

Witness Statement of Doctor Bruce M. Carruthers, MD, CM, FRCP(C)
Consultant Physician, Vancouver, B.C., Canada

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I am the author of this Statement. Unless I state otherwise, the contents of this statement are true within my knowledge. The remainder of the statement is true to the best of my knowledge and belief.

The aim of this Statement is to consider the evidence that the NICE Clinical Guideline CG53 distorts the issues surrounding myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS).

Brief Curriculum Vitae (a full CV is enclosed)

- Graduated from medical school in 1956
- Consultant specialist in general internal medicine since 1965, additionally carrying out clinical and basic research as well as teaching at the University of British Columbia
- For 30 years operated a private clinical practice with a special interest in chronic pain and chronic fatigue
- Principal author of "Myalgic Encephalomyelitis / Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols" (2003), later known in the UK as the "Canadian Guidelines", which were developed by a consensus panel selected by the Canadian Government's primary federal organization Health Canada as an Expert Medical Consensus Panel. It consisted of physicians with extensive clinical expertise in treating patients with ME/CFS and included many with research experience as well (who, between them have seen over 20,000 ME/CFS patients). Besides eight Canadian members, the Canadian Consensus Panel included four invited world leaders in the research and clinical management of ME/CFS as members. The Canadian Guidelines present evidence-based clinical practice guidelines developed from the best available research evidence provided by a panel of world experts. The process through which the Canadian Guidelines were developed is detailed in the Overview cited below.

Comments on the NICE Clinical Guideline 53 on Chronic Fatigue Syndrome / Myalgic Encephalomyelitis

1. Introduction

Myalgic encephalomyelitis (ME) was first documented in the UK medical literature in 1956 as an organic postviral fatigue syndrome. Twenty years later, ME was claimed to be an epidemic of hysteria by two psychiatrists, without their having seen or examined a single patient. This theory of hysteria was then taken up by the "psycho-social school", in which the psychiatric category of hysteria has evolved into the current concept of somatoform disorder.

Meanwhile research from the "organic school" identified many pathophysiological abnormalities in patients with ME/CFS resulting from dysfunction in a number of vital control systems of the body such as the central nervous system, the autonomic nervous system, the endocrinological system and the immune system. These control systems are all vital, exceedingly complex and inter-related.

The attitude of the "psycho-social school" continues to be to largely ignore this research. It seems that they can only maintain their hypothesis by discouraging the search for an organic basis and by denying the published evidence, which they are certainly doing, and by rejecting treatments and interventions based on research into organic causes.

Strongly influenced by the "psycho-social school", the NICE Guideline primarily recommends cognitive behavioural therapy (CBT) and graded exercise therapy (GET) as approved interventions.

Thus this unseemly battle of ideas has been settled politically by proclamation and manipulation, not by science, and not by fair and open means.

Not to define patients accurately is not in the best interests of patients. It is irrational for the "psycho-social school" to ignore the Canadian criteria and to rely on their own case definition, where so-called cases can be diluted with large numbers of patients who suffer fatigue or on-going tiredness that is of psychiatric origin.

It is immediately obvious that the NICE Clinical Guideline 53 is based on a restricted paradigm which is not supported by much of the available medical and scientific data.

In these days of evidence-based medicine (EBM), a thorough assessment of the patient is required to avoid inappropriate diagnosis and treatment regimes. Unfortunately, the NICE Guideline misuses this approach and has adopted an unduly proscriptive approach to what is an exceedingly complex disorder. In so doing, the Guideline fails to identify the disorder about which it professes to offer authoritative guidance to all UK clinicians.

2. Biased selection of GDG membership

I understand that clinicians who have extensive experience in treating patients with ME/CFS from a non-psychiatric perspective were excluded from the GDG.

It is irrational to choose members who are supposedly neutral but who adhere to only one of two major causal theories of the disorder in question, since they cannot come to a balanced decision concerning what is good clinical practice.

In my opinion, the biased way in which the GDG members were selected (i.e. the choice only of participants known to favor the psychosocial model, with many members having connections to the medical insurance industry) and the behavioral interventions that derive from this model, ignore and / or exclude both the scientific process and the existing evidence-base.

3. Comments on the process

My overall opinion regarding the NICE document is that the GDG makes recommendations based exclusively on generalized evidence, and in doing so follows a framework where evidence that is based on the experience of patients and on the cumulative wisdom of the clinicians who look after them is downgraded to the lowest level of evidence and is consequently disregarded.

The Guideline ends up by being of little use in clinical practice, which must orient itself primarily on the basis of individual evidence whilst being informed by scientific knowledge.

As the NICE document in effect relies solely on Systematic Reviews, it cannot advise about nor does it include the type of knowledge required for best judgements in the clinical sphere. The process of diagnosis becomes reduced to a numerical pattern-matching process between the patient's symptoms and the symptom cluster enumerated in their preferred model of the disorder. Biological research and biologically-based therapies have been restricted and dismissed.

4. Terminology (the choice of name) and its consequences

The choice of name used by NICE (CFS/ME) is telling, because it can be regarded as a code that NICE is following the psychosocial model of the disease in which CFS/ME is regarded as a cluster of unexplained symptomatology that is best classified as a primary somatoform disorder.

In comparison, the choice of name used in both the WHO International Classification of Diseases and in the Canadian Guidelines (ME/CFS) is also telling because, contrary to NICE, both regard the biological abnormalities as primary manifestations and any accompanying psychological disturbances as secondary to them.

5. Failure to accept the WHO classification of ME/CFS

Regarding NICE's failure to adopt the WHO classification for ME/CFS (ICD-10. G93.3: myalgic encephalomyelitis / chronic fatigue syndrome / post-viral fatigue syndrome), embedded in the names used by the WHO taxonomy are theories of causation. This is a venerable medical tradition and does not imply that the cause has been found, simply that informed clinicians think that the cause likely lies in that direction. A definition of post-viral fatigue embeds the observation that chronic fatigue often follows a viral infection -- which may be causal -- and thus the subsequent illness is of organic origin.

ME/CFS is placed in the WHO category of disorders of the nervous system, which embeds the clinical observation that many of the manifestations seen in this condition can best be explained as coming from an organic disturbance of the nervous system. However NICE does not include any viral or other microbial investigations in its suggested investigations and in fact it proscribes such investigations, and has declined to accept this WHO classification that has been in use for 40 years.

NICE has produced its own definition of CFS/ME, which does not distinguish between fatigue of physical or psychological origin.

Its failure to accept the WHO classification will further impede and obscure the diagnosis of ME/CFS.

There is, however, a WHO classification that might better fit with NICE's chosen therapeutic interventions: it is neurasthenia (WHO ICD-10:F48), which historically embeds a psychiatric causation of fatigue. The WHO insists that these two categories (G93.3 and F48) be regarded as mutually exclusive, otherwise its system of classification would be meaningless.

The Canadian Guidelines have already clarified the situation by excluding a major subgroup of patients who have fatigue of distinctly psychiatric origin from their case definition of ME/CFS (see Jason et al. JCFSS 2004:12:37-52). It is thus irrational and regressive for NICE to avoid making a clear choice between these two mutually exclusive diagnostic categories.

6. Failure to provide a guide to accurate diagnosis

I now consider the problem of diagnosis that arises from the new case definition produced by the GDG in the NICE Guideline. I understand that some have claimed that the NICE case definition is now a *bona fide* clinical definition. A definition can only be called a clinical definition if it serves to aid a clinician in the process of diagnosing and treating individuals in a clinical context.

The NICE document specifically abjures clinical considerations despite its claim to be a Clinical Guideline, and gives top-down advice/orders instead of showing clinicians how to improve their diagnostic and treatment skills.

NICE seems wedded to diagnosis by pattern matching and diagnosis by numbers (or lack of them). Its own case definition only requires fatigue plus one other symptom to make up the syndrome of CFS/ME (pp165-

166). Only one of the other permitted symptom groups is described in terms of impact on the patient's functioning (cognitive dysfunction). However, the effect of all symptoms on the patient's enjoyment of (and participation in) his/her life must be noted. How sick is the patient? The severity of illness must be noted and heeded.

Dizziness is grouped with nausea, but no other gastro-intestinal symptom is mentioned, even though a required investigational exclusion is coeliac disease. If dizziness is related to cardiovascular dysfunction, it is not to be investigated in the CFS/ME patient using a tilt table test. The presence of cardiopulmonary symptoms are to be regarded as a "red flag" signifying that the patient does not have CFS/ME, although palpitations are allowed as a symptom of CFS/ME but only if they are not due to cardiac pathology. According to NICE, other features regularly seen in ME/CFS such as localising/focal neurological signs, spatial disorientation, inflammatory joint pain, lymphadenopathy, sleep apnoea and weight loss must all form part of a negative differential diagnosis. Is one to include dizziness as a legitimate symptom of CFS/ME, but only if it is not related to spatial disorientation or to cardiac pathology?

The Guideline specifies that the diagnostic search for causes of fatigue should not routinely include any search for specific infections (in particular not chronic viral infections), adrenal or central nervous system causes of fatigue or dizziness, thus the NICE method of diagnosis discourages the diagnostic search for symptom interaction and causal connections. NICE includes basic thyroid testing, but excludes testing of adrenal function: thus according to NICE, the diagnostic investigations of "fatigue" should not include any search for underlying infections, adrenal causes of fatigue, or central nervous system or cardiovascular causes of dizziness.

The diagnostic search is curtailed by NICE according to its own arbitrary and confusing considerations. I consider such a restriction on biomedical assessment not only to be inadequate, but unprofessional and reckless.

Being contradictory as well as incomplete, the list of NICE's diagnostic requirements is a muddle and looks more like a laundry list whose order reflects more the order in which it was thought up rather than suggesting any causally-related symptomatology that might be helpful to a puzzled clinician trying to make sense of his patient's illness.

If the underlying entity is of a "socially constructed" kind, then those who have constructed it presume that there is no underlying disease process. The assumption of no entity, as encapsulated in such illness categories as "unexplained illness" and "somatoform disorder", will distort the differential diagnostic process, since its very inclusion assumes the absence of an underlying disease process before the search for one even commences.

In order to cure a disease, the cause must first be sought, but in the case of ME/CFS, NICE advises that key investigations must not be performed on UK patients.

In my opinion, NICE should not specify which investigations may or may not be performed, since each patient's medical situation is different, nor should NICE forbid or discourage tests for cardiovascular, central nervous and autonomic abnormalities, because abnormalities of these systems are commonly observed and are documented in the world literature on ME/CFS.

The NICE case definition will ensure that the future cohorts of CFS/ME patients used in RCTs are diluted with a goodly number of patients with psychogenic fatigue, who would be expected to respond better to therapies directed towards psychological adjustments (and would thus improve the outcome statistics).

Using too generic and heterogeneous an intervention group, and thereby ignoring subgrouping both with respect to severity and with respect to variable pathogenesis, will also tend to disallow interventions that would undoubtedly benefit specific subgroups.

7. Failure of the GDG to endorse the Canadian Guidelines

NICE discourages the diagnostic search for confirmatory evidence of organic pathology and, importantly, therapeutic interventions which have proved helpful but for which no RCTs exist are actively discouraged.

The Canadian Guidelines can be summarized as follows -- for a diagnosis of ME/CFS the following are required: post-exertional malaise and fatigue; sleep disorder; pain; neurological / cognitive manifestations; autonomic dysfunction; neuroendocrine dysfunction and immunological dysfunction.

They are published in the Journal of Chronic Fatigue Syndrome 2003:11(1):7-115. An Overview of key features can be accessed at:

http://data.eastanglia.me.uk/pdfs/Canadian_ME_Overview_A4.pdf

http://www.investinme.org/Documents/PDFdocuments/Canadian_ME_Overview_A4.pdf

For reasons that are irrational (for example, the GDG claimed that Canadian Guidelines were based on consensus rather than on evidence, yet on its own admission, its own Guideline was based on consensus) the GDG rejected use of the Canadian criteria, preferring not to distinguish between ME/CFS and states of psychiatric fatigue (CFS/ME). This cannot help either patients or their physicians and can only perpetuate the on-going diagnostic confusion.

8. Undue reliance on Random Controlled Trials (RCTs)

In the production of its Clinical Guideline, the GDG has used reliance upon allegedly evidence-based medicine (EBM) to restrict freedom of choice and to restrict "therapy" to just one kind. Questionable EBM has also been used to downgrade the patient experience and clinical experience that forms the core of clinical practice. This is insulting to patients, who rely on their experience to guide their actions, and is a double insult when their experience is rejected after having been solicited as per the AGREE Instrument. It is also insulting to clinicians who rely both on the patient's experience and on their own professional expertise.

The reliance of NICE exclusively on RCTs distorts the function of evidence-based medicine in clinical medicine, especially if the trial cohort is too heterogeneous and ignores subgrouping.

Thus NICE has not provided the right kind of knowledge for decision-making in individual clinical circumstances. NICE's reliance exclusively on RCTs for its so-called evidence-base distorts the function of evidence-based medicine because the GDG has ignored the need for subgrouping, it has not followed patients for a sufficient length of time, and it failed to follow up drop-outs. RCTs are subject to bias, not least because of variable case definitions which greatly influence the composition of the cohort studied, as well as selection bias and drop-out rates.

9. Concerns about CBT/GET

With regard to the therapies supported by NICE, the Guideline recommends only CBT and GET. While these two therapies were evaluated by NICE separately, it is mentioned in the Guideline that they would be expected to be used together. CBT and GET appear to be based on the rationale that patients with CFS/ME have "faulty" belief systems concerning the "dangers" of activity, and that these aberrant beliefs are significant perpetuating factors. If CBT to correct these "false" beliefs can be combined with a graded exercise programme to re-condition these patients (presumably because they have deconditioned themselves as a result of their mistaken attitudes), it is virtually promised in the Guideline that a significant proportion of them will improve both their attitude and their physical functioning, and thus cure their illness.

Using CBT, patients are therefore to be challenged regarding their "aberrant" thoughts and expectations of relapse that "psycho-social school" psychiatrists believe affect symptom improvement and outcomes. Cognitions concerning fatigue-related conditions are to be addressed; these include any alleged "over-vigilance to symptoms" and reassurance-seeking behaviours, and are to be dealt with using re-focusing and distraction techniques (p. 245).

It is when a therapy such as CBT begins to interfere with the natural warning systems, of which both pain and fatigue are a part, that the increased risks arise. The problem occurs because it is impossible to reduce so-called "inappropriate" pain and fatigue without affecting appropriate pain or fatigue, as is being recommended by NICE using CBT as symptomatic therapy, without addressing the underlying disturbances responsible for the symptom in the first place.

In particular, musculo-skeletal pain and fatigue have an essential function in modulating activity when the body is in a state of disease as in ME/CFS. NICE, however, recommends over-riding this essential safety-net, thus the risk of serious harm is increased in this situation of simultaneous activity and symptom denial. This will become a more serious risk in patients with more severe ME/CFS. This situation has aggravated both ME/CFS and other clinical conditions among patients in my own clinical practice, as well as putting patients into a most stressful conflict.

The Guideline mentions working on patients' beliefs and alleged behavioral problems, and it emphasizes treating associated or co-morbid anxiety, depression or mood disorders according to NICE's own clinical guidelines on these conditions. The Guideline does not mention how the recommended interventions are expected to affect other (optional) symptoms included in its list, such as pain of various varieties, nausea, dizziness, cognitive disturbances, general malaise, sore throat, painful lymph nodes and palpitations.

The Guideline does not indicate how the clinician can tell whether patients' beliefs concerning their symptoms are aberrant and/or when the symptoms accurately point to the underlying state of the disease process.

It is hard to discern any consistency in the recommendations for therapies other than CBT and GET; certainly the GDG have not applied their analysis of evidence on a consistent basis for therapies apart from CBT and GET. Thus we are left with an imposed treatment regimen consisting of two non-specific interventions rather than treatment, with the latter being neglected.

NICE's assessment of non- CBT/GET therapies is very sparse and incomplete; any supportive evidence is relegated to the bottom of the GDG's evidence hierarchy. NICE should make allowance for therapies that work for subgroups of patients, not just the total group. Not do so is irrational and restricts patients' choice as well as rigidly curtailing clinicians' autonomy. NICE pretends to listen to patients, but effectively disregards their experience since it is at the bottom of their evidence hierarchy. But for patients it is at the top, and should not be ignored in what purports to be a "Clinical Guideline".

Remedies for which there is no RCT evidence but which will often benefit patients considerably and which many patients have found helpful are dismissed and/or proscribed. A patient and his/her clinician should not be forbidden to search out such remedies just because the State is desirous of standardization and greater control of all aspects of medicine in the UK.

10. Neglect of patients' evidence

The neglect of patient experience is well demonstrated throughout the NICE document. Thus while section 5 of the AGREE Appraisal of Guidelines for Research and Evaluation requires that the development of guidelines include patients' perspectives, it is obvious that the NICE GDG regards patient experience with great distrust.

If one does not trust the patients' experience nor the physician's cumulative experience and expertise as a clinician, both being disparagingly classed as "anecdotal", it becomes very difficult to make appropriate and non-distorted judgments.

Outside their given section 3 ("The experience of people with CFS/ME"), which was largely ignored, attention to the patient experience did occur in two areas of the Guideline: (i) many patients held self-pacing of activity/rest in high regard, and (ii) a significant number of them felt that graded exercise therapy (GET) was harmful. The NICE GDG seemed to have great difficulty even in deciding what pacing was, and then promised to include it in subsequent RCTs despite not knowing what it was. They solved the GET exacerbation problem by excluding patients with "severe CFS/ME" from participation in it until new RCTs could be arranged, which would necessitate the inclusion of the very group of patients for which a GET programme is harmful in the patients' experience (i.e. the seriously affected, and it must be noted that following GET, mild-to-moderately affected patients have progressed to being severely affected). Could such a group ethically be included in any GET RCT programme without at least testing them for underlying pathophysiology such as cardiovascular, cardiopulmonary or oxygen transport problems and without at least monitoring them during the exercise therapy? None of this is to be permitted according to the NICE document. Not only do the GDG members ignore patients' experience, they insult their intelligence and common sense.

For the NICE document to follow the AGREE Instrument requirement of inclusion of patient perspectives but then to ignore them on the basis of alleged bias when compared with supposedly non-biased evidence from the narrow perspective of an RCT not only shows an arrogant attitude by NICE towards the AGREE requirements, but is also deeply insulting to the patients who have good reason not to doubt their own experience.

11. Neglect of clinicians' experience

It is not only the patients' experience that is insulted and ignored, it is also the experience of clinicians who deal with patients on an individual basis. The NICE document has studiously ignored or discredited most of the voluminous 20 year worldwide body of biomedical research which will eventually explain this daunting clinical entity, as well as provide treatments properly based on correcting the underlying pathophysiology. Indeed the clinical practices of diagnosis, prognosis, prevention, estimation of illness severity and disability in individual patients will be seriously distorted by the NICE Clinical Guideline unless it is withdrawn.

The Guideline interferes with a clinician's ability to follow the course of illness, as change in symptom severity is deemed an untrustworthy observation, nor does it allow one to accurately assess the effects of treatments and preventive measures on illness severity in the individual patient, because that patient's entire illness experience is to be mistrusted.

Conclusion

The NICE document does not aid the clinician by offering guidance about the defining symptomatology of ME/CFS as an aid to diagnosis and treatment: all it does is to offer a cook-book diagnostic process that must be followed, and then it recommends two non-specific behavioural approaches that are not treatment-based and which are non-specific to the disorder under review.

Overall, the process and the resulting Guideline are, in my opinion, detrimental to both patients' best interests and to best clinical practice.

The present Guideline cannot by any standards be considered as providing "best practice advice on the care of people with CFS/ME" nor is it "based on the best available evidence" as it claims. In my opinion it should be withdrawn.