Comments from the (UK) ME Association - prepared by Dr Charles Shepherd, Honorary Medical Adviser

This submission is based on the statement placed on the MEA website:

http://www.meassociation.org.uk/2015/01/me-association-gives-a-guarded-welcome-to-the-us-pathways-to-prevention-p2p-report-5-january-2014/

I have referenced the critical comments to the relevant line

The remaining comments relate to conclusions and recommendations that we find constructive and helpful and are not therefore referenced line by line

Dr Charles Shepherd 12 January 2015

NIH Pathways to Prevention Workshop: Draft Executive Summary

This is an important report from the National Institutes of Health (NIH) Pathways to Prevention Workshop that took place on 9 - 10 December 2014.

It is likely to have a significant impact on future ME/CFS research strategy in America, and possibly elsewhere.

The report identifies a number of issues relating to the way research has been carried out in the past - as well as recommendations for how this should change in the future.

It should therefore be required reading for everyone involved in funding research, driving research policy, and carrying out research. I have therefore sent a copy to my colleagues on the ME/CFS Research Collaborative, including Medical Research Council (MRC) representatives.

Overall, the report contains a number of valid, helpful and sensible conclusions and recommendations.

However, the report also contains conclusions and recommendations that I would not agree with.

For example:

The economic burden in America must be well in excess of £1 billion (line 7). The economic burden here in the UK has already been assessed by academics at a figure in excess of this.

I do not agree that there is a significant overlap with major depressive disorder (line 33) and there is no sound evidence to support this statement.

I do not understand why homoeopathy should be regarded as a research priority at this point in time (line 274).

The conclusions and recommendations relating to the use of CBT (cognitive behaviour therapy) and GET (graded exercise therapy) in lines 113 - 117, 135 - 138 and 348 - 349 have failed to take account of the very robust and consistent patient evidence, certainly from here in the UK, that CBT is ineffective for the majority of people with ME/CFS, and that around of 50% of people consistently report that GET makes their condition worse, whilst over 90% report that pacing is the most effective and safe form of activity management.

The MEA submission to NICE, regarding their recommendations relating to the use CBT and GET in their current (2007) guideline on ME/CFS, should help to explain why we take this position:

CBT, GET and Pacing

Our principle reason for requesting a fundamental review of the NICE guideline on ME/CFS relates to the recommendation that CBT and GET should be automatically offered to everyone with mild or moderate ME/CFS.

This is coupled with the continuing failure of NICE to take note of highly consistent patient evidence, dating back to evidence that was published in the 2002 Chief Medical Officer's report on ME/CFS, regarding the efficacy and safety of these two behavioural treatments.

The largest ever survey of patient evidence relating to all aspects of the management of ME/CFS was carried out by The ME Association and published in 2010 (ME Association). The report provided important evidence regarding concerns over the efficacy of CBT and the safety of GET.

***For CBT** (997 responses) Greatly improved: 2.8% Improved: 23.1% No change: 54.6% Slightly worse: 11.6% Much worse: 7.9%*

***For GET** (906 responses) Greatly improved: 3.4% Improved: 18.7% No change: 21.4% Slightly worse: 23.4% Much worse: 33.1%*

***For Pacing** (2137 responses) Greatly improved: 11.6% Improved: 59.6% No change: 24.1% Slightly worse: 3.5% Much worse: 1.2%*

The MEA is currently in the final stages of preparing a further report covering the use of CBT, GET and Pacing – but this time in much greater depth. The report will be based on the answers to questions on the above three treatments that were provided through 3142 responses given by 1429 respondents during 2012.

Overall, the patient evidence contained in this new MEA report is very similar to the evidence contained in the 2010 report. The two MEA surveys show a total of 6599 responses about the effect of treatments on symptoms, and a total of 6838 responses about appropriateness of courses, effectiveness of self management and helpfulness of consultations and general satisfaction.

However, to date NICE has failed to consider any of this patient evidence and both MEA reports support the findings from patient surveys referred to in the Chief Medical Officer's Working Group report into ME/CFS.

We are therefore looking at a consistent picture from patients with regard to all three approaches to management going back over at least a decade and the picture has not improved.

As a result of growing concern amongst people with ME/CFS about the efficacy and safety of CBT and GET, we will be making a number of radical recommendations regarding the future use of CBT and GET in ME/CFS in this report.

This is clearly important new evidence that cannot be ignored by NICE.

The PACE trial and the March 2011 surveillance review

Finally, in relation to CBT and GET and Pacing, we assume that the NICE guideline surveillance review that took place in March 2011, and which followed publication of the PACE trial results in February 2011, simply 'rubber stamped' the 2007 NICE guideline recommendations on the basis that the PACE trial had supported the recommendations relating to CBT and GET.

However, there has been widespread and valid criticism about the way in which the PACE trial was carried out, as well as the way in which the results were presented and reported.

In addition, it should be noted that the cost effectiveness paper by McCrone et al reported that take up of state sickness benefits had increased during the PACE trial for all four treatments (i.e. CBT, GET, Pacing and Standard Medical Care). The MEA report will also contain similar information on benefit status.

And while research funding is briefly referred to in lines 317 - 327, a great deal more thought needs to be given as to how these research objectives can be achieved without a recognition from government funded research bodies (on an international basis) that biomedical research into ME/CFS is not proportionate to the number of people affected, along with the high level of disability and ill health that this disease causes. So there has to be a very significant shift in who funds biomedical research into ME/CFS. This can no longer be largely left to the charity sector - such as The MEA Ramsay Research Fund.

There are also some clear factual inaccuracies, in particular:

a research focus on men in line 52

and questions to which the answers are already substantially there:

Does mononucleosis lead to ME/CFS in adolescents? in line 173. Answer: Yes it can - look at the literature!

POSITIVE CONCLUSIONS AND RECOMMENDATIONS

As already indicated, I want to concentrate on what I regard as the positive and constructive aspects of this NIH Workshop report - because a number of statements have been made that are going to be helpful in both recognition of the problem facing research and the solutions to these problems.

INTRODUCTION and BACKGROUND

- ME/CFS is a chronic, complex, multifaceted condition

- ME/CFS results in major disability for a large proportion of those affected

- ME/CFS is an unmet health need with a large economic burden

- ME/CFS is an area where the research and medical community has frustrated its constituents by failing to assess and treat the disease and allowed patients to be stigmatised

- ME/CFS has a physical, psychological, social and economic impact at the individual and family level

- Society and the medical profession often treats patients with disdain, suspicion and disrespect

- Although psychological complications (e.g. depression) often follow ME/CFS, this is not a psychological or psychiatric disease in aetiology (= cause)

- Patients do not want to be labeled as complainers - they want their stories to be heard.

EPIDEMIOLOGY AND RESEARCH METHODS

- Lack of a universally accepted case definition for ME/CFS has led to difficulty in determining the prevalence (= total number of cases) and incidence (= number of new cases per year) and has led to variability in the estimated numbers being reported

- The Oxford criteria are flawed and include people with other conditions, confounding the ability to interpret the science. Continuing use of Oxford criteria may impair progress and cause harm.

- The Oxford criteria should be retired and the ME/CFS community should agree on a single case definition - even though it is not perfect

- Patients, clinicians and researchers should agree on a definition of meaningful recovery

- The lack of a consistent, specific, sensitive diagnostic test and set of diagnostic criteria has hampered research on pathogenesis (= cause) and treatment. This has prevented ME/CFS from being considered to be a distinct pathogenic entity.

RESEARCH FINDINGS AND RESEARCH CHALLENGES

- Over the past twenty years minimal progress has been made to improve the state of science for patients with ME/CFS

- Studies of ME/CFS are fraught with methodological problems - no agreed parameters for defining ME/CFS; small sample sizes; inclusion of participants with differing symptoms across studies; lack of inclusion of severe/housebound cases etc

- Many instruments used to evaluate ME/CFS are not validated, are inappropriate, and may be misleading

- Studies are too small to have power for subgroup analysis; do not address early disease or ME/CFS in children; fail to address harms or who dropped out or why; and include only short follow up

- Patients want their concerns to be heard, a meaningful recovery, and a cure

- The research community has a responsibility to address issues that are meaningful to patients.

- Strong evidence indicates immunological and inflammatory pathologies, neurotransmitter signalling disruption, microbiome pertubation, and metabolic or mitochondrial abnormalities

- There is reproducible evidence of neurocognitive dysfunction with abnormalities in functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies

- Current research has neglected many of the biological factors underlying ME/CFS onset and progression

- Small poor-quality studies and a lack of a gold standard for diagnosis and treatment has led to confusion

- Findings in the literature are inconsistent and there are many gaps

RESEARCH RECOMMENDATIONS

- It is critical to include patients with limited access to clinical services (e.g housebound) in research studies

- A clear case definition with validated diagnostic tools is required

- To advance the field, retrospective, prospective and longitudinal studies that are practical and reproducible are needed

- Longer follow up and lifespan perspectives are needed

- Endpoints need to be clarified - what is clinically and statistically significant

- Innovative biomedical research is urgently needed to identify risk and therapeutic targets

SPECIFIC RESEARCH RECOMMENDATIONS

- Assemble a team of stakeholders - patients, clinicians, researchers etc - to reach consensus on the definition of ME/CFS

- Develop valid prognostic tests that can guide treatment strategies using genomic, epigenomic, proteomic and metabolomic strategies to identify critical biomarkers

- Develop a registry/repository of all patients with ME/CFS and establish a central archive of de-identified data and tissue sharing. CS note: This is what we are already starting to do here in the UK with the ME Biobank at UCL and the post-mortem research we are collaborating on and funding.

- Immunologic mechanisms of ME/CFS and pathways associated with disease progression must be defined and characterised – e.g defining cytokine profiles involved in pathogenesis; studying inflammation; comprehending the basis for natural killer cell dysfunction.

- Studies of gene expression among identical twins to identify gene expression biomarkers

- Future studies (clinical trials) must be collaborative, multicentre efforts and must include large, diverse samples across the lifespan

TREATMENT

- Patients usually have to make extraordinary efforts, at extreme personal costs, to find a physician who will correctly diagnose and treat ME/CFS symptoms

- Patients are frequently treated with psychiatric and other drugs that may cause harm

- Limited patient and professional education has impaired progress in managing ME/CFS

- Clinicians have a poor understanding of ME/CFS

- ME/CFS is a distinct disease that requires a high quality multidisciplinary care team: physicians, nurses etc to optimise care

- Proper training of that workforce is crucial

- In general, little attention has been given to how self-management may empower and improve health and quality of life for people with ME/CFS

- Physicians are inadequately trained to instruct patients in self management skills such as pacing

- Patients must become active participants in their overall treatment and decision-making.