
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

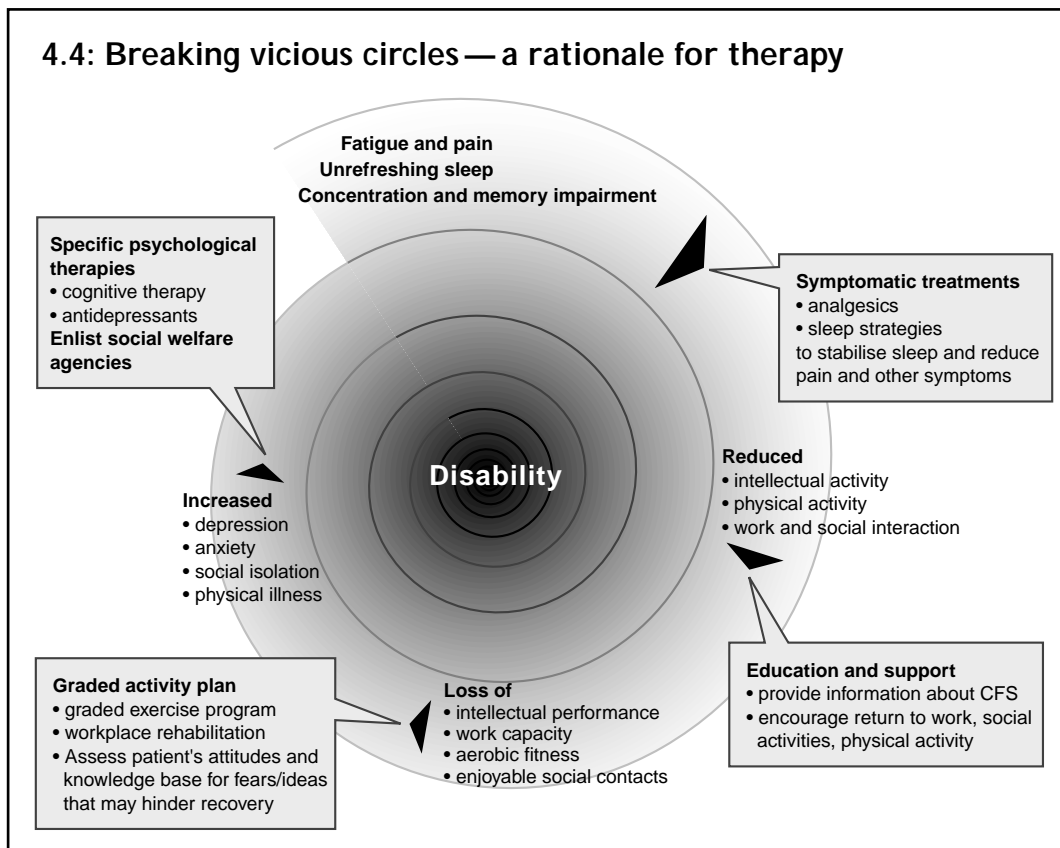
Perspectives

"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 ■

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 ■



■ 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 ■

What is the role of sleep management?

People with CFS experience a range of changes in sleep (Moldofsky, 1993; Whelton et al. 1992; Morriss et al. 1993; Krupp et al. 1993; Buchwald et al. 1994; Fischler et al. 1997). The most important features are reduced sleep efficiency, increased awakenings during sleep, increased total sleep time and disturbance of circadian rhythm. Behavioural approaches to managing these difficulties are likely to be more successful than pharmacological approaches, as the latter do not induce normal sleep. If people with CFS have a concurrent primary sleep pathology (e.g., sleep apnoea), this requires specific intervention.

In CFS, sleeping longer does not improve physical or mental functioning. Excessive periods of sleep only serve to further disrupt circadian rhythm. The purpose of sleep management is therefore to encourage regular sleep-wake times:

- restricting the sleep period to about eight night-time hours

■ 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 ■

- avoiding stimulants during the evening period
- reducing or abolishing daytime naps
- promoting daytime physical and mental activity.

Should a doctor put the person with CFS in contact with support groups?

Support groups have become an important adjunct to medical practice by providing services that traditionally have been poorly catered for within the health care system. They can:

- provide individual and group support to people with CFS and their families
- collect practical information with regard to the availability and quality of medical and government services
- disseminate scientific information to lay people
- lobby government agencies to improve funding for patient services
- promote service delivery and research by raising funds
- increase community awareness of the plight of sufferers.

Inevitably, members of CFS support groups tend to include those with the most prolonged illnesses (Sharpe et al. 1992). Therefore, the groups may inadvertently reinforce stereotypes of chronicity and disability. Depending on the nature of the groups, some may serve to increase alienation from medical and government agencies and encourage forms of treatment that lack scientific evaluation.

5: What are the associations of CFS that could explain the disorder?

What are the major research findings in people with CFS?

The pathophysiological basis of CFS is unclear. The leading hypotheses are summarised in Boxes 5.1 to 5.4 and include:

- a unique pattern of infection with a recognised or novel pathogen (Straus 1993)
- altered CNS function due to an abnormal immune response against a common antigen (Lloyd et al. 1993; Hickie and Lloyd 1995)
- a neuroendocrine disturbance (Demitrack 1994)
- a neuropsychiatric disorder with clinical and neurobiological aspects suggesting a link to depressive disorders (Wesely 1993)
- a psychologically determined response to infection or other stimuli occurring in “vulnerable” individuals (Imboden et al. 1961; Abbey 1993).

Many other hypotheses exist but have not been scientifically evaluated. The recognised heterogeneity within patient groups labelled as having CFS makes it highly likely that there are multiple contributing factors in the disorder.

What are the gaps in our knowledge and priorities for future research?

Although many studies have been reviewed in the development of these guidelines, it is apparent that evidence providing clues to the pathophysiology of CFS is very limited.

However, there is good evidence excluding several candidate mechanisms for the disorder, including retroviral infection, neuromuscular disturbance and structural brain damage. The case for other proposed mechanisms, including an immunological, virological, metabolic or neurohormonal disturbance, remains unresolved and warrants further investigation.

The key confounding variables in studies of CFS include the likely heterogeneity within patient groups being studied and the need for standardisation of laboratory methods used in the investigations. Future studies must seek to identify potentially homogeneous patient groups, including subjects collected prospectively from defined infectious or other putative causes of CFS. Control subjects should include both matched healthy individuals and those with other fatigue-related conditions. The laboratory techniques must be sufficiently reliable, standardised and adequately described for the studies to be replicated.

As effective treatments for people with CFS are likely to follow (not precede) delineation of the pathological processes underlying the disorder, considerable research

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 II)
- ◆ Retroviruses do not 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
- ◆ Premorbid and concurrent depression are common in people with CFS (Level I)
- ◆ Neuromuscular performance in people with CFS is normal, implicating the central nervous system as the likely site of pathophysiological disturbance (Level I)
- ◆ Neurocognitive performance in people with CFS is impaired (Level I)

For an explanation of the rating of levels of evidence, see part 6, page 26

efforts are required to define the pathophysiology. In the meantime, symptomatic drug therapy is likely to remain one of the cornerstones of management, along with the other approaches outlined in Part 4.

Because of the heterogeneity of people with CFS, symptomatic treatment must be individualised. It is therefore difficult to evaluate proposed new therapies of this kind in a systematic way. However, methodology for “*N*=1” randomised trials in individual patients has been described, and is well suited for determining optimal therapy in people with CFS (Guyatt et al. 1986).

5.1: 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 (e.g., herpesviruses, enteroviruses) are common, but are of no pathophysiological or diagnostic significance (Harwitz et al. 1985; Jones et al. 1985; Straus et al. 1985; Buchwald et al. 1987a, 1987b, 1992, 1996; Calder et al. 1987; Holmes et al. 1987; Bell et al. 1988; Hellinger et al. 1988; Miller et al. 1991; Kitani et al. 1996) (Level I)
- Common, non-specific infections (e.g., upper respiratory tract infections) are not likely to trigger CFS (Wessely et al. 1995) (Level II)

Epstein–Barr virus

- Infectious mononucleosis can trigger CFS (White et al. 1995a, 1995b) (Level II)
- Reactivation of EBV replication is not increased in prevalence (Gold et al. 1990; Sumaya 1991; Jones 1993) (Level II)

Enteroviruses

- Earlier reports of enteroviral RNA particles in the muscles have not been confirmed by more comprehensive studies (Archard et al. 1988; Gow et al. 1991, 1994; Bowles et al. 1993; Clements et al. 1995; Galbraith et al. 1995; McArdle et al. 1996; Lindh et al. 1996) (Level I)

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

Retroviruses

- Strong evidence against a role for retroviruses in CFS (Defreitas et al. 1991; Flugel et al. 1992; Gow et al. 1992; Folks et al. 1993; Khan et al. 1993; Heneine et al. 1994) (Level I)

Human herpesvirus 6

- Conflicting evidence for reactivation of HHV-6 replication (Buchwald et al. 1992; Hay and Jenkins 1994; Yalcin et al. 1994; DiLuca et al. 1995; Patriak et al. 1995; Kitani et al. 1996) (Level III-4)

Ross River virus

- Retrospective studies suggest CFS may follow RRV infection (Lloyd et al. 1990; Selden and Cameron 1996; Westley-Wise et al. 1996) (Level III-2)

Non-viral infections (Q fever, Lyme disease)

- Retrospective studies suggest CFS may follow adequately treated Q fever or Lyme disease (Bujak et al. 1993, 1996; Shaddick et al. 1994; Sigal 1994; Ayres et al. 1996; Eltumi et al. 1996; Marmion et al. 1996) (Level IV)
- The existence of Lyme disease in Australia has not been confirmed (Hudson et al. 1994) (Level III-3)

5.2: 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 (reviewed in Lloyd et al. 1993; Strober 1994) (Level III-4)

Lymphocytes

- Reduced lymphocyte proliferation and natural killer cell cytotoxicity are common but non-specific findings (Landay et al. 1983; Behan et al. 1985; Kibler et al. 1985; Caliguri et al. 1987; Lloyd et al. 1989, 1992; Gold et al. 1990; Klimas et al. 1990; Gupta and Vayuvegula 1991; Ho-Yen et al. 1991; Morrison et al. 1991; Straus et al. 1993; Barker et al. 1994; Ojo-Amaize et al. 1994; Tirelli et al. 1994; Peakman et al. 1997; Mawle et al. 1997) (Level I)
- Despite numerous studies there is no consensus on the pattern and prevalence of changes in peripheral blood lymphocyte subpopulations or activation status (Landay et al. 1983; Klimas et al. 1990; Gupta and Vayuvegula 1991; Straus et al. 1993; Barker et al. 1994; Tirelli et al. 1994; Swanink et al. 1996; Peakman et al. 1997; Mawle et al. 1997) (Level III-4)

Immunoglobulins

- Conflicting evidence for reduced serum immunoglobulin G (IgG) and IgG subclass levels (Bennett et al. 1996; Read et al. 1988; Linde et al. 1988; Lloyd et al. 1989; Wakefield et al. 1990; Peterson et al. 1990) (Level III-4)

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.

Atopy

- Conflicting evidence for an increased prevalence of atopy (Tobi et al. 1982; Straus et al. 1985; Tobi and Straus 1985; Olson et al. 1986a, 1996b; Straus 1988b; MacDonald et al. 1996) (Level III-4).

Delayed type hypersensitivity skin responses

- Conflicting evidence for impaired DTH skin responses (Lloyd et al. 1988b, 1989, 1990, 1992; Mawle et al. 1997) (Level III-4)

Cytokines

- Numerous studies using different methodologies have yielded conflicting evidence for increased serum levels of cytokines or cytokine production (Kibler et al. 1985; Lever et al. 1988; Lloyd et al. 1991; Morte et al. 1988, 1989; Cheney et al. 1989; Straus et al. 1989; Chao et al. 1990, 1991; Gold et al. 1990; Linde et al. 1992; Swanink et al. 1996; Buchwald et al. 1997; Cannon et al. 1997; Mawle et al. 1997) (Level III-4)

Autoimmunity

- A single study found an increased prevalence of novel antinuclear envelope autoantibodies (Konstantinov et al. 1996; von Mikecz et al. 1997) (Level III-3)
- Sicca symptoms are common and a subset of people with CFS meet clinical but not laboratory criteria for Sjögren's syndrome (Komaroff and Buchwald 1991; Kuratsune et al. 1992; Calabrese et al. 1994; Nishikai et al. 1996) (Level II)

5.3: 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 demonstrated (Demitrack et al. 1991; Bearn et al. 1995; Cleare et al. 1995) (Level III-2)
- Conflicting evidence for reduced levels of insulin-like growth factors (IGFs) (Buchwald et al. 1996; Allain et al. 1997) (Level III-4)

Sleep

- Disturbances of sleep maintenance (e.g., frequent awakenings) are prevalent (Whelton et al. 1992; Morriss et al. 1993; Krupp et al. 1993; Buchwald et al. 1994; Fischler et al. 1997) (Level III-2)
- Circadian rhythm may be disturbed (Williams et al. 1996) (Level III-3)
- Sleep disruption or circadian rhythm disturbance may perpetuate musculoskeletal symptoms (Moldofsky and Scarisbrick 1976; Moldofsky 1993; Leese et al. 1996) (Level III-3)

Sympathetic nervous system function

- Altered blood pressure responses to postural change, consistent with neurally-mediated hypotension, have been demonstrated (Bou-Holaigah et al. 1995; Freeman and Komaroff 1997) (Level III-2)
- Reduced sympathetic nervous system markers have been demonstrated (Demitrack et al. 1992; Clauw et al. 1995) (Level III-2)

Neurotransmitter function

- Conflicting evidence for an increased sensitivity of serotonin and dopamine receptors to antagonists (Bakheit et al. 1992; Cleare et al. 1995; Bearn et al. 1995; Sharpe et al. 1996) (Level III-4)

Comment: Several lines of evidence suggest that a pathophysiological disturbance within the central nervous system is likely 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 disease processes in these two syndromes.

Mood

- Changes in biological markers (e.g., HPA axis function, immunity, sleep architecture) in patients with major depression are different from those in patients with CFS (Lloyd et al. 1992; Cleare et al. 1995; Fischler et al. 1997) (Level III-2)

Brain structure

- Conflicting evidence for an increased prevalence of white matter abnormalities on magnetic resonance imaging (Simon et al. 1991; Buchwald et al. 1992; Costa et al. 1992, 1995; Ichise et al. 1992; Natelson et al. 1993; Schwartz et al. 1994a, 1994b; Cope et al. 1995; Goldstein et al. 1995; Osmanagaoglu et al. 1995; Patterson et al. 1995; Fischler et al. 1996) (Level III-4)
- Regional cerebral blood flow studies (e.g., SPECT) have found conflicting results (Simon et al. 1991; Buchwald et al. 1992; Costa et al. 1992, 1995; Ichise et al. 1992; Natelson et al. 1993; Schwartz et al. 1994a, 1994b; Cope et al. 1995; Goldstein et al. 1995; Osmanagaoglu et al. 1995; Patterson et al. 1995; Fischler et al. 1996) (Level III-4)

Cognitive performance

- Attention and concentration are impaired (Fischler et al. 1996; Johnson et al. 1996; Marcel et al. 1996; Marshall et al. 1996b, 1997; Michiels et al. 1996; Moss-Morris et al. 1996; Wearden and Appleby 1996; Kane et al. 1997; Landro et al. 1997; Vollmer-Conna et al. 1997) (Level I)
- Conflicting evidence for impaired visual and auditory memory (Fischler et al. 1996; Johnson et al. 1996; Marcel et al. 1996; Marshall et al. 1996b, 1997; Michiels et al. 1996; Moss-Morris et al. 1996; Wearden and Appleby 1996; Kane et al. 1997; Landro et al. 1997; Vollmer-Conna et al. 1997) (Level III-4)

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

Neuromuscular disorder

- Muscle strength, endurance and recovery are normal (Holmes et al. 1987; Stokes et al. 1988; Riley et al. 1990; Lloyd et al. 1991; Edwards et al. 1993; Gibson et al. 1993) (Level I)
- Conflicting evidence for a disturbance in mitochondrial function (McCully et al. 1996; Byrne 1985) (Level III-4)

Metabolic disturbance

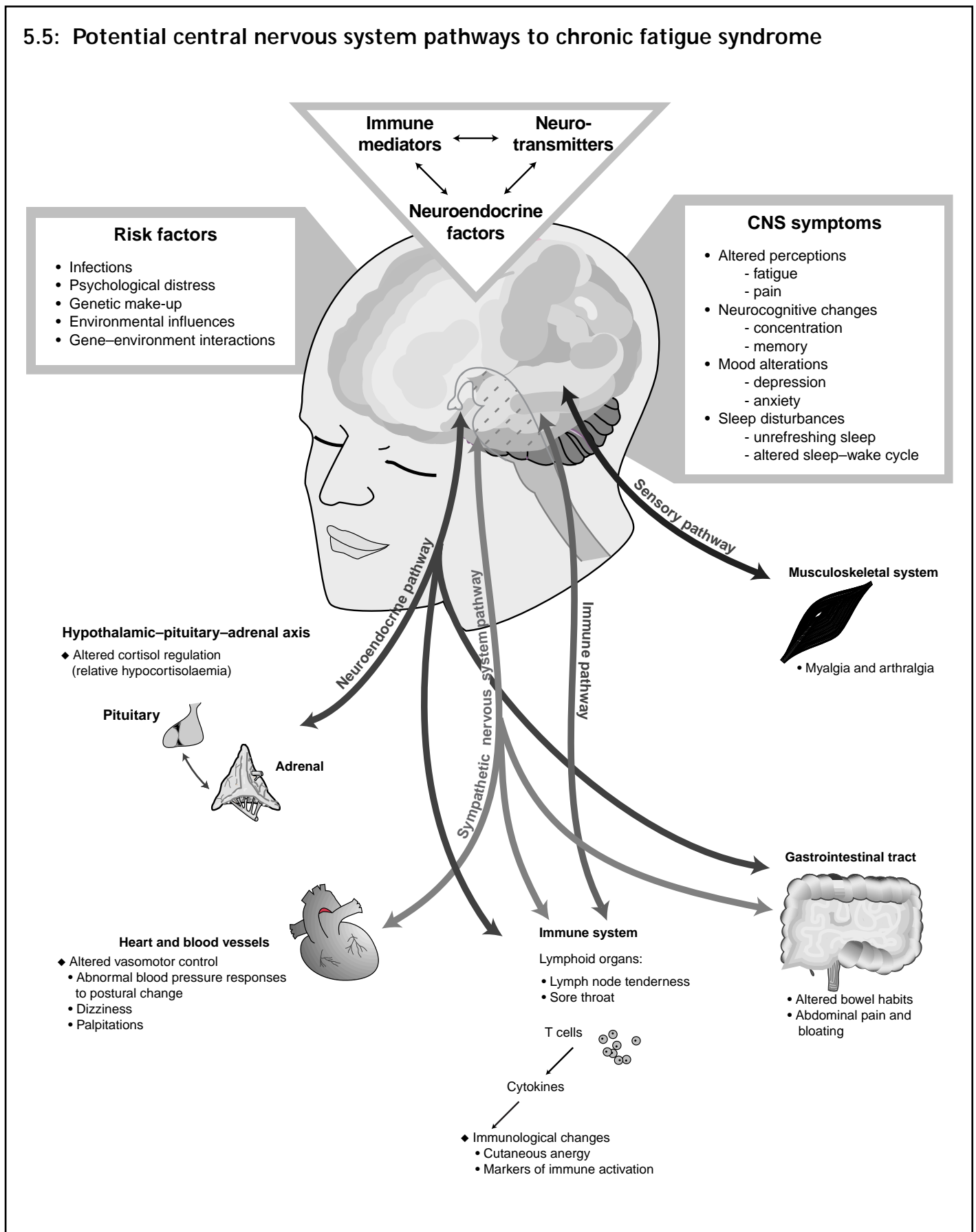
- Urinary excretion of protein metabolites may be altered (McGregor et al. 1996a, 1996b)

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 limited preliminary evidence of other possible factors linked to CFS.

Poisoning

- Levels of chlorinated hydrocarbons may be increased (Dunstan et al. 1995) (Level III-3)
- Chronic exposure to industrial solvents, insecticides or pesticides may cause an illness resembling CFS (Hoffman et al. 1986; Orbaek and Nise 1989; Behan 1996) (Level IV)
- Silicone breast implants may be associated with a syndrome resembling CFS (Goldenberg et al. 1990; Wolfe et al. 1990; Buchwald and Garrity 1994; Solomon 1994; Vasey et al. 1994; Bridges 1995; Gatenby 1996) (Level IV)
- Ciguatera poisoning may precipitate a syndrome resembling CFS (Pearn 1996, 1997) (Level IV)

5.5: Potential central nervous system pathways to chronic fatigue syndrome



6: How were these clinical practice guidelines developed?

The Working Group conducted an exhaustive review and evaluation of the relevant scientific literature on prolonged fatigue, chronic fatigue and CFS. Although the working group recognised that CFS overlaps significantly with other fatigue-related syndromes, such as fibromyalgia or irritable bowel syndrome (see Part 2), the significance of these overlaps for pathophysiology and treatment is not clear. Hence, the Working Group focused on published studies whose principal topic was CFS.

The evidence contained within published studies was systematically evaluated according to the process outlined in the NHMRC *Guidelines for the development and implementation of clinical practice guidelines* (National Health and Medical Research Council 1995). Rankings were based upon scientific principles for comparison between published studies (Sackett 1996; Sackett 1994; National Health and Medical Research Council, 1995):

- Genuine hypothesis testing requires use of appropriate research methodologies including collection of relevant control data, and suitable statistical analysis.
- The interpretation of individual study findings may be constrained by factors such as whether the cohort examined was adequately representative of the patient population in general.
- Replication across studies and in independent research centres is a key factor in the reliability of evidence.

The **quality of evidence ratings** chosen for these clinical practice guidelines were modified from existing guides (Sackett 1994; National Health and Medical Research Council, 1995). The amendments provided an integrated system for evaluating epidemiological and laboratory-based pathophysiological studies, as well as controlled treatment trials, as the former are not usually included in existing guides, which focus on treatment interventions.

Compelling evidence for clinical practice recommendations comes from consistent findings in two or more well-constructed, controlled trials or population-based epidemiological studies (i.e., Level I or Level II evidence; see “Quality of evidence ratings”).

By contrast, clinical practice guidelines with Level IV evidence represent consensus statements of the expert panel, based upon clinical experience and limited scientific data. Although these statements may influence current practice, they are likely to be modified in response to further research findings.

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). However, when the overwhelming body of data was strongly in

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 methodologies 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 methodologies 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.

favour of one outcome, thereby negating a single conflicting study, the ranking chosen was Level I.

Data from a single case series without control subjects provide little more than a stimulus for subsequent hypothesis testing. Such reports were not included in the systematic analysis of evidence upon which these guidelines are based.

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Australian patient support groups

New South Wales

ME/CFS Society of NSW Inc
Royal South Sydney Community Health Complex
Joynton Avenue
Zetland NSW 2017
Tel. (02) 9439 6026

Australian Capital Territory

ACT ME/CFS Society Inc
C/- SHOUT Office
PO Box 717
Mawson ACT 2607
Tel. (02) 6290 1984

Western Australia

ME/CFS Support Group (WA)
Refer enquiries to:
WISH (Western Institute of Self-Help)
335-337 Pier Street
PO Box 8140
Perth Business Centre
Perth WA 6849
Tel. (08) 9228 4488

South Australia

ME/CFS Society (SA) Inc.
GPO Box 383
Adelaide SA 5001
Tel. (08) 8266 5833

Northern Territory

Darwin ME/CFS Society
C/- PO Box 1062
Palmerston NT 5787

Victoria and Tasmania

ME/CFS Society of Victoria Inc
23 Livingstone Close
Burwood VIC 3125
Tel. (03) 9888 8798

Queensland

ME/CFS Society of Queensland Inc
134 St Pauls Terrace
Spring Hill QLD 4000
Tel. (07) 3832 9744