National Institute for Health and Clinical Excellence
CHRONIC FATIGUE SYNDROME / MYALGIC ENCEPHALOMYELITIS (CFS/ME) GUIDELINE
Stakeholder Comments; 23rd November 2006

Organisation: ME Research UK

Address: The Gateway, North Methven St, Perth PH1 5PP, UK; http://www.meresearch.org.uk/

Author of comments: Dr Neil Abbot, Director of Operations

The draft produced by the Guideline Development Group (GDG) is unsafe and unsatisfactory ("unfit for purpose") because it does not engage with key issues involved in the diagnosis and management of ME/CFS. These comments briefly outline the areas where core difficulties arise, and then present a line-by-line critique of the main limitations. These core areas of difficulty can be divided into the following:
1. The problem of the diagnostic rubric and the need for research-based subsets.
2. The skewing of the RCT evidence-base examined by the GDG, and the devaluation of evidence from scientific studies and surveys.
3. The limitations of the evidence base for non-specific management and coping strategies.

---

1. Problem of diagnosis and the need for research-based subsets

As the draft guidelines point out, ME/CFS is a diagnosis of exclusion based on a collection of vaguely defined symptoms that it shares with other illnesses. While the GDG has tried in good faith to fulfill its remit – to suggest guidelines for "diagnosis and management" – it has failed to ask what the "diagnosis" means and which patients or groups of patients it contains. Without addressing these issues, the guidance is no more than the blind leading the blind round in circles.

Terminology is the 'hot' issue in ME/CFS: it energises the debate between patients and healthcare professionals, and it impacts on patient management, clinical practice, and the results of clinical trials (which are heavily dependent on the entrance criteria used to recruit subjects). The issue can be simply put. The original case description of the illness, myalgic encephalomyelitis (ME) - Acheson, 1959; Dowsett et al, 1990 - referred to a condition, commonly of infectious onset, characterised by:

a) Exercise-induced myalgia and fatigue precipitated by trivial exertion (physical or mental).
b) Neurological disturbance, especially of cognitive, autonomic, and sensory systems. This could include impairment of short-term memory and loss of powers of concentration, usually coupled with emotional lability, nominal dysphasia, disturbed sleep patterns, dysequilibrium and/or tinnitus.
c) An extended and relapsing course with fluctuation of symptoms, usually precipitated by either physical or mental exercise; typically, the symptoms vary capriciously from hour-to-hour and day-to-day with varying involvement of the cardiac, gastro-intestinal, and lymphoid systems.

Since the late 1980s, however, the medical profession has been urged by a small subset of its members to adopt the term Chronic Fatigue Syndrome (CFS), a more wide-ranging diagnostic category which includes patients whose dominant symptom is medically unexplained, on-going, or chronic fatigue (in conjunction with several other physical or psychological symptoms) who would not necessarily fulfil the original criteria for ME.

There are now several definitions of CFS, all still unvalidated in 2006; the Guideline Development Group (GDG) has mentioned these (FULL Guideline, page 111-2), but has not grasped their significance. In the USA, the 1994 CDC case-definition of CFS is currently utilised (Fukuda et al, 1994), supplanting its predecessor, the 1988 CDC criteria. However, in the UK, a frequently-used case definition is the 'Oxford criteria' (Sharpe 1991) which can include patients with no physical signs and inadvertently selects subgroups of patients with high levels of psychological diagnoses (Katon & Russo 1992; Freiberg 1999). Since the adoption of a particular case-definition of CFS will greatly influence the outcome of particular studies, it is perhaps no surprise that groups researching biopsychosocial management and coping strategies have tended to use the broader Oxford criteria, whereas groups outside the UK (mainly in the USA) have tended to use the Fukuda et al 1994 definition for their biomedical research.

Today – whichever definition is used – the term ME/CFS (or CFS/ME which the GDG prefers) is an impossibly wide "umbrella term", based on a collection of vague non-specific symptoms shared with other illnesses, that contains different patient groups. The issues surrounding the establishment of CFS as a diagnostic category, and the inaccurate and biased characterisations of CFS that have subsequently arisen, were well-reviewed a decade ago by Jason et al (1997), and their key points are still valid:

"...A significant complicating factor in understanding the dynamics of this illness is that there are probably different types of illnesses now contained within the CFS construct... We believe that it is crucial for CFS research to move beyond fuzzy recapitulations of the neurasthenia concept and clearly delineate precise criteria for diagnosing pure CFS and CFS that is comorbid with psychiatric disorders. It is also necessary to better differentiate CFS from other disorders which share some CFS symptoms but are not true CFS cases."

Importantly, many people with ME/CFS across the world point out a key fact, namely that though they are "diagnosed" and placed under the ME/CFS umbrella:

a) Fatigue is not their primary problem: musculoskeletal pain and post-exertional myalgia along with other physical signs are far more prominent, corresponding more closely to the classical definition of ME.
b) The World Health Organisation International Classification of Diseases (ICD) has, since 1969, classified ME separately as a neurological problem (ICD 10 93.3), with 'CFS' incorporated into the current ICD as a sometime synonym for ME. The chronic fatigue states per se are listed under mental and behavioural disorders (F 48.0), a category which specifically excludes ME/PVFS/CFS.

It is now recognised by clinical champions – and by most charities representing patients in the UK and overseas – that there is a strong, perhaps overwhelming, case for unpacking the term 'ME/CFS' and reclassifying and renaming in accordance with more specific clinical criteria (e.g., De Becker et al 2001; Tan et al 2002). Indeed, the further categorisation or substratification on the research-based subsets, or the need for it, is so often alluded to in the scientific literature on ME/CFS (vide http://www.cfids-cab.org/MESA/subsets.html) that it is now a commonplace (though this body of literature has eluded the GDG). Examples in the past two years alone include: Jason, Neuropsychology Review 2005; Natelson, Clinical and Diagnostic Immunology 2005; de Lange FP, Neuroimage 2005; Baraniuk, BMC Neurology 2005; Kaushik N, J Clin Pathol 2005; Nijs J, Med Sci Sports Exerc 2005; Chia J, Journal of Clinical Pathology 2005; Lange G, Neuroimage 2005; Reeves, BMC Med 2005).

Alongside this groundswell for change, there have been attempts to revise the CDC-1994 criteria directly (e.g., Reeves 2005), including suggestions for subclassification by mode of onset – rapid post-viral onset versus gradual onset – given that there appears to be a genetic basis for this distinction. In addition, the recent Canadian Consensus Document produced by the Expert Medical Consensus Panel in Canada (Carruthers 2003) was a valiant first attempt at arriving at an evidence-based yet historically consistent system of subgrouping patients based on their specific symptoms and signs. As these authors say, "The CDC [1994] definition, by singling out severe, prolonged fatigue as the sole major (compulsory) criterion, de-emphasized the importance of other cardinal symptoms, including post-

exertional malaise, pain, sleep disturbances, and cognitive dysfunction. This makes it more difficult for the clinician to distinguish the pathological fatigue of ME/CFS from ordinary fatigue or other fatiguing illnesses." The lack of any substantive allusion to this Canadian Consensus Document (2003) in the current GDG guidelines is a serious omission, and one which diminishes the authority of the GDG.

Our key point is that CFS/ME or ME/CFS is a wide umbrella term recognised by clinical champions, patient charities, leaders of ME/CFS support groups, and scientific researchers to contain many different patient groups. Without addressing this core issue, the efforts of the GDG to give diagnostic and management guidance that goes beyond the recommendation of anodyne, non-specific interventions will be inadequate and probably constitute misguidance.

---

2. The skewing of the RCT evidence-base examined by the GDG, and the devaluation of evidence from scientific studies and surveys

While RCTs are the best evidence of "efficacy", there is a particular problem in the case of the diagnostic rubric ME/CFS. The large majority of "good quality" RCTs have examined the use of the non-specific management and coping strategies cognitive behavioural therapy (CBT) and graded exercise therapy (GET). Such trials are very expensive to conduct, and their authors have had the impetus - and been able to access the resources - to conduct them. This means that systematic reviews, such as that conducted by the GDG and ancillary staff – building on Whiting 2001, Mulrow 2001 and Chambers 2006 – find that the most prominent RCT evidence is for these non-specific management and coping strategies which (by their very non-specificity, with inadequate blinding and in the absence of a truly indistinguishable control intervention) are prone to result in mildly positive outcomes. The fact that these trials of CBT and GET have had relatively unspectacular results is less important to reviewers than the fact that they are "positive".

In short, the accepted strategy of looking at formal "evidence" is flawed in ME/CFS because the evidence-base is skewed towards the small group of mildly positive RCTs. It is not a case of finding the "best" evidence garnered from the work of a range of biomedical and biopsychosocial scientists working on a level playing field, but rather finding quite modest evidence in a forgotten field put there by proponents of one model of the illness – the biopsychosocial model – a construct which contrasts with the biomedical model which implies that a primary disease entity exists and that biopsychosocial aspects are secondary (the two models discussed in the report to the UK Chief Medical Officer in 2002). Contrast this situation with, say, breast cancer which has been well supplied with funding for biomedical trials, and in which meta-analysis can arrive at a best estimate of treatment effects from a large number of different studies, including replicate investigations on different populations by different research groups (vide NICE Guidance on Cancer Services Improving Outcomes in Breast Cancer, 2002). Breast cancer with the formal evidence-base that currently exists for ME/CFS would be no less a physical illness, and the non-specific management and coping strategies would be no more specifically effective for the underlying disease. Our point is that a NICE guideline on the diagnosis and treatment of breast cancer in the face of such an evidence-base would not be meaningful, or fair to the patients.

A corollary of this is that the importance of evidence from non-RCT scientific studies is diminished or discounted. There is no need for us to list here the range of biomedical investigations already conducted on people with ME/CFS – these have already been flagged for the attention of the GDG, and a full database of over 3000 abstracts exists at http://www.meresearch.org.uk/. Most are not RCTs or controlled trials, and come lower in the hierarchy of research evidence, but given the paucity of clinical trials in ME/CFS (a function of lack of the basic funding needed to test hypotheses) and the skewing of the small RCT evidence-base that exists, they do, in fact, represent a considerable body of evidence that biomedical investigation can uncover, within subgroups of people with ME/CFS, biological anomalies that might well help to explain many of the clinical features associated with the illness and indicate areas for therapeutic treatment.

Similarly, patient survey evidence is largely discounted because, in the GDG's words (FULL guideline, page 43/269, line 22), "surveys from self selected respondents are subject to bias and not necessarily representative of the wider population of people with CFS/ME". Of course, surveys come low in the hierarchy of research designs, since they are not deemed valuable for determining causation or the true effect of treatment, and tend to come from apparently "self-selecting" groups of people with self-reported symptoms. However, there are two things to be said. First, the evidence for the effectiveness of non-specific management and coping strategies is itself gathered by self-selecting professionals promoting their areas of expertise with access to central funding, and who also have difficulty ascribing causation or determining the true treatment effects. Second, such soft survey data contains real, hard experience – the experience of thousands of patients who have no access to funding for trials, and no way to publish their experience in the scientific literature. And while they are limited as formal evidence, yet they are surely not meaningless or valueless. When they say – as in one large survey (CMO report 2002, page 49) – that only 7% of respondents found CBT "helpful", compared with 26% who believed it made them "worse", the remaining 67% reporting "no change", they are not joking, and nor are the 79% of patients in the same survey who answered that they had severe pain sometimes, much of the time, or all of the time. Clearly, community-based surveys can be very useful for describing the experiences of people with severe and less severe ME/CFS and can help uncover widespread areas of concern (such as the lack of community care provision), or highlight areas where new research is needed (such as the urgent need for pain relief). In short, they can provide a systematic record of individual suffering, and point to ways to alleviate it. In this regard, they should be taken seriously by the GDG.

ME Research UK and the wider ME/CFS community are not alone in pointing out such concerns. The central point was well put in recent letter (The Guardian, Oct 26 2006) by Dr Stilgoe of Demos, and Prof. Irwin and Dr Jones; "The experiences of patients and the professional judgments of doctors are important. It is not a simple battle between evidence and anecdote... NICE needs to do more than just look at published science. It needs to start listening to people, patients and doctors."

---

3. The limitations of the evidence base for non-specific management and coping strategies

As the recent review by Chambers et al (2006) – which informs and is informed by the deliberations of the GDG – shows, there have been only 5 trials of CBT which have a validity score >10, one of which is negative for the intervention; and only 3 RCTs of GET with a validity score >10. The total number of available trials is small; numbers are relatively low; no trial contains a "control" intervention adequate to determine specific "efficacy"; and their results are relatively modest (for example, one of the flagship trials (Prins 2001) described as having "cure of chronic fatigue syndrome as its explicit goal of therapy", reported no improvement on the fatigue severity endpoint in 56/83 patients after 8 months and in 38/58 after 14 months. The result was significantly better than in the control groups, but was modest nevertheless). In addition, some of the studies (particularly those on GET) have used the Oxford criteria (Sharpe 1991) for diagnosis, a rubric which allows selection of patients with chronic fatigue states, raising the question of the applicability of their results to patients with specific symptoms and signs. Again, the heterogeneity of the trials, the potential effect of publication or funding bias for which there is some evidence, and professional doubts about the evidence base for some behavioural therapies themselves give grounds for caution as regards the usefulness of this evidence-base to direct the management of people with ME/CFS. A commentary in the British Medical Journal (Bolsover 2002) is particularly relevant to the deliberations of the GDG: "Until the limitations of the evidence base for cognitive behavioural therapy are recognised, there is a risk that psychological treatments in the NHS will be guided by research that is not relevant to actual clinical practice and is less robust than is claimed."

These concerns have been echoed by reviews in the past, which have recommended caution in interpretation of the evidence-base: Whiting et al. 2001 stated, "all conclusions about effectiveness should be considered together with the methodological inadequacies of the studies. Interventions that have shown promising results include CBT and GET";

and Mulrow et al. 2001 stated, "…it is unlikely that the beneficial effects of such general treatments are specific or limited only to patients with CFS. In other words, although these therapies may help some people with CFS, their effectiveness does not help establish an underlying aetiology or cause of CFS." Indeed, a large body of both professional and lay opinion considers that these essentially adjunctive techniques have little more to offer than good medical care alone, and questions what specific additional therapeutic value they bring. As Carruthers et al (2003) have pointed out: “The question arises whether a formal CBT or GET program adds anything to what is available in the ordinary medical setting. A well informed physician empowers the patient by respecting their experiences, counsels the patients in coping strategies, and helps them achieve optimal exercise and activity levels within their limits in a common sense, non-ideological manner, which is not tied to deadlines or other hidden agenda.”

It would be preferable for NICE and the GDG to recognise that specific, rigorous, evidence-based recommendations for treatment cannot be made at present than to incorporate an inadequate evidence-base into established guidelines which feed into clinical care and government policy to the detriment of people with ME/CFS.

SPECIFIC COMMENTS ON THE DRAFT (line references omitted for clarity)

"...like other chronic illnesses with no certain disease process...."

This leaves open the possibility that there might not be a disease process at all, when there are thousands of people with a physical illness.

REPLACE WITH “like other chronic illnesses whose causes have yet to be discovered and disease processes elucidated...

"... Communication should be supported by the provision of evidence-based information....."

Given the particular problems with the meaning and relevance of the RCT evidence in ME/CFS, evidence-based information should have a wider scope.

REPLACE WITH “Communication should be supported by the provision of evidence-based biomedical and scientific information from the international literature, as well as evidence-based suggestions for coping with symptoms...

"... CBT is an evidence based treatment for CFS/ME...."

It is not. The evidence base consists of only 5 trials which have a validity score >10, one of which is negative for the intervention (vide Chambers 2006). Again, “treatment” is too strong a word for the relatively modest (and probably non-specific) effects seen in these trials. As proponents of the biopsychosocial model of ME/CFS (CMO report 2002, page 24) themselves make clear: it is “not a cure” (Deale 2001); it is "modestly effective" and not “remotely curative" and "not the answer to CFS” (Wessely 2001); and “...it should be kept in mind that evidence from randomized trials bears no guarantee for treatment success in routine practice. In fact, many CFS patients, in specialized treatment centres and the wider world, do not benefit from these interventions. When it comes to the management and treatment of CFS patients, there is still a lot to be learned.” (Huibers and Wessely 2006). We note that the most

recently published RCT on CBT (O'Dowd 2006) states, "...there was, however, no evidence that the treatment restored normal levels of function for the majority of patients".

Furthermore, the methodological problems with these trials have been well-described by Carruthers et al (2003): "The complexity of CBT studies, their varied inclusion and exclusion criteria, the very limited portions that can be properly blinded, and the subjective means used for most evaluations, puts in question the validity of their results. In addition, the numerous variables between the CBT studies, the CBTs and control programs, the different comparison therapies, and the varied frequency and duration of therapy, make it very challenging to determine which parts are responsible for any perceived improvement. Are any effects due to the shift in cognitive beliefs, the exercise involved, the amount and quality of the attention and counseling, the discontinuance of other medical therapies during the test period, etc? Thus the Powell et al [2001] study found GET alone to be as effective as CBT, and the Ridsdale et al [2001] study found CBT to be no more effective than counseling."

REPLACE WITH: .... While cognitive behavioural therapy most likely has some role in helping patients with all illnesses, including cancer and MS, to better cope with their symptoms until a cure is found, this role is limited and essentially non-curative...

"... CBT or psychological approaches to CFS/ME do not imply that symptoms are psychological, 'made up' or in the patient's head. It is used in many health settings including cardiac, cancer, diabetes and chronic pain as well as with mood disorders such as anxiety and depression...."

This is a disingenuous paragraph. The British Association for Behavioural and Cognitive Psychotherapies website (http://www.babcp.org.uk/) states that "CBT is an approach to help people experiencing a wide range of mental health difficulties. The basis of CBT is that what people think affects how they feel emotionally and also alters what they do....CBT practitioners... aim to work jointly with the person to help them begin to identify and then change their extreme thinking and unhelpful behaviour...." CBT is universally recognised to be a form of psychotherapy used to treat a variety of psychological impairments, but also used as a therapeutic adjunct for symptom management and coping in illnesses such as cardiac, cancer, diabetes and chronic pain. Indeed, we note that when references to CBT appear in the document, "Multiple Sclerosis: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care" (2004), it is in the context that psychological management strategies be employed IF the patient is depressed or anxious, but not otherwise.

Interestingly, the rationale for using CBT in ME/CFS is that inaccurate beliefs/ineffective coping maintain and perpetuate the illness, but it has never been proven that these illness beliefs have caused or maintain the illness, and correlations (where they exist) might just as well have arisen from the valid belief that illness DOES have a physical cause, and that activity avoidance IS the correct course of action.

The GDG guidelines could follow the NICE Guidelines for Multiple Sclerosis, and reinforce the adjunctive, supportive role of CBT in ME/CFS by stating as below:

REPLACE WITH: .... CBT or psychological approaches to CFS/ME do not imply that symptoms are psychological, 'made up' or in the patient's head. Rather, they can be thought of as essentially adjunctive management and coping strategies which might be useful for some people some of the time.....

"... GET is an evidence-based self-management approach to CFS/ME...."

It is not. The evidence base consists of only 3 RCTs with a validity score >10, one of which concludes, “...graded exercise produces small but clinically significant improvements in case level fatigue and functional work capacity in CFS patients....” (Wearden 1998). Given that all three trials recruited patients on the basis of the Oxford criteria which selects an over-broad group of patients including those with idiopathic chronic fatigue; that there is a strong likelihood of significant non-specific effects given the design of the studies; and the likelihood that self-pacing or good quality clinical care would produce similar small effects much more cheaply (free, in fact), this management approach cannot be called properly evidence-based or cost-effective in ME/CFS at present.

THIS SHOULD BE DELETED

"...Severity...These definitions were agreed by the GDG and have been derived from definitions in the Royal College of Paediatrics and Child Health Guidelines and the CMO report...."

These three severity levels are not evidence-based. Levels should be based on clinical observation of clusters of symptoms, each scored according to severity, to allow accurate ascription of a patient to a category of severity. The simple but effective “Symptom Severity Chart” of the Canadian Consensus Document (Carruthers 2003) – which allows for scoring – would be a good starting point.

REPLACE WITH: .... Severity...These definitions are ad hoc and essentially based on mobility, and efforts are underway to derive a symptom-based scale.

"...they have usually stopped work...."

REPLACE WITH: ...they have usually been forced by illness to stop working...

"... When the adult or child’s main goal is to return to normal activities..."

There is a suspicion that this would not be written of patients with other illnesses, and that it is included to suggest that some people with ME/CFS could be malingerers.

THIS CLAUSE SHOULD BE DELETED

"... then the therapies of first choice should be CBT or GET because there is good evidence of benefit for this condition in mild to moderately affected adults and some evidence in mild to moderately affected children."

This is not true for adults (as discussed above). As regards children, the updated systematic review which informs the GDG (Chambers 2006) says: “The recommendations for children and young people were largely developed by consensus because of a lack of specific evidence for this age group. GET and CBT were recommended for consideration based on extrapolation from studies in adults. The effectiveness of CBT for adolescents is supported by a recent high-quality RCT (Stulemeijer 2005) although this had only 69 participants.” (It is also the only positive RCT on children with a validity score >10.) And the GDG’s draft guidelines subsequently say, in section 4.1, “There is no evidence for the use or effectiveness of these strategies in these two patient groups [young people and the severely affected].”

THIS RECOMMENDATION SHOULD BE DELETED

"... When an acute infection is followed by excessive fatigue, the adult or child should receive advice on how to promote recovery...."

REPLACE WITH: ... When an acute infection has characteristic sequelae of ME/CFS, then the adult or child should receive advice on how to receive treatment and promote recovery.....

"... Healthcare professionals should be proactive in advising about fitness for work and education..."

This is not a standard phrase used in NICE Guidelines for other chronic conditions. The GDG should show why it is necessary to use this phrase here since there is a suspicion that this phrase would not be written of patients with other illnesses. What evidence is there – to inform evidence-based guidelines – that people with ME/CFS need unusual prompting from healthcare professionals to return to their pre-illness lives and jobs?

THIS SHOULD BE DELETED

"... A documented, individualised management plan should be developed with the adult or child with CFS/ME, and the carer, where appropriate to include.....education or employment plans..."

As above, this seems to imply that people with ME/CFS need a healthcare professional to prompt them into education or employment.

THIS SHOULD BE AMENDED

"... CFS/ME is recognised on clinical grounds alone...."

The reasons for this, and its implications for the validity of any guidelines produced by NICE, have been discussed in the long preamble to these specific comments. However, the clinical-basedness of the rubric ME/CFS does not mean that widening it further (as proposed by the GDG – see below) is sensible. Nor does it mean that other supportive evidence of illness need be absent. For example:

a) The paper by Devanur and Kerr (2006) expresses the biomedical evidence well – and there is a range of reviews in a similar vein: “Studies of pathogenesis have revealed immune system abnormalities and chronic immune activation, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, brain abnormalities, evidence of emotional stress (comprising host aspects) and evidence of exogenous insults, for example, various microbial infections (Epstein-Barr virus, enteroviruses, parvovirus B19, Coxiella burnetii and Chlamydia pneumoniae), vaccinations and exposure to organophosphate chemicals and other toxins (comprising environmental aspects).”

b) The Canadian Consensus Document (Carruthers 2003) is a diagnostic guideline distilled from the panel’s collective extensive clinical experience of diagnosing and/or treating more than twenty thousand ME/CFS patients. The clinical definition derived “encompasses the broad cluster of symptoms and signs that give ME/CFS its distinctive character. Diagnosis is based on these characteristic symptom patterns, which reflect specific areas of pathogenesis.” This is a superb 108-page document which should inform the deliberations of the GDG.

c) There is clinical evidence, and some research evidence, that frank signs can be found if clinicians look for them. For example, of the quadriceps muscle, “To our surprise, the patients with CFS were physically weaker than both the depressed patients and sedentary subjects” (Fulcher & White 2002), and more generally, “In all three groups, a majority of patients exhibited muscle weakness in the lower limbs, and significant numbers of patients had absent or abnormal reflexes.” (Kennedy et al 2004).

NICE has a great opportunity to look beyond the significantly rudimentary and skewed RCT evidence-base towards a fresh assessment of the biomedical evidence in ME/CFS, and the revision of the symptoms and signs in people with the illness. A full examination of the Canadian Consensus Document (2003) would be a good starting point.

"...CFS/ME should be considered if an adult or child has fatigue that is all of the following:..."

This section introduces a novel – and entirely unvalidated – method of “diagnosing” CFS clinically. The criticism of the most widely used “research” definition – the CDC (Fukuda) 1994 – is that it is impossibly broad, being based on “fatigue” plus 4/8 concurrent “minor criteria” symptoms, thereby lacking specificity since it does not, in practice, completely exclude patients with other biomedical conditions or, indeed, those with a primary psychiatric basis for their fatigue.

This attempt by the GDG in section 1.2.1.2 to define a clinical definition – on a basis other than systematised clinical experience – makes the situation far worse. It introduces a diagnosis based on “fatigue” plus ONE or more of 9 vague, ill-defined symptoms shared with many other illnesses. To be clear, if (as many believe on the basis of evidence) the current CDC-1994 research definition is an “umbrella term” covering diverse groups of patients, then NICE is proposing to replace it with a marquis similar to a circus tent. The widened diagnosis would include many thousands of patients currently diagnosed with idiopathic fatigue (most of whom could report at least one of nine common concurrent symptoms); it would lead to significantly increased heterogeneity within the diagnostic category (which could contain a still-working person with a sore throat alongside a bed-bound person with all 9 symptoms to a severe degree; yes, they might have the same illness at a different stage of development, but NICE has no evidence of that); and it would not be taken seriously since it flies in the face of other expert opinion. For example, even the CFS Working Group at the CDC has recommended that symptom severity be taken into consideration, and standardised outcome measures be used to improve its specificity (Reeves 2005). Furthermore, the experts devising the Canadian Consensus Document (Carruthers 2003) derived a diagnostic rubric based on characteristic symptom patterns, which reflect specific areas of pathogenesis.

The central issue has been put very nicely by Dr Charles Shepherd of the ME Association in a letter to the BMJ (December 2004; 329: 1405): "The medical profession has only itself to blame for the awful mess that currently surrounds ME/CFS. It has created an illness that covers a wide variety of fatigue state clinical presentations, with or without psychiatric co-morbidity, and almost certainly an equally diverse range of possible pathological and physiological explanations. Doctors who deal with patients suffering from unexplained abdominal pain, arthralgia or headaches do not work on the basis that they all have the same pathoaetiology and will therefore respond to the same form of treatment. So why apply this form of flawed logic to ME/CFS?"

The “clinical” revision proposed by the GDG in these guidelines can only worsen the pre-existing mess.

THE ATTEMPT TO ARRIVE AT A CLINICAL DEFINITION SHOULD BE POSTPONED UNTIL INTERNATIONAL EXPERTS ON ME/CFS HAVE BEEN CONSULTED AND EXISTING CLINICAL EVIDENCE EVALUATED

“...physical or mental exertion making symptoms worse...”

This “symptom” is almost synonymous with “characterised by post-exertion malaise and/or fatigue” of the major fatigue criteria. Is this an indication that the novel revision of the clinical criteria by the GDG needs revising?

THE ATTEMPT TO ARRIVE AT A CLINICAL DEFINITION SHOULD BE POSTPONED UNTIL INTERNATIONAL EXPERTS IN ME/CFS HAVE BEEN CONSULTED AND EXISTING CLINICAL EVIDENCE EVALUATED•

"...Some serious underlying diseases might present with similar symptoms and signs as CFS/ME. The following should be regarded as ’red flags’, indicating a higher index of suspicion of serious underlying pathology.
• Abnormal neurological signs.
• Features of cardiovascular problems.
• Weight loss.
• Features of sleep apnoea.
• Features of anxiety and depression...."

Most patients currently diagnosed with ME/CFS – including the 20,000 members of ME/CFS self-help groups – have arrived there after some minor clinical investigations by their GPs that have had negative results. They remain ill, however, and – in the absence of investigations for clinical signs, or in the face of disbelief – lose faith in clinical services. However, the umbrella diagnosis certainly contains people who could benefit from full and comprehensive clinical examinations, and in whom alternative diagnoses (e.g. Lyme disease; frank sleep apnoea; Addison’s disease – just some of the re-diagnoses that have come to our attention) could be found if healthcare professionals and researchers were motivated to find them.

"...the following tests should not be done routinely....The head-up tilt test...
...Serology testing for chronic bacterial infections (for example, borelliosis) in the absence of any indicative history.
.. Serology for chronic virus infections: HIV, hepatitis B and C, in the absence of any indicative history. ..
..Serology for general viruses (for example, heterophile antibody tests for infectious mononucleosis) in the absence of any indicative history.
...Serology testing for latent infections: toxoplasma, EBV (Epstein Barr virus), CMV (cytomegalovirus) in the absence of any indicative history."

These recommendations are in direct contrast to those forming the basis of the Canadian Consensus Document (Carruthers 2003) which have been distilled from the panel’s collective extensive clinical experience diagnosing and/or treating more than twenty thousand ME/CFS patients. Examples of their recommendations include the below:

"Autonomic Manifestations
...Orthostatic intolerance is commonly seen in ME/CFS patients and includes neurally mediated hypotension (NMH); postural orthostatic tachycardia syndrome (POTS); and delayed postural hypotension...
Laboratory and Investigative Protocol
...a) Further Laboratory Testing: diurnal cortisol levels, 24 hour urine free cortisol; hormones including free testosterone, B 12 and folate levels, DHEA sulphate, 5-HIAA screen, abdominal ultrasound, stool for ova and parasites, NK cell activity, flow cytometry for lymphocyte activity, Western blot test for Lyme disease, hepatitis B and C, chest x-ray, TB skin test and HIV testing. Do the 37-kDa 2-5A RNase L immunoassay when it becomes available. b) Differential Brain Function and Static Testing: MRI: those with significant neurological finding should be considered for a MRI to rule out multiple sclerosis (MS), and cervical stenosis. Quantitative EEG, SPECT and PET Scans and Spectography: qEEG analysis of brain waves, SPECT estimation of dynamic brain blood flow and PET analysis of brain metabolism show diagnostic promise and will become more important as these techniques are refined and research confirms their

diagnostic value. c) Tilt Table Test d). Sleep Study; e) 24-Hour Holter Monitoring: if a significant arrhythmia is suspected. f) Neuropsychological Testing: can be utilized to identify cognitive dysfunction and/or confirm diagnosis. If done, it should focus on the abnormalities known to differentiate ME/CFS from other causes of organic brain dysfunctions etc....."

There is a clear mismatch between the truncated recommendations of the GDG, and the routine examinations recommended by ME/CFS clinicians across the world.

THIS RECOMMENDATION SHOULD BE REVISED AND RE-EXAMINED IN LIGHT OF BEST PRACTICE AND CURRENT RESEARCH

"... When a diagnosis is made, a prognosis of cautious optimism should be conveyed. With appropriate management, most children and adults, but not all, will have some improvement and some will recover fully...."

This is not true (and again the problem involves “what” diagnosis and using "which" definition). Two separate recent reviews have concluded that, "…patients exhibit severe, long-term functional impairment. Substantial improvement is uncommon and is less than 6%" (Andersen 2004); and, "Full recovery... is rare" (Cairns and Hotopf 2005).

REPLACE WITH: .... When a precise diagnosis is made, a prognosis of cautious optimism should be conveyed. With appropriate management, most children and some adults can improve or even recover fully, though the patient must be left in no doubt that long-tern morbidity can be high....

"....When the adult or child’s main goal is to return to normal activities..."

There is a suspicion that this phrase would not be written of patients with other illnesses, and that it is included to suggest that some people with ME/CFS could be malingerers.

THIS SHOULD BE DELETED

General Global Comments on Guidelines section 1.3 (Management)

This section consists of recommendations for management that include:
Cognitive behavioural therapy
Graded exercise therapy

Neither cognitive behavioural therapy (a form of psychotherapy designed to manage dysfunctional illness beliefs) nor graded exercise therapy (which is used as part of a biopsychosocial programme predicated on a model of physical deconditioning) are evidence-based to a level that would allow NICE to recommend that these management strategies be rolled out to the 120,000–240,000 people with ME/CFS in the UK. In addition, in the few good quality RCTs which exist, the effect is modest and non-curative, and there is more than a strong suspicion that much of the apparent treatment outcome relates to the non-specific effects, i.e., that good quality usual clinical care (in the case of CBT) and self-pacing (in the case of GET) would produce similar results.

Also, the evidence from formal RCTs is opposed by evidence from patient surveys which overwhelmingly find against the usefulness of these strategies. As the FULL guideline (56/269, line 2) states, “Graded exercise was felt to be the treatment that made more people worse than any other. 39% were made worse by this whereas, in contrast, only 2%

were made worse by diet. Graded exercise was also considered to be the least helpful treatment or management schedule; only 13% said that it helped a lot and 26% said that it helped a little [n=347]" Again, as regards cognitive behavioural therapy, the FULL guideline (pages, 56 and 58, Table) states that only "7% reported to be helped by CBT whereas 67% were unaffected and 26% made worse".

Accordingly, the emphasis on these strategies in the NICE guideline draft is misplaced, as described in the preamble above.

THE ENTIRE SECTION 1.3 (PAGES 17–24) SHOULD BE REMOVED, OR TRUNCATED TO A PASSAGE SUCH AS THAT BELOW:

...Cognitive behavioural therapy (CBT) and graded exercise therapy (GET) are comparatively expensive symptom management strategies which some patients might want to try until the cause(s) of ME/CFS are unravelled and a cure identified....

"…Cognitive behaviour therapy (CBT) …A programme of CBT should include: …explanation of the CBT model for CFS/ME…"

There is no CBT model for ME/CFS per se. Rather there is CBT, a form of psychotherapy, which can be applied to all illnesses through the supposed biopsychosocial model. Even though CBT has its critics – such as Holmes (2002), "...the foundations on which [CBT] rests are not as secure as some of its proponents would have us believe." – there is some evidence that it can be used as a tool to help some patients cope with some symptoms. Its application for people with ME/CFS would therefore be as a management tool, and not as an overarching model for the pathophysiology of illness.

REPLACE WITH:
……Cognitive behaviour therapy (CBT) …A programme of CBT should include: …explanation of how CBT, a form of psychotherapy, might be a useful as part of a management strategy for coping with symptoms.

"…discussion of the patient's attitudes and expectations…
…developing awareness of thoughts or expectations, or beliefs
and defining fatigue-related cognitions and behaviour…
…challenging cognitions which may adversely affect rehabilitation and/or symptom management, for example, fear of activity and perfectionist beliefs…
…decreasing somatic attributions and addressing symptom overvigilance...
…problem solving using activity management and homework tasks to test out alternative thoughts or beliefs…"

Such sentences, characteristic of proponents of the pure generalist biopsychosocial model, have been given undue prominence by the GDG. There is a suspicion that they would not be so prominently displayed in NICE guidelines for other illnesses; indeed, we note that they do not appear in the document, "Multiple Sclerosis: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care 2004" (despite the fact that fatigue is one of the dominant symptoms of most people with MS) which recommends (on the basis of three positive trials of CBT for MS) that psychological management strategies be employed IF the patient is depressed or anxious, but not otherwise.

A quote from the Canadian Consensus Document (Carruthers 2003) expresses well how many ME/CFS patients and charities feel when they see such statement so prominently displayed: "…there is much that is objectionable in the very value-laden…hypothesis, with its implied primary causal role of cognitive, behavioural and emotional processes in

the genesis of ME/CFS. This hypothesis is far from being confirmed, either on the basis of research findings or from its empirical results. Nevertheless, the assumption of its truth by some has been used to influence attitudes and decisions within the medical community and the general cultural and social milieu of ME/CFS. To ignore the demonstrated biological pathology of this illness, to disregard the patient's autonomy and experience and tell them to ignore their symptoms, all too often leads to blaming patients for their illness and withholding medical support and treatment…Crucially, there is a serious question mark over whether a program of formal CBT or GET program adds anything to what is available in the ordinary medical setting."

THE GUIDELINE SHOULD REMOVE THESE AND SUGGEST THAT – LIKE THE NICE GUIDELINES FOR MULTIPLE SCLEROSIS – PSYCHOLOGICAL STRATEGIES MIGHT BE USEFUL FOR ANXIETY AND DEPRESSION.

"...Health professionals should be aware that there is no evidence for the following strategies:
....those which encourage complete rest (cognitive, physical and emotional) during significant increases in symptoms..."

There is well-founded support from patient surveys and from established ME/CFS clinicians that during periods of stabilisation of illness (as well as in the very early post-infectious phases) periods of rest are very important (vide Shepherd and Chaudhuri 2001).

"..Adults with mild or moderate CFS/ME should be offered a programme that includes planned increases in duration of physical activity/exercise followed by increases in intensity leading to aerobic exercise (that is, exercise which increases the pulse rate) such as GET...."

Much of the current thinking about ME/CFS is driven by models of deconditioning, predicated on the belief that deconditioning is a factor in the perpetuation of the illness. However, there is good evidence that deconditioning is not a significant factor (Brazelmans 2001; Van der Werf 2000) and that it cannot account for delayed post-exertional symptoms or the documented changes in muscle metabolism (Lane 1998 and 2000). Historically, Myalgic Encephalomyelitis is characterised by a delay in muscle recovery after exercise (with pain and fatigue 24 or 48 hours after exertion), a phenomenon which few have studied and which the deconditioning hypothesis does not address.

In modern ME/CFS patients, there is both clinical and anecdotal evidence that exercise can exacerbate symptoms and cause relapse, particularly the some 50% of the patient group whose illness had a post-infectious onset. One study, however, has confirmed patients' experience by demonstrating that CFS patients fail to recover properly from a fatiguing exercise protocol and that the failure was more pronounced after 24 hours (Paul 1999). Further, the new "CFS Toolkit for Health Care Professionals: Managing Activity" (2006) produced by the CDC in Atlanta (vide http://www.cdc.gov/cfs/toolkit.htm) is clear that "Advising patients who have chronic fatigue syndrome to engage in aerobic exercise... can be detrimental. Most CFS patients cannot tolerate traditional exercise routines aimed at optimizing aerobic capacity. Instead of helping patients, such vigorous exercise can cause postexertional malaise, a hallmark of CFS that is defined as exacerbation of fatigue and other symptoms following physical or mental exertion. Even worse, this kind of exercise can precipitate a full-scale relapse that lasts for days or weeks. A different way of defining exercise and managing activity is needed for CFS patients and their health care team." And a similar view is expressed in the Canadian Consensus Document (Carruthers 2003) "Exercise programmes must be entered cautiously as clinical studies have indicated that symptoms worsened in approximately half of the ME/CFS patients" And again, Dr Charles Lapp re-emphasised at the American Association for Chronic Fatigue Syndrome (AACFS) 6th International Conference in 2003, "....although many clinicians have heard that graded exercise can be helpful, patients should not embark on an exercise regime which increases the severity of illness, a phenomenon occurs, as many experienced clinicians recognise, when patients push themselves too much". Finally, people with ME/CFS themselves consistently

report the phenomenon of post-exercise worsening of symptoms: in one report of 1,214 patients graded exercise therapy was reported to make 50% of patients worse (CMO report 2002) - the greatest number of 'worse' reports of any therapy; and the survey of the severely affected (25% ME Group, 2004) found 82% of ME patients reporting that exercise therapy worsened their condition, with only 5% finding it useful.

There may be sound physiological reasons for the specific post-exercise malaise encountered. First, post-viral fatigue (which is not related to the muscle disuse and deconditioning that can result from the initial period of illness; Lane 2003) might result in a long-term smouldering infection involving glutathione depletion (Pierce and Pierce 2006), and be exacerbated by exercise; or there might be an exercise-induced physiologically-significant delivery of free radicals, not because of disuse of muscle and deconditioning, but because there is something organically wrong with muscle metabolism and/or vascular endothelial function. Whatever the reason, it is important to remember that the current evidence for deconditioning from the psychosocial literature is not based on scientific investigations of muscle but on suppositions about patients with "fatigue".

Thus, issues regarding the role of rest and exercise (whether in the form of GET or not) for people with ME/CFS is not as clear-cut as the GDG suggests. And, as Shepherd (2001) has pointed out, physicians must take as much care in prescribing appropriate exercise as in prescribing medications to ME/CFS patients. And physicians should only approve of exercise programs in which the patient's autonomy is respected, appropriate pacing is encouraged, fluctuations in severity of symptoms are taken into account, and adequate rest periods are incorporated (Carruthers 2003).

THE GDG SHOULD TAKE ACCOUNT OF THESE POINTS IN SUBSEQUENT REVISIONS TO ITS DRAFT

"...Management of Setbacks.. People with CFS/ME have variations in the severity of their symptoms and will experience setbacks or transient increases in fatigue and other symptoms.."

The usual term used in the ME/CFS literature is "crash" (e.g., Carruthers 2003) or "relapse" (e.g., CDC, "CFS Toolkit for Health Care Professionals: Managing Activity" 2006). Relapses are reported to occur frequently in people with ME/CFS, and can be long-lasting and affect all areas of life, and be much more than transient.

THE WORD RELAPSE SHOULD BE REINSTATED AND ROLE OF RELAPSES EXAMINED

"1.4 Key principles of care for people with severe CFS/ME...."

It is generally agreed that severely affected people could make up 25% of the total number of ME/CFS patients, though some estimates put the figure higher; the late Dr Melvin Ramsay, the doyen of ME patients in the UK, stated that one third of patients experience "a severe and debilitating downhill course", and one Members Survey of November 2000 reported some 34% classifying themselves as severely affected. It is surprising then that the care and management of people with severe illness takes up only 1.5 pages in the guideline draft produced by the GDG.

For the benefit of the Guideline Development Group, the article by Crowhurst (2005) is an excellent starting point for the development of meaningful and patient-specific principles of care; indeed the tabled section, "impact and service response" would do credit to NICE guidelines, and we hope NICE will consider their incorporation in its final document.

"....GET may be an appropriate addition to help patients to develop their physical capacity and functioning....

"...Activity management should be the core therapeutic strategy but elements of CBT may be suitable for some adults and children...."

This is disingenuous. As regards activity, a survey by The 25% Severe ME Group (2004), 82 per cent of patients with severe ME/CFS stated that their condition was exacerbated by graded exercise therapy, of which activity management is a satellite in this context (as stated in section 1.3.1.4 on the NICE Guideline draft). Also, the statement that follows this section (NICE Guideline draft Section 4.1) states: “There is no evidence for the use or effectiveness of these strategies in these two patient groups [children and the severely affected].... Patient experience suggests that some of these interventions may be harmful and/or not effective.....”

The support for the statement of the possible usefulness of CBT for the most severely ill patients is a single report in the scientific literature (Powell et al, 1999) which describes two wheelchair-bound patients who had dramatic improvements in health following a “pragmatic rehabilitation regimen”. Two other seemingly relevant reports in the scientific literature are, in fact, small pilot studies that refer to inpatient treatments within psychiatric wards (vide Chalder et al 1996 and Essame et al 1998).

General Comment on section 1.3.4 "Pharmacological interventions"

There is now much clinical experience to inform this section – which comprises only 1.5 pages in the NICE guideline. For example, recent reviews (Carruthers 2003; Shepherd and Chaudhuri 2001; and Spotilla 2005) have much to say, and revisions to this guideline should reflect these.

General Comment on section "Research recommendations" - page 258 Full Guidelines

The research recommendations consist of refining existing biopsychosocial coping strategies, assessing their cost-effectiveness, looking at rates of prevalence, and tinkering with outcome measures. Crucially no research recommendations are given for strategies to uncover the cause(s) of the illness or find a cure.

While the GDG were asked to produce a guideline on “Diagnosis and Management”, the very remit begs the questions: Diagnose what, and manage what? ME/CFS is a diagnosis of exclusion – albeit one that the NICE guideline draft would widen impossibly (see above) – containing patients who apparently do not fit squarely into any other category. The human beings inside it are a heterogeneous group who might all have the same illness at varying degrees of severity, but might not - the GDG doesn’t know where the truth lies, but fills the gap with general non-specific management and coping strategies which might help some in a modest way but solve nothing for most.

A programme of research is indeed urgently required, but to boost and extend physiological and biochemical abnormalities found in groups of patients meeting the broad criteria for ME/CFS. Examples of anomalies that can be found include: Oxidative stress (e.g., Kennedy 2005); Dysregulation of anti-viral pathways (e.g., De Meirleir 2000); Endothelial dysregulation (e.g., Khan 2004); Altered brain perfusion (e.g., Tirelli et al., 1998); Orthostatic hypotension (e.g., Spence and Stewart 2004); Brain metabolic abnormalities (e.g., Chaudhuri et al., 2003); and Cardiac anomalies (e.g., Lerner 2004); Altered muscle metabolism (e.g., Fulle et al., 2003); Abnormal response to exercise (e.g., McCully et al., 2004); Enteroviral sequences in muscle (e.g., Lane et al., 2003) ....and so on.....

THESE RESEARCH RECOMMENDATIONS SHOULD BE REMOVED FOR RENOVATION

Comparisons between the FULL guideline and the NICE Guideline

Since the shorter NICE guideline is the one read by 99% of interested parties, including healthcare professionals, it is important that the caveats of the FULL version be reproduced in the NICE version. These include:

a) …The GDG did not regard CBT or other behavioural treatments as curative or directed at the underlying disease process, which remains unknown. Rather, such treatments can help some patients cope with the condition and consequently experience an improved quality of life….

b) ...substantial number of patients will pursue a fluctuating course with periods of relative remission and relapse, and a significant minority become severely, and perhaps, permanently disabled....
.... recovery rates of 8% to 63% (median 40%), with full recovery being rare (5–10% achieving total remission)...

c) ...the GDG considered that patients should take the lead on any behavioural approaches to manage their CFS/ME. The objectives of any programme must be agreed with the patient who must understand the aims and objectives and must be willing to take part.....

OMISSIONS

1. The Analysis Report (2004) by the 25% ME Group for Severe Sufferers which was submitted to the Guideline Development Group previously, is not mentioned in either the FULL or the NICE guidance. This reported that 93% of respondents found CBT unhelpful and that GET was found to be unhelpful by 95%. It may be, as the FULL guideline says (page 43/269, line 22), "surveys from self selected respondents are subject to bias and not necessarily representative of the wider population of people with CFS/ME". But this report is still valuable and full of meaning, coming from a group representing over 1000 house- and bedbound people with ME/CFS, and does not deserve to drop off the edge of the evidential world.

2. There is a need for clear criteria for referral to psychology/psychiatry services. The guideline draft is vague regarding the circumstances under which a patient can be referred for cognitive behavioural/graded exercise and other similar interventions, and for psychiatric/psychological assessment. We understand this to be an area of great concern for some people with ME/CFS, and so we feel that precise criteria for such referrals should be published as part of the final guidelines. Openness is a key element of modern NHS reform, and the publication of clearly-defined criteria would be both a major step towards reassuring parents and carers, and a signpost for professionals working in this area. The concern of some people with ME/CFS is that unless this is done, most cases will be referred for psychology/psychiatry services routinely. Given some of the statements in the current draft - which can read as thinly-veiled invitations to uncover psychological dysfunction - these concerns may, in fact, be valid.

3. The GDG fails to make a positive statement about the entitlement of people with ME/CFS to Disability Living Allowance/Incapacity Benefit. This is a perplexing issue for the many thousands of people with this illness who rely on disability benefits.

References

25% ME Group. 2004. Severely affected ME (myalgic encephalomyelitis) analysis report on a questionnaire issued January 2004. 25% ME Group, Troon, Ayrshire, UK. http://www.25megroup.org/

Acheson ED. The clinical syndrome variously called benign myalgic encephalomyelitis, Icelandic disease and epidemic neuromyasthenia. American Journal of Medicine 1959; 569: 595.

Andersen MM, Permin H, Albrecht F. Illness and disability in Danish Chronic Fatigue Syndrome patients at diagnosis and 5-year follow-up. J Psychosom Res 2004 ;56(2): 217-29.

Bolsover N. Commentary: the evidence is weaker than claimed. British Medical Journal 2002; 384: 294.

Baraniuk JN et al. A chronic fatigue syndrome – related proteome in human cerebrospinal fluid.BMC Neurology 2005; 5: 22.

Bazelmans E, Bleijenberg G, Van Der Meer JW, Folgering H. Is physical deconditioning a perpetuating factor in chronic fatigue syndrome? A controlled study on maximal exercise performance and relations with fatigue, impairment and physical activity. Psychol Med. 2001 Jan;31(1):107-14.

Cairns R, Hotopf M. A systematic review describing the prognosis of chronic fatigue syndrome. Occup Med (Lond). 2005 Jan;55(1):20-31.

Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner AM, Bested AC, Flor-Henry P, Joshi P, Powles ACP, Sherkey JA, van de Sande MI. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. Journal of Chronic Fatigue Syndrome 2003; 11 (1): 7-116.

Chalder et al. Inpatient treatment of CFS. Behav Cognit Psych 1996; 24: 351-365.

Chambers D, Bagnall AM, Hempel S, Forbes C. Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis: an updated systematic review. J R Soc Med 2006; 99(10): 506-20.

Chia JKS. The role of enterovirus in chronic fatigue syndrome", Journal of Clinical Pathology, 2005; 58: 1126-1132.

Chief Medical Officer. A Report of the CFS/ME Working Group. Report to the Chief Medical Officer of an Independent Working Group. February 2002.

Crowhurst G. Supporting people with severe myalgic encephalomyelitis. Nurs Stand 2005; 19(21): 38-43.

De Becker et al. A definition based analysis of symptoms in a large cohort of patients whith CFS. Journal of Internal Medicine 2001; 250: 334-40.

De Meirleir K, Bisbal C, Campine I, De Becker P, Salehzada T, Demettre E, Lebleu B. A 37 kDa 2-5A binding protein as a potential biochemical marker for chronic fatigue syndrome. Am J Med 2000; 108(2): 99-105.

Deale A, Husain K, Chalder T, Wessely S. Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. Am J Psychiatry 2001; 158(12): 2038-42.

Devanur LD, Kerr JR. Chronic fatigue syndrome. J Clin Virol 2006; 37(3): 139-50.

De Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. Neuroimage 2005; 26(3): 777-81.

Dowsett EG et al. Myalgic encephalitis - a persistent enteroviral infection? Postgraduate Medical Journal 1990; 66: 526-30.

Essame CS, et al. Pilot study of a multidisciplinary inpatient rehabilitation of severely incapacitated patients with CFS. JCFS 1998; 4(2): 51-60.

Freiberg F. A subgroup analysis of cognitive behavioural treatment studies. Journal of Chronic Fatigue Syndrome 1999; 5: 3-4 & 149-59.

Fukuda K et al. The chronic fatigue syndrome: A comprehensive approach to its definition and study. Annals of Internal Medicine 1994; 121: 953-9.

Fulcher KY & White PD. 2000. Strength and physiological response to exercise in patients with chronic fatigue syndrome. Journal of Neurology, Neurosurgery, and Psychiatry 69: 302-307.

Fulle S, Belia S, Vecchiet J, Morabito C, Vecchiet L, Fano G. Modification of the functional capacity of sarcoplasmic reticulum membranes in patients suffering from chronic fatigue syndrome. Neuromuscul Disord 2003; 13(6): 479-84.

Holmes J. All you need is cognitive behavioural therapy? British Medical Journal 2002; 384: 288-90.

Huibers MJ, Wessely S. The act of diagnosis: pros and cons of labelling chronic fatigue syndrome. Psychol Med 2006; 36(7): 895-900.

Jason LA et al. Politics, Science, and the Emergence of a New Disease: The Case of Chronic Fatigue Syndrome. American Psychologist 1997; 52(9): 973-83.

Jason LA et al. Chronic Fatigue Syndrome: The Need for Subtypes. Neuropsychology Review 2005; 15(1): 29-58.

Katon W, Russo J. Chronic fatigue syndrome criteria. A critique of the requirement for multiple physical complaints. Archives of Internal Medicine 1992; 152: 1604-9.

Kaushik N, Fear D, Richards SC, McDermott CR, Nuwaysir EF, Kellam P, Harrison TJ, Wilkinson RJ, Tyrrell DA, Holgate ST, Kerr JR. Gene expression in peripheral blood mononuclear cells from patients with chronic fatigue syndrome. J Clin Pathol 2005; 58(8): 826-32.

Kennedy G, Spence VA, McLaren M, Hill A, Underwood C, Belch JJ. Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms. Free Radic Biol Med 2005; 39(5): 584-9.

Kennedy G, Abbot NC, Spence V, Underwood C, Belch JJ. The specificity of the CDC-1994 criteria for chronic fatigue syndrome: comparison of health status in three groups of patients who fulfill the criteria. Ann Epidemiol 2004; 14(2): 95-100.

Khan F, Kennedy G, Spence VA, Newton DJ, Belch JJ. Peripheral cholinergic function in humans with chronic fatigue syndrome, Gulf War syndrome and with illness following organophosphate exposure. Clin Sci (Lond) 2004; 106(2): 183-9.

Lane RJ et al. Muscle fibre characteristics and lactate responses to exercise in chronic fatigue syndrome. Journal of Neurology, Neurosurgery and Psychiatry 1998; 64: 362-7.

Lane RJ. Chronic fatigue syndrome: is it physical? Journal of Neurology, Neurosurgery and Psychiatry 2000; 69: 280.

Lane RJM, Soteriou BA, Zhang H, Archard LC. Enterovirus related metabolic myopathy: a postviral fatigue syndrome. Journal of Neurology, Neurosurgery, and Psychiatry 2003; 74: 1382-1386.

Lange G, Steffener J, Cook DB, Bly BM, Christodoulou C, Liu WC, Deluca J, Natelson BH. "Objective evidence of cognitive complaints in Chronic Fatigue Syndrome: a BOLD fMRI study of verbal working memory." Neuroimage. 2005 Jun;26(2):513-24.[PDF Format]

Lerner AM, Dworkin HJ, Sayyed T, et al. Prevalence of abnormal cardiac wall motion in the cardiomyopathy associated with incomplete multiplication of Epstein-barr Virus and/or cytomegalovirus in patients with chronic fatigue syndrome. In Vivo 2004; 18(4): 417-24.

McCully KK, Smith S, Rajaei S, Leigh JS Jr, Natelson BH. Muscle metabolism with blood flow restriction in chronic fatigue syndrome. J Appl Physiol 2004; 96(3): 871-8.

Mulrow CD, Ramirez G, Cornell JE, et al. Defining and Managing Chronic Fatigue Syndrome. Evidence Report/Technology Assessment No. 42. AHRQ Publication No. 02-E001. Rockville (MD): Agency for Healthcare Research and Quality: October 2001. Available from: www.ahrq.gov.

Natelson BH, Weaver SA, Chin-Lin Tseng, and Ottenweller, JE. "Spinal Fluid Abnormalities in Patients with Chronic Fatigue Syndrome" Clinical and Diagnostic Immunology. Jan. 2005. p. 562-55. [PDF Format]

Nijs J, Meeus M, McGregor NR, Meeusen R, De Schutter G, Van Hoof E, De Meirleir K. Chronic fatigue syndrome: exercise performance related to immune dysfunction. Medicine and Science in Sports and Exercise 2005; 37(10): 1647-1654.

O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A. Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme. Health Technol Assess 2006; 10(37): 1-140.

Paul L, Wood L, Behan WM, Maclaren WM. Demonstration of delayed recovery from fatiguing exercise in chronic fatigue syndrome. European Journal of Neurology 1999; 6(1): 63-9.

Pierce S and Pierce PW. The physiology of exercise intolerance in patients with myalgic encephalomyelitis (ME) and the utility of graded exercise therapy. In Press. 2006.

Powell et al. The treatment of wheelchair-bound chronic fatigue syndrome patients: two case studies of a pragmatic rehabilitation approach. Behavioural and Cognitive Psychotherapy 1999; 27: 249-60.

Powell P, Bentall RP, Nye FJ, Edwards RH. Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. BMJ 2001;322:387–90

Prins JB et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. Lancet 2001; 357: 841-7.

Reeves WC, Wagner D, Nisenbaum R, Jones JF, Gurbaxani B, Solomon L, Papanicolaou DA, Unger ER, Vernon SD, Heim C. Chronic fatigue syndrome - a clinically empirical approach to its definition and study. BMC Med 2005 15; 3: 19.

Ridsdale L, Godfrey E, Chalder T, Seed P, King M, et al. Chronic fatigue in general practice: is counseling as good as cognitive behaviour therapy? A UK randomised trial. Br J Gener Pract, Jan. 2001;51:19-24.

Sharpe MC, Archard LC, Banatvala JE, Borysiewicz LK, Clare AW, David A, Edwards RH, Hawton KE, Lambert HP, Lane RJ, et al. A report--chronic fatigue syndrome: guidelines for research. J R Soc Med. 1991; 84(2): 118-21.

Shepherd C, Chaudhuri A. ME/CFS/PVFS - An exploraiton of key clinical issues. ME Association 2001.

Shepherd C. Pacing and exercise in chronic fatigue syndrome. Physiotherapy 2001; 87: 395-6.

Spence VA, Stewart JM. Standing up for ME. The Biologist 2004; 51(2): 65-70.

Spotila L. Pharmacotherapy for CFS. CFIDS Chronical: Special Research Issue. 2005.

Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ 2005; 330: 14-49

Tan EM et al. The case definition of chronic fatigue syndrome. Journal of Clinical Immunology 2002; 22: 8-12.

Tirelli U, Chierichetti F, Tavio M, Simonelli C, Bianchin G, Zanco P, Ferlin G. Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. Am J Med 1998; 105(3A): 54S-58S.

Van der Werf et al. Identifying physical activity patterns in chronic fatigue syndrome using actigraphic assessment. Journal of Psychomotor Research 2000; 49: 373-9.

Wearden AJ, Morriss RK, Mullis R, Strickland PL, Pearson DJ, Appleby L, Campbell IT, Morris JA. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. Br J Psychiatry 1998; 172: 485-90.

Wessely S. Chronic fatigue syndrome-trials and tribulations. Journal of the American Medical Association 2001; 286: 1378.

Whiting P, Bagnall A-M, Sowden AJ, et al. Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. Journal of the American Medical Association. 2001;286:1360-8.