Is Graded Exercise Safe?

It is in relation to the endorsement of exercise that the urgent need to subgroup patients appropriately is most pressing. All interventions offered to any patient population should be as safe as possible. Lack of understanding of aetiology or cause does not mean that safety cannot be considered. The ethics of this in the case of ME/CFS are particularly relevant given the wealth of research findings which raise substantial questions about the safe prescription of exercise. Given that the diagnosis of CFS currently encompasses a heterogeneous population, there appears to be a considerable lack of effort within clinical practice and at health policy level to take account of research indicating that the health of some patients is adversely affected by exercise.

The widespread promotion of graded exercise - and cognitive behavioural therapy aimed at increasing activity levels - has resulted in these behavioural interventions being prescribed in good faith by General Practitioners and other clinicians. However, the extent to which practitioners have knowledge of the internationally reported contra-indications for some sufferers within the 'chronic fatigue syndrome' banner is questionable.

Furthermore, there has been virtually no attempt to subgroup those being referred to local services for these interventions. General Practitioners have neither been provided with guidance as to which 'CFS' patients are likely to benefit from exercise, nor been advised on the need to investigate for the presence of physiological factors which would contra-indicate advising a patient to exercise.

Suggested urgent action

- *Every possible precaution must be taken to ensure that all medical services proposed for patients currently subsumed under the heterogeneous banner of chronic fatigue syndrome, including behavioural interventions, are safe. This would include provision of advice on contra-indications.*
- *GPs and other medic and related professionals should be familiarised with the diagnostic protocol for ME/strictly defined CFS (Carruthers et al. 2003), in order to be able to identify patients with ME from the wider group of patients currently subsumed under the broad 'CFS' banner that currently operates in UK diagnostic practice.*
- *Careful analysis and due consideration should be given to the findings of patient surveys and the numerous research studies which have indicated physiological abnormalities indicating abnormal response to exercise, including studies suggesting that the condition of some patients is made considerably worse by exercise.*

Both graded exercise and CBT aimed at increasing activity, often through exercise, are predicated on the belief that the condition can be overcome and patients rehabilitated by changes in behaviour.

This paper presents some examples of research findings which challenge the view that graded exercise may be safely considered to be both relevant and helpful to all patients who present with a diagnosis of 'chronic fatigue syndrome', which includes patients with the distinctive clinical presentation of myalgic encephalomyelitis (M.E.). The reports of findings set out here are taken from a variety of sources including, in some instances, direct from the relevant publication. This evidence also challenges the perspective that cognitive behavioural therapy, when aimed at increasing activity levels, may be considered a safe and helpful intervention for such patients.

While this does not purport to be a comprehensive or a systematic overview of the evidence on this subject, it does set out a wide range of relevant research findings which can and must be taken into account in provision of advice to general practitioners and from GPs to their patients, including:

- evidence that patients' clinical presentation cannot be explained by physiological de-conditioning consequent on inactivity;
- evidence of abnormal response to exercise;
- evidence of physiological characteristics which would contra-indicate exercise.

Examples of Research Findings

(presented in chronological order)

Excessive intracellular acidosis of skeletal muscles on exercise in the post viral exhaustion / fatigue syndrome: a ^{31}P-NMR Study. DL Arnold *et al.* Proceedings of third Annual Meeting of the Society for Magnetic Resonance in Medicine, New York, 1984, 12-13.

^{31}P-Nuclear Magnetic Reasonance permits continuous 'live' assessment of muscle metabolism. This study demonstrated that there is a significant abnormality in oxidative muscle metabolism with a resultant acceleration in glycolysis (the breakdown of glucose by enzymes with the liberation of energy). [See also the research by PJR Barnes *et al*. and by McCully *et al*. from the 1990s, below.]

***The Postviral Fatigue Syndrome: an analysis of findings in 50 cases*.** PO Behan *et al. The Journal of Infectious Disease* 1985; 10: 211 – 222.

This study revealed a variety of abnormalities in patients' muscle biopsies, including mitochondrial abnormalities.

Clinical studies of the postviral fatigue syndrome with special reference to skeletal muscle function. Teahon *et al.* Clinical Science 1988; 75 (18): 45.

This study showed significantly lower levels of intracellular muscle RNA content in sufferers, suggesting that these patients may have an impaired capacity to synthesise muscle protein, a finding which cannot be explained by disuse.

Talk by Prof. T Peters given at a meeting of microbiologists held at Cambridge University, April 1989, referring to the findings of various research studies.

Research has found decreased levels inside the cell of a key enzyme called succinct dehydrogenase, which plays an important role in energy production inside the mitochondria – the power house of the cell.

Mitochondrial abnormalities in the post viral fatigue syndrome. WMH Behan *et al*. Acta Neuoropathologica 1991; 83: 61-65.

In this study on a fairly homogeneous population, 80% of the biopsies showed evidence of structural damage to the mitochondria.

Skeletal muscle bioenergetics in the CFS. PJR Barnes *et al*. Journal of Neurology Neurosurgery and Psychiatry 1993; 56: 679-683

This study demonstrated that there is a significant abnormality in oxidative muscle metabolism with a resultant acceleration in glycolysis (the breakdown of glucose by enzymes with the liberation of energy).

SPECT imaging of the brain: comparison of findings in patients with chronic fatigue syndromes, AIDS, dementia complex and major unipolar depression. RB Schwartz *et al.* American Journal of Roentgenology 1994; 120 (11): 972-973.

This research, which used brain scans (PET & SPECT) to measure metabolic activity generated during brain functions, revealed that whereas in healthy controls or people suffering with depression metabolism increases with exercise, in the patients studied it is diminished for a considerable period. Diminished metabolism in the brain stem (which also houses a nerve network, the reticular activating system, charged with keeping us awake and attentive) may help explain one of the most disabling symptoms of this illness – the unpredictable onset of central nervous system exhaustion following minor or physical or mental activity.

Exercise responses and psychiatric disorder in chronic fatigue syndrome RJM Lane *et al.* British Medical Journal 1995; 311: 544-545.

This study measured lactate acid levels in response to exercise. *"Our results suggest that some patients with the chronic fatigue syndrome have impaired muscle energy metabolism that is not readily explained by physical inactivity or psychiatric disorder. This adds to the growing body of evidence that the syndrome is heterogeneous."* (NOTE: Subjects were recruited for the study using broad fatigue criteria [known as the 'Oxford' criteria].)

Lung function test findings in patients with chronic fatigue syndrome. De Lorenzo *et al.* Australia and New Zealand Journal of Medicine 1996; 26 (4): 563-564.
This study found a significant reduction in all lung function parameters tested.

Reduced oxidative muscle metabolism in CFS. KK McCully *et al*. Muscle Nerve. 1996, 19, 621-625.
A further study demonstrating that there is a significant abnormality in oxidative muscle metabolism with a resultant acceleration in glycolysis (the breakdown of glucose by enzymes with the liberation of energy).

Does the CFS involve the autonomic nervous system? R Freeman & AL Komaroff, American Journal of Medicine 1997; 102: 4357-4364.
This study provides evidence that symptoms indicative of autonomic nervous system dysfunction are not related to psychiatric disorder and cannot be explained by deconditioning.

Fatigue and activity patterns of people with CFS. TL Packer *et al*. The Occupational Therapy Journal of Research 1997; 17, 3, 186-199.
Evidence from this study indicates that most patients with CFS do not spend the whole of the daytime resting. Note: Very low levels of activity indeed are required for debilitating deconditioning to occur - *"Remember that muscles remain constantly in tone if you only move between bedroom and bathroom."* [1]

Influence of exhaustive treadmill exercise on cognitive functioning in chronic fatigue syndrome. JJ La Manca *et al*.American Journal of Medicine 1998; 105(3A): 59S-65S.
These researchers concluded that, after physically demanding exercise, CFS subjects demonstrated impaired cognitive processing compared with healthy individuals.

Muscle fibre characteristics and lactate responses to exercise in chronic fatigue syndrome RJM Lane *et al.* Journal of Neurology Neurosurgery and Psychiatry 1998; 64 (3); pages 362-367.
In general, following exercise the patients studied showed more type one muscle fibre predominance and infrequent fibre atrophy, unlike what is expected in healthy sedentary people.

Demonstration of delayed recovery from fatiguing exercise in CFS. L Paul *et al*. European Journal of Neurology 1999; 6: 63-69.
CFS patients were compared with healthy but sedentary controls. The results demonstrated that patients with CFS but not the sedentary controls failed to recover properly from a fatiguing exercise protocol, and that this failure was more pronounced a full 24 hours after exercise.
"This exercise study provides a conclusive demonstration that recovery is significantly delayed in patients with CFS. … the fact that the CFS patients do not recover to initial force levels at 24 hours, while the sedentary controls … do, suggests that failure to recover is more related to the nature of CFS than to simple de-conditioning."

Impaired oxygen delivery to muscle in chronic fatigue syndrome. KK McCully and B Natelson. Clinical Science 1999; 97: 603-608.
This study showed impaired oxygen delivery to muscle. Oxygen delivery represents the ability to get oxygen into the small vessels of the muscle. The study found that recovery rates for oxygen saturation were 60% lower than normal subjects, demonstrating reduced exercise capacity.

Serum Potassium and Hormone Responses to Exercises in Chronic Fatigue Syndrome Dr R Burnet *et al.* Findings presented at 1999 Sydney ME/CFS Conference.
Potassium release on exercise was delayed and the peak level lower. This suggests an abnormal potassium response to exercise. The abnormality in potassium handling could be due to reduced total body potassium, or there could be some other reason for reduced potassium flux across cell membranes – such as the channelopathy emerging from other research studies. (e.g. research by J Nijs *et al.* 2003, referenced below.)

[1] From *Time to put the exercise cure to rest;* Dr E Dowsett; available on the 25% ME Group website www.25megroup.org at the Information/Medical Publications/M.E. Specialists section.

Exercise capacity in chronic fatigue syndrome P De Becker *et al.* Archives of Internal Medicine 2000: 160 (21); 3270 – 3277

This study compared female patients to a control group of healthy sedentary women. Subjects performed a test involving graded increase on a bicycle ergometer. Reporting results, the authors observe that *"… the exercise response characteristics of the CFS and the control subjects were very dissimilar …"*, with the patients showing a significantly decreased exercise capacity. For example:

- the maximal workload attained by the patients was almost half that achieved by the control group;
- *as was* the maximal oxygen uptake attained.

This would affect their physical abilities to a moderate or severe extent, leading the authors to comment: *"This study clearly shows that patients with CFS are limited in their physical capacities."*

The authors note that *"… variation in heart rate was strongly related to changes in exercise capacity in the patients with CFS."* Specifically:

- the resting heart rate of the patient group was higher than the healthy sedentary control group;
- *but* their maximal heart rate at exhaustion was lower;

These and other findings *"indicate that suboptimal cardiac function is a major limiting factor in exercise capacity in patients with CFS."* Other research is discussed, suggesting that this finding could reflect autonomic disturbances.

Even the subset of study patients (just over one third) who did achieve the target heart rate as well as another (respiratory) measure of 'maximal effort' exhibited abnormally low exercise capacity: *"… the exercise capacity in the patients with CFS who reached their maximal response was still quite different from that of the control subjects."*

Referring to other studies, which reported only slight reductions in aerobic power, the authors conclude: *"We believe that failure to assess the more severely affected patients appears to have led to a disparity in study conclusions about the exercise capacity in patients with CFS."*

Monitoring a Hypothetical Channelopathy in Chronic Fatigue Syndrome: Preliminary Observations. J Nijs *et al*. **.** Journal of Chronic Fatigue Syndrome 2003, Volume 11, Number 1, pages 117-134.

"This study was aimed at monitoring a previously suggested channelopathy, and searching for possible explanations by means of immune system characteristics. … In conclusion, the observations recorded suggested a channelopathy in a subset of CFS patients, probably induced by the deregulated 2-5A Rnase L antiviral pathway." [abstract, page 117].

Enterovirus related metabolic myopathy: a postviral fatigue syndrome. RJM Lane *et al*. Journal of Neurology Neurosurgery & Psychiatry 2003; 74: 1382-1386.

This study of skeletal muscle tissue provides evidence of impaired mitochondrial structure and function.

Complement activation in a model of chronic fatigue syndrome. B Sorevsen *et al.* Journal of Allergy and Clinical Immunology, August 2003; 112; pages 397-403.

This study looked at post-exercise immune changes. A significant increase in the split complement protein C4a was detected in the CFS group six hours post exercise, correlating with post-exercise symptom reports. In healthy subjects, C4a generation is only stimulated at much higher exercise levels than those involved in this study, and levels return to normal within three hours. The authors note that the exercise challenge allowed them to study CFS subjects in an exacerbated state of illness, as the patients subsequently showed significant increases in symptoms.

Findings presented at the 7th AACFS International Conference held in Madison, Wisconsin, from 8-10th October 2004.

An analysis of metabolic features using MRSI (magnetic resonance spectroscopy imaging) showed elevated lactate levels, suggesting mitochondrial metabolic dysfunction similar to mitochondrial encephalomyopathy.

Findings presented by Anna Garcia-Quintana at the 7th AACFS International Conference held in Madison, Wisconsin, from 8-10th October 2004.

This research on aerobic exercise provided evidence of low maximal oxygen uptake. Among the patients studied the average maximal oxygen uptake was only 15.2, whilst for sedentary healthy controls it was 25.9 and for physically active controls it was 66.6.

Findings presented by Jo Nijs at the 7th AACFS International Conference held in Madison, Wisconsin, from 8-10th October 2004.

This research provided evidence of underlying lung damage through intracellular immune dysregulation, with impairment of cardiopulmonary function.

Acetylcholine Mediated Vasodilatation in the Microcirculation of patients with CFS. VA Spence *et al*. Prostaglandins, Leukotrienes and Essential Fatty Acids 2004: 70; 403-407.

This research demonstrates that, most unusually for sick people, the response of the endothelium (the internal lining of the blood vessels) to acetylcholine is to dilate rather than to contract. Dilation is characteristic of highly conditioned individuals such as athletes. *"Most diseases are accompanied by a blunted response to acetylcholine but the opposite is true for CFS. Such sensitivity is normally associated with physical training so the finding in CFS is anomalous and may well be relevant to vascular symptoms that characterise many patients."* [page 403]

Chronic fatigue syndrome: assessment of increased oxidative stress and altered muscle excitability in response to incremental exercise Y Jammes *et al*. Journal Intern. Medicine 2005; 257 (3): 299– 310.

The data reported here were taken from well-rested subjects and recent research has demonstrated that incremental exercise challenge potentiates a prolonged and accentuated oxidant stress that might well account for post-exercise symptoms in CFS patients.

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