

## NICE LITERATURE REVIEW CRITIQUE

### Executive Summary

This letter has been written in response to the recently issued literature review (Bagnall et al 2005) for the NICE guidelines. There are serious concerns regarding the information contained within this document, some of which were covered in the recent critique by Hooper and Reid. In this letter, the overall philosophy of ME/CFS as set out in the Bagnall review as well as a more detailed analysis of the inadequacies of the missing information is discussed. Rather than considering the review on a question-by-question basis, which would be somewhat repetitive, key areas such as the disease paradigm, information on GET/CBT, diagnostics and pharmacological interventions have been critiqued.

### LETTER CONTENTS

1. Introduction
2. Disease paradigm
3. Inclusion criteria
4. GET/CBT information
5. Diagnostic information
6. Pharmacological Intervention information

#### 1. Introduction

The depiction of ME/CFS in the Bagnall review appears to be highly biased in favour of unproven psychiatric theories and lacking in some of the most important biomedical research areas published to date. Methodological flaws with the Bagnall review include, as reported by Hooper and Reid, the restriction to Randomised Controlled Trials (RCT), which are considered by the reviewers to be the only studies of a sufficient quality to warrant inclusion. In doing so, the statistical approach adopted by the researchers of these studies included is strictly vetted which has resulted in a large body of evidence being excluded. Conversely, other factors that might have been used to assess the quality of the research: authors' bias on the nature of ME/CFS (e.g. psychiatric vs. biomedical); the validity of the selection criteria i.e. whether the criteria are in line with the WHO ICD-10 neurological status of ME/CFS; the validity of the authors' interpretation and conclusions of their data and any disagreement with other researchers were not taken into account.

This letter sets out how a much more factual and balanced picture could have been obtained, had the reviewers taken the current WHO ICD-10 neurological status of ME/CFS as the starting point for choosing publications to be included in their study – rather than taking the psychiatric view that ME/CFS is simply a condition with no certain disease process. The need for NICE to realise and address the flaws in the Bagnall review is imperative, if a set of guidelines that will ultimately help rather than hinder ME/CFS patients is to be achieved. To ignore these flaws has significant ethical and long-term financial consequences that should be completely unacceptable to a developed nation such as the UK. That they have previously been ignored and that this may continue, raises human rights issues that the ME/CFS community will need to address if the current psychological bias

towards them is not rejected.

## 2. Disease paradigm

Problems with the approach in recognising ME/CFS in the UK and with the Bagnall review stem from an initial caveat that ME/CFS is a ‘syndrome’ with no certain disease process. Starting from this point, the review then gives a vastly incomplete picture of the effects of psychosocial treatment regimes, diagnostics and pharmacological interventions. The Bagnall review does not appear to acknowledge the polarisation in the opinions of the nature of ME/CFS in terms of a strong, although poorly funded biomedical group and a highly influential well-funded psychiatric lobby. Instead comments throughout the review hint at support for the latter. Specific examples of issues covered in the report that fit under the psychiatric paradigm include:

- 1 *CFS/ME*: Throughout the review – there is use of the composite term ‘CFS/ME’ that is highly unpopular with the proponents of the accepted neurological status of the disease who prefer ‘ME/CFS’ or ‘ME/ICD-CFS’.
- 2 *Rehabilitation*: ‘Rehabilitation’ of ME/CFS features heavily in the Bagnall review, and in particular the use of CBT as a ‘rehabilitative’ technique. Rehabilitation and recovery has been observed in only a very small percentage of ME/CFS patients and furthermore is not clear how it can be proven that any recovery was due to intervention, or just the natural course of the disease in a particular group of patients. Likewise any later relapse in these patients has not been monitored. Use of CBT in rehabilitation is a concept favoured more by the psychiatric lobby that believe that such psychosocial interventions are curative rather than a method to improve patient’s coping skills where necessary. This was set out in the Canadian Clinical Guidelines as follows:

*The second hypothesis is based on the premise that the patient’s impairments are learned due to wrong thinking, and “considers the pathophysiology of CFS to be entirely reversible and perpetuated only by the interaction of cognition, behavior, and emotional processes. According to this model, CBT should not only improve the quality of the patient’s life, but could be potentially curative” (105). Some proponents suggest that “ideally general practitioners should diagnose CFS and refer patients to a psychotherapist for CBT without detours to medical specialists as in other functional somatic syndromes” (106,107). ‘*

- 3 *Wessely School*: The research carried out by the Wessely School is included throughout the review regardless of the psychiatric bias of these researchers. Professor Simon Wessely and his co-workers are repeatedly on record as stating that ME/CFS is nothing but an illness belief, or a functional somatic syndrome. Having held an erroneous view for such a long period of time, and in still suggesting that other related illnesses such as Gulf War Syndrome (GWS) do not have a biomedical basis, it is not clear as to why the research of this group is still trusted (and in many cases preferred) for inclusion in a review intended to help achieve a more accurate and helpful set of clinical guidelines for ME/CFS. Although recently, the presence of an ‘organic trigger’ for the illness with perpetuating psychological factors thereafter has been considered by these researchers, this is still not supported by the biomedical literature which shows clear multi-systemic abnormalities throughout the disease duration.

### 3. Inclusion criteria

- 1 A large number of databases were searched using a broad range of search terms, some of which are not accepted by the World Health Organisation as being synonymous with ME/CFS, e.g. neuromyasthenia and myalgic encephalopathy.
- 2 Studies that selected patients using a set of criteria which actively exclude neurological sufferers of ME/CFS (Oxford Criteria) or that do not allow sufficient differentiation from patients suffering from psychiatric illnesses such as depression (Fukuda) were not considered to be of a low quality or inappropriate for inclusion in the review.
- 3 The Canadian Criteria receive less attention in the Bagnall review than other definitions. (Canada/Canadian mentioned in 11 places, compared with 42 citations of Oxford Criteria, 16 citations of Fukuda and 4 of London). The inclusion criteria in the Bagnall review are such that only definitions that have been established for many years and that have been used to select patients are represented. The newness of the Canadian Criteria is held against them, despite the advantage they represent in having pulled together biomedical evidence on 20,000 patients.
- 4 As described by Hooper and Reid (2006), the use of a highly restrictive inclusion criteria to only Randomised Controlled Trials (RCT) has led to a large body of evidence supporting the biomedical nature of ME/CFS (as a disease of the Central Nervous System) being ignored

### 4. GET/CBT information

No reference is made to the patient surveys indicating the harmful results of GET/CBT therapy such as the 25%ME group survey or the AFME survey. Often in the text of the review document it is stated that there were improvements to patients symptoms following GET/CBT. (Mostly using the 1994 CDC or Oxford criteria). Specific comments on the studies included or excluded from the review are:

- 1 Ref 151 Prins et al. CBT study on ME/CFS. The patients had to meet the CDC criteria “with the exception of the criterion requiring four of eight additional symptoms to be present.” Therefore prolonged fatigue was the only symptom necessary for inclusion into the trial and while some ME/CFS sufferers might have been included, they would not have been distinguishable from chronic fatigue sufferers with other physical or psychiatric co-morbid conditions. 26% of eligible patients refused to take part and 41% did not complete the trial.
- 2 Ref 157 Fulcher KY, White PD. Randomised controlled trial of graded exercise. This trial compared use of graded exercise to ‘flexibility training’. Patients were selected using the ‘Oxford Criteria’ that specifically exclude sufferers of organic brain disease. In addition, the trial exclude any patients with a sleep disturbance due to the negative effect poor sleep has on fatigue in spite of disruptions to sleep in ME/CFS sufferers being well documented. In this study, 9 patients were excluded as they had ‘organic causes for their fatigue’, 7 patients from the trial dropped out and according to the authors, 2 of these said the treatment made them worse. These patients were said to have gone on to develop ‘major

depressive disorders' although, it is not clear whether these 2 patient's level of physical disability was permanently worsened by the trial, nor for the 7 patients who dropped out. If this were the case, surely the regime adopted by the trial should be abandoned? After all, if a pharmaceutical drug caused a severe and adverse reaction in this percentage of trial patients, it might never make it to market.

- 3 Ref 158 Wearden AJ, Morriss RK, Mullis R, Strickland PL, Pearson DJ, Appleby L, et al. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *Br J Psychiatry* 1998;172:485-92. 37% of patients (25/68) dropped out of the exercise trial. I don't have the full text of the article, so it is not easy to tell what adverse affects might have taken place. Considering the high drop out rate, it does not seem correct that the article reviews this study as one of a number that demonstrate a resulting improvement in patients' symptoms.
- 4 Ref162. 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. This study used the Oxford Criteria, and is heavily biased towards a psychological etiology of ME/CFS stating that:

*"Patients' beliefs are based on evidence they find convincing.1 As most of the symptoms of chronic fatigue syndrome are physical, patients develop a strong physical perception of the condition. In the absence of medical explanation, many attribute intense and unpleasant symptoms to an underlying disease and are disinclined to accept that psychological factors may have a role. Attributing symptoms to ongoing physical disease is an important predictor of poor prognosis.2"*

The very title of this paper alone implies bias and preferential outcome to 'encourage' graded-exercise as though ME/CFS patients' main difficulty is in willingness and motivation for physical activity.

- 1 Ref 159. Powell P, Bentall RP, Nye FJ, Edwards RH. Patient education to encourage graded exercise in chronic fatigue syndrome. 2-year follow-up of randomised controlled trial. *Br J Psychiatry* 2004;184:142-6. The Linbury Trust funded this trial, which is a follow-up of the patients in the study in Ref 159. Considering the bias and flaws in the original study, the follow up cannot be considered that useful.
- 2 Ref 160 Moss-Morris R, Sharon C, Tobin R, Baldi JC. A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. *J Health Psychol* 2005;10:245-59. Patients were assessed using the Fukuda criteria. Assessments were made of 'illness beliefs' and 'symptom focusing' indicating an expectation of psychological 'risk factors' in the patient group. No one apparently dropped out of the exercise trial due to any adverse affect although the authors acknowledge that the exercise regime adopted was gentler than in other studies. Notably the outcome did not affect patients' illness beliefs or 'physical fitness beliefs', nor did it improve aerobic fitness. For some reason the exercise group were on average 36.7 years old and had been suffering for 2.7 years whereas the control group was 45.5 years and had been suffering symptoms for 5 years. Whether these differences had any affect on the statistical outcome of the results it is not possible to tell.

- 3 Ref 161. Wallman KE, Morton AR, Goodman C, Grove R, Guilfoyle AM. Randomised controlled trial of graded exercise in chronic fatigue syndrome. *Med J Aust* 2004;180:444-8. Used the Fukuda criteria to select patients. The exercise method employed involved pacing, with exercise sessions shortened or cancelled if patients' experienced a relapse in symptoms and this may account for patients not withdrawing from the trial. However with the use of the Fukuda criteria, it is impossible to know whether in fact any of the participants were suffering from neurological ME/CFS.
- 4 Shepherd C. Pacing and exercise in chronic fatigue syndrome. *Physiother* 2001 Aug; 87(8): 395-396. This study is missing from the review. The results found that 1214 of 2338 ME/CFS patients had tried graded exercise. Of these 416 found it to be helpful, 197 reported no change and 610 (50%) indicated that it made their condition worse. This study with a much larger patient population than all the other studies (combined) would have changed the view of GET/CBT in the overall picture considerably. Its exclusion severely biases the impression of GET/CBT success rate as a result.

#### 5. Diagnostic Information

The RNaseL research included in the report seems to be incomplete and somewhat biased towards studies that dispute the differences in RNaseL between ME/CFS sufferers and healthy controls and the usefulness of the RNaseL test as a diagnostic (e.g. Gow, Levine). I have listed some key studies/research that I would have thought should have been included as part of the evidence for both Questions 2 and 3. I am sure there are more, but have not carried out an exhaustive search.

- 1 Suhadolnik et al. Biochemical evidence for a novel low molecular weight 2-5A-dependent RNaseL in chronic fatigue syndrome. (*J. Interferon Cytokine Res.* 1997; 17: 377-85)
- 2 De Meirleir et al A 37 kDa 2-5A binding protein as potential biomarker for chronic fatigue syndrome (*The American Journal of Medicine* 2000; 108: 99-105)
- 3 Horvath et al Biochemical evidence for a RNaseL enzyme dysfunction in individuals with CFS (*J Interferon Cytokine Res* 1997,17(S2):S104)
- 4 E. Demetree et al Ribonuclease L Proteolysis in Peripheral Blood Mononuclear Cells of Chronic Fatigue Syndrome Patients *J. Biol. Chem.*, Vol. 277, Issue 38, 35746-35751, September 20, 2002
- 5 World Patent # WO03061605; issued July 31, 2003; filed January 10, 2003; titled Methods of treatment of chronic immune disease; Inventors: El Bakkouri K, Englebienne P, DeMeirleir K, Herst CVT; Applicant: R.E.D. Laboratories, N.V.

Other key research that would 'support the diagnosis of chronic fatigue syndrome in adults and children' seems to be completely lacking. There is no mention of SPECT scans, PET scans, MRI scans, EKG, 24-hr Holter monitor, presence of viruses or gene expression although the tilt test is included.

In terms of the overall attitude to diagnostic testing within the review, the following comment is quite revealing:

*'It is perhaps not surprising that no definitive diagnostic test has been described for CFS/ME, given that CFS/ME is a syndrome, as such defined by symptoms rather than cause. It is probably unlikely that a diagnostic marker would be found before a cause or causes of the syndrome are identified.'*

This statement is a self-defeating prophecy and is wholly inaccurate. In deciding that causality, symptom definitions and diagnostics must all three be perfectly accurate and understood before ME/CFS can be regarded as a disease, is to set an impossibly high goal post that few if any other diseases could be expected to achieve.

In many diseases, a set of symptoms is noted, a diagnostic is found and then causation is studied. A particularly good example is Multiple Sclerosis (MS) – which has a wide variation in symptoms, severity and pattern without full understanding of causation, yet it is still recognized as a neurological disease. (Although it is noteworthy that as with ME/CFS, this patient group were once also branded as 'hysterical' by many psychiatrists). MS is still very difficult to diagnose, with patient symptomology, presence of specific brain lesions on MRI, abnormal lumbar puncture and neurological examination necessary to confirm the diagnosis. Yet the requirement for use of a multi-faceted diagnostic approach and inability to provide curative treatment has not resulted in MS being regarded as a syndrome with no certain disease process that can only be treated with psychosocial techniques. Nor has it resulted in the need for a thorough approach starting with properly funded and detailed biomedical research being rubbish. Skipping straight to a 'management programme' for ME/CFS (which has proved to be harmful for many) is simply a flimsy patch on a gaping wound, and NICE should consider when looking at this review, the financial and ethical consequences of ignoring the body of research to date supporting the existing neurological status of ME/CFS and therefore the impropriety of GET/CBT treatment regimes.

Large groups of patients with symptoms that have been documented in ME/CFS have been found to show positive results for various diagnostics (24-hr Holter Monitor, PET, SPECT, MRI, RNASE1). Many tests have a high specificity for ME/CFS in particular, the RNASE1 test is outlined as being as high as 95% in accuracy – and it is completely erroneous therefore to say that no definitive diagnostic test has been described.

It seems that if the research to date on diagnostics were seriously considered and adopted, the issues of defining and testing for ME/CFS could be largely resolved or at least significantly improved. Moreover, common sense would dictate that for a disease with a large number of symptoms that overlap with many other diseases, a good set of clinical tests is absolutely essential.

If a large patient cohort with a similar set of symptoms is found to show statistically similar results for an identical set of diagnostics, then it should not be necessary to understand causation before defining the disease. A cause in any case is unlikely to be established while criteria for selection in research remains so diverse. Likewise, it is not sensible to define such a disease as a 'syndrome' listing out what appear to be the most common symptoms and to regard diagnostic tests as unnecessary – to do so is to seriously increase the possibility of misdiagnoses and to hamper efforts in improving understanding of the disease.

What is necessary is for as specific as possible set of criteria to be adopted (currently the Canadian Definition) and a set of diagnostics to be clinicised. Whilst over time, it is likely that further improvements on definitions, understanding of causality, and diagnostics will be made; there is much that could already be implemented. A faster and more reliable diagnosis may allow better treatment of the patient in the initial stages of the disease and likely result in fewer patient-doctor consultations, which often result from the patient's frustration and uncertainty with the inadequate explanation of his symptoms.

The Canadian Criteria lays the basis for diagnosis, and the specificity of the definition is such that there is no mistaking the disease for depression or another neurological condition such as MS – which (if one were just to look at symptoms) WOULD be possible using other definitions of ME/CFS. The bottom line is that a disease must be defined primarily in terms of underlying biological abnormalities and only then in terms of its symptoms. Any new set of guidelines of ME/CFS should focus more on separating symptoms from diagnostic features in the same manner that has been observed for MS.

### Symptoms and Diagnostic Criteria of Multiple Sclerosis

| <i>Symptoms</i>   |   |
|---|---|
| <p><i>Common</i></p> <p>Bladder/Bowel Dysfunction<br/>           Cognitive Dysfunction (memory, attention, problem solving)<br/>           Dizziness/Vertigo<br/>           Depression/Emotional Changes<br/>           Mobility problems (balance, coordination)<br/>           Pain<br/>           Abnormal sensation (numbness, pins and needles)<br/>           Sexual Dysfunction<br/>           Spasticity<br/>           Visual Problems, optical neuritis</p>   | <p><i>Less Common</i></p> <p>Headache<br/>           Hearing Loss<br/>           Itching<br/>           Seizures<br/>           Speech and Swallowing Disorders<br/>           Tremor</p> |
| <i>Diagnostic Criteria (McDonald 2005 Revised)</i>  |   |
| <p>There are two ways to show DIT using imaging:</p> <ol style="list-style-type: none"> <li>Detecting gadolinium enhancement at least 3 months after the onset of the initial clinical event, if not at the site corresponding to the initial event.</li> <li>Detecting a NEW T2 lesion if it appears at any time compared to a reference scan done at least 30 days after the onset of the initial clinical event.</li> </ol> <p>Three out of four of the following:</p> <ol style="list-style-type: none"> <li>One gadolinium enhancing lesion or nine T2 hyperintense lesions if there is no gadolinium enhancing lesion</li> <li>At least one infratentorial lesion</li> <li>At least one juxtacortical lesion</li> <li>At least three periventricular lesions</li> </ol> <p>One year of disease progression (retrospectively or prospectively determined)</p> <p><b>PLUS</b> 2 out of the following 3:</p> <ol style="list-style-type: none"> <li>Positive brain MRI (9 T2 lesions or 4 or more T2 lesions with +VEP)</li> <li>Positive spinal cord MRI (2 focal T2 lesions)</li> <li>Positive CSF (isoelectric focusing evidence of OCB and/or elevated IgG index)</li> </ol> <p>NOTE: A spinal cord lesion can be considered equivalent to a brain infratentorial lesion: an enhancing spinal cord lesion is considered to be equivalent to an enhancing brain lesion, and individual spinal cord lesions can contribute along with individual brain lesions to reach the required number of T2 lesions.</p> |   |

*Additional Data:*

Dissemination in space, demonstrated by:

MRI OR 2 or more MRI detected lesions consistent with MS plus positive CSF OR Await further clinical attack implicating a different site

Dissemination in time, demonstrated by MRI OR

Second clinical attack

Dissemination in space, demonstrated by:

MRI OR 2 or more MRI-detected lesions consistent with MS plus positive CSF

AND

Dissemination in time, demonstrated by: MRI OR Second clinical attack

One year of disease progression (retrospectively or prospectively determined)

AND

Two out of three of the following:

a. Positive brain MRI (9 T2 lesions or 4 or more T2 lesions with positive visual evoked potentials;

b. Positive spinal cord MRI (two or more focal T2 lesions);

c. Positive CSF

Source: National MS Society (USA) ([www.nmss.org](http://www.nmss.org)).

### Symptoms and Diagnostic Criteria of ME/CFS

| <i>Symptoms</i>   |                          |
|---|--------------------------|
| Symptom worsening on exercise.  | Joint Dysfunction        |
| Pain  | Muscle Dysfunction       |
| Cardiac/Cardiovascular abnormalities: hypotension, orthostatic intolerance, chest pain  | Allergies                |
| Cognitive and Neurological Dysfunction. Short-term memory loss, delayed visual and verbal recall.   | Oral Dysfunction         |
| Digestive Dysfunction   | Reproductive Dysfunction |
| Endocrine and Neuroendocrine Dysfunction  | Respiratory Problems     |
| Headaches   | Seizures                 |
| Hearing, Vestibular and Speech Dysfunction  | Skin, Hair and Nails     |
| Hypoglycemia  | Urinary Tract Infections |
| Immune System Dysfunction   | Visual Dysfunctions      |
|   | Weather Sensitivity      |
|   | Weight Changes           |
| <i>Diagnostic Criteria</i>  |                          |
| SPECT and xenon SPECT scans of the brain.   |                          |
| MRI scans to check for the presence of small white matter lesions predominantly in the frontal lobes.   |                          |
| PET scans to check for decreased metabolism of glucose in the right mediofrontal cortex and generalised hypoperfusion of the brain with a particular pattern of decreased neuronal metabolism in the brain stem |                          |
| Neuropsychological testing.   |                          |
| QEEG brain maps.  |                          |
| Romberg or Tandem Romberg – abnormality to test for brain stem dysfunction  |                          |

## General Neurological Examination

### Immune System Testing:

- Increased numbers of activated cytotoxic T cells (most patients have evidence of T-cell activation)
- Low natural killer cell numbers/percentage and function (cytotoxicity)
- Elevated immune complexes
- Atypical lymphocyte count
- Significantly reduced CD8 suppressor cell population and increased activation marker (CD38, HLA-DR) on CD8 cells
- Abnormal CD4/CD8 ratio
- Elevations of circulating cytokines
- Immunoglobulin deficiencies (most often IgG 1 and IgG 3)

RNase L : increased activity and dysfunction of the 2-5A RNase-L antiviral pathway in lymphocytes. Evidence of an up-regulated 2-5A antiviral pathway.

Erythrocyte Sedimentation Rate (ESR) An unusually low sedimentation rate (ESR) of <5mm/hr is common in ME/ICD-CFS

### Insulin Levels and Glucose Tolerance Tests Derangement of insulin response

24 Hour Holter Monitor showing repetitively oscillating T-wave inversions and/or a flat T-wave may be found. Holter monitors may also show heart rates as high as (or higher than) 150 beats per minute as an immediate or delayed response to the patient maintaining an upright posture, or at rest. Heart rates as low as 40 beats per minute may also be observed (during sleep).

Tilt Table Examination: presence of orthostatic intolerance, neurally mediated hypotension (NMH): Postural orthostatic tachycardia syndrome (POTS) or Delayed postural hypotension.

Cardiopulmonary exercise testing (CPX) presence of heart rate and blood pressure responses during the exercise test including: lower cardiovascular and ventilatory values at peak exercise (patients only being able to attain half the expected maximal workload and oxygen uptake compared to sedentary controls), elevated resting heart rates and reduced maximum heart rates (suggesting cardiac or peripheral insufficiency and/or reduced blood volume).

Sources: 1. Ultra Comprehensive Symptom List (Bassett, 2005) 2. Testing for ME/CFS (Bassett, 2006)

## 6. Pharmacological intervention information

- 1 The information included on Ampligen therapy is scant. The review lists out one study by Strayer in 1994. In fact Ampligen is being developed by Hemispherx Biopharma for the indication of ME/CFS and has completed Phase III clinical trials and a contract manufacturer has built a plant to manufacture the drug! This is not really reflected in the review. Information on Ampligen that should have been included such as the results of the Phase III trial carried out on 234 patients that showed a significant improvement in exercise tolerance in ME/CFS sufferers' vs. healthy controls. The FDA has granted Ampligen IND and Orphan Status. See the article on this result at:

[http://www.immunesupport.com/library/showarticle.cfm/ID/6019/e/1/T/CFIDS\\_FM](http://www.immunesupport.com/library/showarticle.cfm/ID/6019/e/1/T/CFIDS_FM)

- 2 Ref178. Blacker CV, Greenwood DT, Wesnes KA, Wilson R, Woodward C, Howe I, et al. Effect of galantamine hydrobromide in chronic fatigue syndrome: a randomized controlled trial. *JAMA* 2004; 292:1195-204. In this study, 'CFS patients' were

administered galantamine hydrobromide but the patient group excluded sufferers of neurological disease and those who would have suffered exposure to organophosphates.