

Post-Exertional Malaise (PEM)  
and  
Graded Exercise Therapy (GET)  
in  
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome  
(ME/CFS)

by  
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Emerge Australia is pleased to endorse this primer which presents  
the latest research evidence and highlights the potential harm  
from Graded Exercise Therapy for people with ME/CFS



## Preface:

*“The public have an insatiable curiosity to know everything, except what is worth knowing.”*

— Oscar Wilde

Until Europeans discovered Australia, Black Swans did not exist, let alone could they even be imagined. They did not make sense, nor could they be, as they challenged common sense and common knowledge at that time in our history.

Common sense is what we rely on every day, even though it is often wrong.

Common sense is derived through experience and example. We fine tune it as we mature and then set it down as a driving truth. We recognise through our labours the benefits of exercise, the euphoria of achievement well earned through struggle and striving. Our bodies and minds enjoy challenges that encourage the fitness and flow that increasingly satisfy our desire to succeed in our endeavours. Such success serves to reinforce our certainty that exercise is always good.

In health, we learn that by well applied exercise, we increase our capacities to function. Effort, exertion, focused attention and concentration, all empower the body, and lift us up again after illnesses that decondition us. Our existing truth is that anything to the contrary is counterintuitive and is counterproductive.

This is the historical wisdom of the human struggle which has become deeply imbedded in our general knowledge of self and society, and which is an integral part of self respect and accomplishment, both in the work place and in recreation. We thus praise the hero who surpasses all measures of endurance and suffering.

Consequently, the prevailing view of exercise as the key to strength and cardiovascular fitness is rarely challenged, and its benefits are hailed and reinforced by doctors and psychiatrists alike. After all, exercise lifts our spirits, and awakens our sleepy and tired minds. How could it ever be otherwise?

S. Eyssens challenges us to rethink exercise in this elegant and well referenced Primer. It turns out that Chronic Fatigue Syndrome is a Black Swan. How so?

What exactly makes Chronic Fatigue Syndrome different remains to be clearly elucidated. Our initial enquiries prompted us to challenge it, as it challenges us deeply and in uncomfortable ways. Our human minds have a right to prod and poke this unusual beast as we yield reluctantly to how it affects and imposes on our beliefs and personal experiences.

A great deal of research has therefore been applied to this field, lest we be fooled by counterfeit.

This Primer reports on such research in a well documented manner, and by Oscar Wilde’s words, should compel us to move on from doubt and incredulity beyond to the next chapter in this human endeavour of discovery.

The new paradigm that exercise does not always prove to be beneficial exposes us to new questions as to how the body and mind work under such circumstances, and beseeches us to dig into our molecular and genetic makeup in order to resolve the suffering that underlies this counterintuitive disease.

The contents of this Primer accurately reflects the interplay of exercise and Chronic Fatigue Syndrome after over three decades of serious scientific interrogation. It also reflects the honest experiences of patients with this disorder and the ongoing observations of perceptive clinicians who devote themselves to their care.

A thorough read of this Primer should serve to educate the public, and new generations of clinicians charged with researching further into this enigmatic disease.

Dr John L Whiting  
Australian Physician  
October 2017

## Introduction:

The purpose of this primer is to provide an overview of the core symptom of Post-Exertional Malaise (PEM) in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), as well an analysis of the evidence base for the commonly recommended treatment of Graded Exercise Therapy (GET), and to highlight the risk of harm which GET poses to people with ME/CFS.

PEM is an “exacerbation of some or all of an individual’s ME/CFS symptoms that occurs after physical or cognitive exertion and leads to a reduction in functional ability” (National Academy of Medicine, 2015a, p. 78). GET is a treatment intervention, commonly recommended to people with ME/CFS, which is based on the premise that ME/CFS is a condition driven largely by deconditioning from lack of activity. By gradually increasing activity, the assumption is that deconditioning can be reversed and the individual will return to health. Despite the evidence supporting GET as a treatment for ME/CFS being weak (following a review of the evidence, the US Agency for Healthcare Research and Quality (AHRQ) downgraded the evidence for GET to insufficient in 2016), and the common reporting of harm from GET by people with ME/CFS, GET continues to be recommended.

## Executive Summary:

1. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a serious and debilitating, multi-system disease, in which physiological abnormalities can be found in many body systems. ME/CFS affects an estimated up to 240,000 Australians, approximately 25% of whom are bedbound or housebound.
2. Post-Exertional Malaise (PEM) is the exacerbation of all symptoms (including symptoms not normally found in healthy people following exercise) following exertion (whether physical, cognitive or emotional), and is considered to be the cardinal symptom of ME/CFS.
3. There are four main diagnostic criteria used in ME/CFS research. Not all require the presence or reporting of PEM for diagnosis. Diagnostic criteria used in ME/CFS research should ensure that participants selected do experience PEM, in order to ensure that this key aspect of the condition is being studied. Studies which use the Oxford criteria may have few (or no) participants who experience PEM, and it has been recommended that these criteria no longer be used. The Canadian Consensus Criteria (CCC) and International Consensus Criteria (ICC) have been recommended for ME/CFS research, because these diagnostic criteria require PEM for diagnosis, and are more precise than other criteria.
4. Graded Exercise Therapy (GET) studies focus on fatigue, not PEM, and use broad criteria, which do not require the presence or reporting of PEM. When excluding studies which used the broadest diagnostic criteria (Oxford) from a review of the evidence that GET is a beneficial treatment for ME/CFS, the US Agency for Healthcare Research and Quality (AHRQ) downgraded evidence for GET to insufficient in 2016. There are currently no GET studies which have used ME/CFS diagnostic criteria which require PEM for diagnosis. These studies are therefore drawing conclusions about the safety and effectiveness of GET for people who experience PEM, whilst being unable to determine how many of the participants in their sample actually experience PEM. Despite this, results of GET studies are routinely applied to people with ME/CFS, who do experience PEM.

5. GET studies frequently use only subjective measures to measure the results of GET. Such measures are subject to bias (especially when used in non-blinded trials). However, when objective measures (like actimeters or pedometers, 6 minute walk test, return to work or welfare rates) are used, results do not support the use of GET for ME/CFS, nor do they support the deconditioning model of ME/CFS. In other words, objective measures tend to show that GET does not result in increased activity levels (even though the deconditioning model would suggest that it should).
6. GET studies have been criticised for inadequate reporting of harm experienced from the intervention. Such inadequate reporting has led to the conclusion that GET is safe for people with ME/CFS, however patient reports tell a different story. Doctors and patients should be aware of the risk of GET worsening ME/CFS. Blanket recommendations of GET for ME/CFS are likely to be harmful.
7. The fear-avoidance/deconditioning model of ME/CFS has been dominant for decades, despite the flaws in the research on which it is based. As a result, ME/CFS is often seen as a non-permanent condition, that is treatable with GET, despite recovery rates from the condition being low, and there being no evidence of reversal of the condition following GET interventions. GET studies tend to include only participants with mild forms of ME/CFS, but GET interventions are recommended to patients regardless of their illness severity. All of this has implications for people seeking to access support services like Disability Support Pension (DSP) and National Disability Insurance Scheme (NDIS).
8. Exercise may be possible with ME/CFS, provided the program is based on an understanding of PEM, and includes appropriate safety measures. Very few (if any) GET programs include the sort of safeguards which are recommended. These “safe” exercise programs differ from GET in key ways:
  - a. They are based on the assumption that deconditioning is a consequence (not cause) of the condition.
  - b. They are intended as an adjunctive treatment. These exercise programs are a management approach to help improve functional strength, rather than an active treatment to address the underlying dysfunction.
  - c. They focus on building functional strength whilst avoiding triggering PEM, by remaining within the limits of a dysfunctional energy production system.
  - d. They encourage adequate rest both within and between exercise sessions. Heart rate monitoring is used within the session to ensure the patient stays below their anaerobic threshold and avoids PEM.
9. Given the evidence to support the physiological nature of PEM as a core feature of the condition, the risk of harm for people with ME/CFS from GET interventions, and the lack of evidence to support the effectiveness of the treatment, GET programs should not be considered an appropriate treatment for ME/CFS.

## 1. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) & Post-Exertional Malaise (PEM)

### Summary:

ME/CFS is a multi-system disease, with physiological abnormalities found in many body systems. PEM is considered to be the central feature of ME/CFS, and differentiates ME/CFS from idiopathic fatigue. PEM can be measured using a two-day CPET, which has been proposed as a diagnostic test, though it has a high risk of harm for patients.

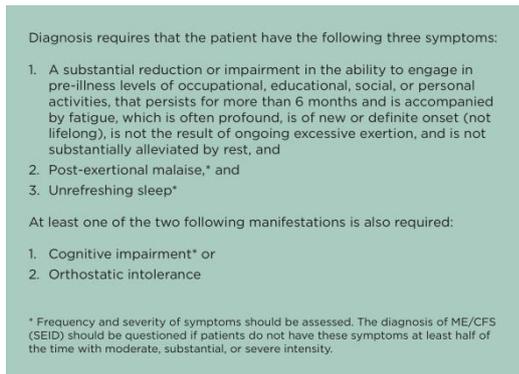
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a "serious, chronic, complex and multisystem disease that frequently and dramatically limits the activities of affected patients" (National Academy of Medicine, 2015a, p. 209). People with ME/CFS can be more impaired than people with heart disease, multiple sclerosis or kidney failure (Begg et al., 2007), with an estimated 25% of people with the condition who are bedbound or housebound (National Academy of Medicine). Prevalence rates vary, depending on whether studies utilise self report or clinical diagnosis, and depending on which diagnostic criteria are used. Conservative estimates range from 0.4-1.0% (Jason et al., 1999; Johnston, Brenu, Staines, & Marshall-Gradisnik, 2013; Lorusso et al., 2009), meaning that as many as 240,000 Australians may be affected by ME/CFS.

Whilst no definitive diagnostic biomarker has as yet been identified, physiological abnormalities have been observed in many different body systems, including the **central nervous system** (Ferrero, Silver, Cocchetto, Masliah, & Langford, 2017; Nakatomi et al., 2014; Natelson et al., 2017; Natelson, Weaver, Tseng, & Ottenweller, 2005; Schwartz, Komaroff, et al., 1994; Schwartz, Garada, et al., 1994; Shan et al., 2016; Zeineh et al., 2014), **autonomic nervous system** (Hoad, Spickett, Elliott, & Newton, 2008; Lewis, Pairman, Spickett, & Newton, 2013; Newton et al., 2007; Reynolds, Lewis, Richardson, & Lidbury, 2014; Schondorf, Benoit, Wein, & Phaneuf, 1999; Stewart, 2000; Streeten, Thomas, & Bell, 2000), **immune system** (Fletcher, Zeng, Barnes, Levis, & Klimas, 2009; Fletcher et al., 2010; Hornig et al., 2015; Klimas, Salvato, Morgan, & Fletcher, 1990; Maes, Twisk, Kubera, & Ringel, 2012; Nguyen et al., 2017; Siegel et al., 2006), **neuroendocrine system** (Allain et al., 1997; Chaudhuri, Majeed, Dinan, & Behan, 1997; Fuite, Vernon, & Broderick, 2008; Papadopoulos & Cleare, 2012), **energy production** (Armstrong, McGregor, Lewis, Butt, & Gooley, 2015; Armstrong et al., 2012; Fluge et al., 2016; Myhill, Booth, & McLaren-Howard, 2009; Naviaux et al., 2016), and **gastrointestinal system** (Armstrong, McGregor, Lewis, Butt, & Gooley, 2017; Giloteaux et al., 2016; Nagy-Szakal et al., 2017; Wallis, Butt, Ball, Lewis, & Bruck, 2016).

Post-Exertional Malaise (PEM), the exacerbation of all symptoms (including symptoms not normally found in healthy people following exercise) following exertion, is increasingly considered to be the cardinal symptom of ME/CFS (Agency for Healthcare Research and Quality, 2014; Chronic Fatigue Syndrome Advisory Committee, 2015, 2016; Jason et al., 2011; National Academy of Medicine, 2015a; Twisk, 2015), and that there is "sufficient evidence that PEM is a primary feature that helps distinguish ME/CFS from other conditions" (National Academy of Medicine, 2015a, p. 86). Prevalence estimates of PEM in people with ME/CFS range from 69-100% (Jason, et al., 2011; Kerr et al., 2010; Nacul et al., 2011).

In 2015, the US National Academy of Medicine (then the Institute of Medicine), following a review of the ME/CFS scientific literature, recommended changing the name of the illness to Systemic Exertion Intolerance Disease (SEID) (National Academy of Medicine, 2015a) to reflect the fact that PEM and exertion intolerance are core features of the condition. Dr Francis Collins (Director, US National Institutes of Health (NIH)) and Dr Walter Koroshetz (Director, US National Institute of Neurological Disorders and Stroke (NINDS), NIH) in the

March, 2017 edition of the NIH Director's blog on the topic of ME/CFS indicated that, "Any exertion just makes [people with ME/CFS] worse" (Koroshetz & Collins, 2017).



The US National Academy of Medicine's (2015a, b) recommended diagnostic criteria for ME/CFS also give prominence to PEM, which is one of the 3 required symptoms. The first symptom focuses on impairment accompanied by fatigue, rather than fatigue alone.

Image from US National Academy of Medicine (2015b, p. 3)

Key points about PEM:

- Triggered by physical, mental or emotional exertion.
- Exacerbation of all symptoms, including symptoms which do not normally follow exercise in healthy people (eg: sore throat, cognitive impairment, orthostatic intolerance, extreme exhaustion).
- Can have delayed onset (eg: up to three days).
- Can last for days, weeks or months (or even years, in extreme cases).

### Measuring PEM

The Cardio-Pulmonary Exercise Test (CPET) is a gold standard for measuring physical impairment and exercise intolerance (American Thoracic Society, 2003), as it is an objective measure, and can distinguish between lack of physical capacity and lack of conscious effort.

The two-day CPET is considered a robust and reliable measure of PEM (Snell, Stevens, Davenport, & Van Ness, 2013), and has been proposed as a possible diagnostic test for ME/CFS (Keller, Pryor, & Giloteaux, 2014). However, as it is risky for patients (some take months to recover) (National Academy of Medicine, 2015a), and only suitable for those with milder forms of the illness (Snell, et al.), it is not widely used for diagnostic purposes.

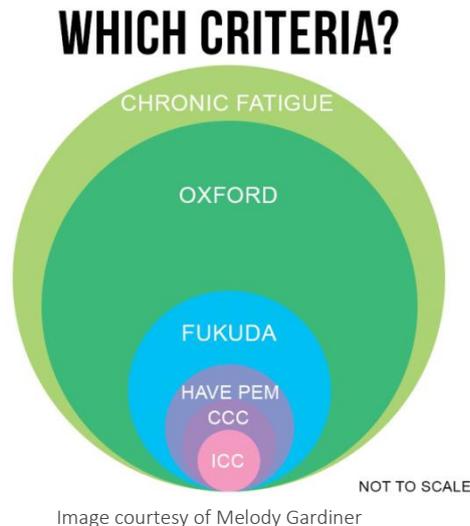
The two-day CPET consists of two maximal exercise tests, 24 hours apart. On the second day, people with ME/CFS are typically unable to perform to the same level as they did on the first day, which is considered to be an indicator of PEM (Snell, et al.; Twisk, 2015; VanNess, Snell, & Stevens, 2007). This pattern of results is not found in healthy, sedentary controls (Snell, et al.; Twisk).

In recent years, researchers have utilised **exercise provocation studies** to measure the effects of PEM in ME/CFS. Amongst the results, these studies have found **changes in gene expression** (Light, White, Hughen, & Light, 2009; Meyer, Light, Stegner, Shukla, & Cook, 2012; Meyer et al., 2013), **decreased cognitive functioning** (Blackwood, MacHale, Power, Goodwin, & Lawrie, 1998; Cook et al., 2017; LaManca et al., 1998; VanNess, Snell, Stevens, & Stiles, 2007), **altered immune response** (Nijs et al., 2005; Nijs et al., 2014), **decreased pain threshold** (Van Oosterwijck et al., 2010), **delayed muscle recovery** (Meeus et al., 2016; Paul, Wood, Behan, & Maclaren, 1999) and **changes in gut microbiome** (Shukla et al., 2015) in people with ME/CFS following exercise. As these changes are not found in healthy, sedentary controls, they are not considered to be simply due to deconditioning.

## 2. Diagnostic criteria

### Summary:

There are four main diagnostic criteria used in ME/CFS research. Not all require PEM for diagnosis. Studies which use the Oxford criteria may have few (or no) participants who experience PEM, and it has been recommended that these criteria no longer be used. The Canadian Consensus Criteria (CCC) and International Consensus Criteria (ICC) have been recommended for ME/CFS research, because these diagnostic criteria require PEM for diagnosis, and are more precise than other criteria.



Whilst there are several different diagnostic criteria for ME/CFS, four main diagnostic criteria are used in ME/CFS research:

- Oxford criteria (Sharpe et al., 1991)
- Fukuda (Centers for Disease Control (CDC)), (Fukuda et al., 1994)
- Canadian Consensus Criteria (CCC), (Carruthers et al., 2003)
- International Consensus Criteria (ICC), (Carruthers et al., 2011)

**Oxford criteria:** Only one symptom is required to meet the Oxford criteria for CFS: six months of unexplained fatigue. The Oxford criteria are so broad that two significant US reports recommended that the Oxford criteria no longer be used, due to its lack of specificity (Agency for Healthcare Research and Quality, 2014; National Institutes of Health, 2014), concluding that they pose "a high risk of including patients who may have an alternate fatiguing illness, or whose illness resolves spontaneously with time" (Agency for Healthcare Research and Quality, 2014, pp. ES-10) and that their continued use could "impair progress and cause harm" ((National Institutes of Health, p. 16).

**Fukuda (CDC) criteria:** The Fukuda criteria require 6 months of fatigue, plus 4 of the 8 symptoms below for a diagnosis of CFS. Whilst PEM is on the list of symptoms, it is not a required symptom:

- substantial impairment in short-term memory or concentration;
- sore throat;
- tender lymph nodes;
- muscle pain;
- multi-joint pain without swelling or redness;
- headaches of a new type, pattern, or severity;

- unrefreshing sleep; and
- post-exertional malaise lasting more than 24 hours.

**Canadian Consensus Criteria (CCC) & International Consensus Criteria (ICC):** Both the CCC and ICC have PEM as a required symptom. These criteria are also more specific than the Fukuda (Jason et al., 2012), and have been recommended for use in ME/CFS research (see submissions for the NIH's Request for Information (RFI)(National Institutes of Health, 2016), and the US CFS Advisory Committee (CFSAC) (Chronic Fatigue Syndrome Advisory Committee, 2015)).

### 3. Graded Exercise Therapy (GET) - diagnostic criteria and conflation of ME/CFS with “chronic fatigue”

#### Summary:

GET is a treatment intervention, commonly recommended to people with ME/CFS, which is based on the premise that ME/CFS is a condition driven largely by deconditioning from lack of activity. By gradually increasing activity, the assumption is that deconditioning can be reversed and the individual will return to health.

GET studies tend to focus on fatigue, not PEM, and use broad criteria, which do not require the presence or reporting of PEM. When excluding studies which used the broadest diagnostic criteria (Oxford) from a review of the evidence that GET is a beneficial treatment for ME/CFS, the US Agency for Healthcare Research and Quality (AHRQ) downgraded evidence for GET to insufficient in 2016. There are currently no GET studies which have used ME/CFS diagnostic criteria which require PEM for diagnosis. These studies are therefore drawing conclusions about the safety and effectiveness of GET for people who experience PEM, whilst being unable to determine how many of the participants in their sample actually experience PEM. Despite this, results of GET studies are routinely applied to people with ME/CFS, who do experience PEM.

Graded Exercise Therapy (GET) is an intervention commonly recommended as a treatment for ME/CFS (often in combination with Cognitive Behaviour Therapy (CBT)). GET is based on the fear-avoidance/deconditioning (or biopsychosocial) model of ME/CFS, which posits that the symptoms of ME/CFS are largely due to deconditioning (lack of fitness) and are perpetuated by a fear (and avoidance) of activity (Bavinton, Darbishire, & White, 2004; Burgess & Chalder, 2004). According to this model, too much rest will lead to further deconditioning and will result in the perpetuation (and exacerbation) of symptoms, and is thus discouraged (Bavinton, et al., 2004). GET is recommended based on the assumption that “increasing activity (behaviour) may gradually reduce the fear (cognitions) that activity leads to worsening of symptoms” (Burgess & Chalder, 2004, p. 13), and is intended to reverse the assumed deconditioning and allow the individual to return to health.

Proponents of the fear-avoidance/deconditioning model of ME/CFS focus on fatigue, rather than PEM, as the defining feature of the illness (Goudsmit & Howes, 2017), and often conflate ME/CFS with “chronic fatigue” or “chronic fatigue states” (eg: Sandler et al., 2016; Wearden et al., 2006). For example, Professor Peter White has said that the PACE trial (of which he was lead author) “does not purport to be studying CFS/ME but CFS defined simply as a principal complaint of fatigue that is disabling, having lasted six months, with no alternative medical explanation (Oxford criteria)” (Sense about Science USA, 2016), which differs significantly from the description of the illness by others (Agency for Healthcare Research and Quality, 2014; National Academy of Medicine, 2015a). Despite this, the results of these studies (including the PACE trial) are routinely applied to people with ME/CFS, for whom PEM is the key feature.

Studies of GET treatment for ME/CFS use broad diagnostic criteria (either the Oxford or Fukuda criteria), which do not require PEM for diagnosis. A recent Cochrane review, which concluded that GET is useful for ME/CFS, included just eight studies: five of which used the Oxford criteria and three of which used the Fukuda criteria (Larun, Brurberg, Odgaard-Jensen, & Price, 2017). However, in an addendum to its initial report, the AHRQ revisited the evidence for GET as a treatment for ME/CFS. After excluding studies which used the Oxford criteria (which it had recommended be retired from use), the AHRQ downgraded the evidence for GET from moderate to insufficient (Agency for Healthcare Research and Quality, 2016). The report also noted the absence of any exercise studies which used diagnostic criteria which include PEM as a mandatory symptom (such as the CCC or ICC), despite PEM being widely regarded as the cardinal feature of the condition. Extrapolating findings from people who do not experience PEM, to those who do, has the potential to cause enormous harm (Twisk & Arnoldus, 2012).

#### 4. GET studies - subjective outcome measures

##### Summary:

GET studies frequently use only subjective measures, which are subject to bias (especially when used in non-blinded trials). When objective measures are used, results do not support the use of GET for ME/CFS, nor do they support the deconditioning model of ME/CFS.

Studies which have reported positive results from GET frequently use subjective outcome measures. For example, in the well-known PACE trial, after a year of GET, results of the subjective (self-report) measures suggested that GET was superior to other treatments (White et al., 2011). Similarly, in a recent Australian study, participants' subjective ratings indicated an improvement of functioning following the GET intervention (Sandler, et al., 2016).

However, subjective outcome measures (especially in non-blinded trials, which all GET studies necessarily are) are at significant risk of bias (Hróbjartsson et al., 2013) and "Objective measures of physical activity have been found previously to correlate poorly with self-reported outcomes" (White, Goldsmith, Johnson, Chalder, & Sharpe, 2013, p. 2232). For example, Wechsler et al (2011), in a comparison of three treatments for asthma (albuterol, sham acupuncture or placebo inhaler), found that, based on patients' subjective reports, there were no significant differences between the three treatments, and an overall 45-50% improvement in asthma symptoms across all treatments. However, when using an objective measure (maximum forced expiratory volume in 1 second), albuterol was shown to result in significantly greater improvement (20%) than the other treatments (7%). The rates of improvement were also notably lower on the objective, compared with the subjective, measure. The authors concluded that patient self report is an unreliable measure.

With GET studies, whilst subjective outcome measures may yield positive results, when objective measures are used (eg: actimeters, step test, 6 minute walk test (6MWT), return to work rates, rates of accessing welfare), results generally show little or no improvement from GET. For example, results of the 6MWT in the PACE trial showed little functional improvement (White, et al., 2011). After a year of the exercise intervention, the average distance walked in the 6 minutes increased just 67m, to an average of 379m, which is comparable to that of someone with congestive heart failure (Rasekaba, Lee, Naughton, Williams, & Holland, 2009). The average results on the 6MWT for a healthy person (depending on age, gender, weight & height) is 500-700m (Rasekaba et al). There was also no significant improvement in a step test (Chalder, Goldsmith, White, Sharpe, & Pickles, 2015). The PACE trial authors did not include the results from either the 6MWT or the step test in their recovery measures. It is also worth noting that, at long term follow up (a minimum of two years after the beginning of the study), there were no significant differences between the treatment arms on subjective measures in the PACE trial (Sharpe et al., 2015).

Another UK study (known as the FINE trial) also found no significant differences between groups on a step test, after a GET intervention (Wearden & Emsley, 2013). A Belgian study found that, whilst self-reported levels of fatigue improved after the exercise intervention, the average performance on exercise tests did not change (Stordeur, Thiry, & Eyssen, 2008). This study also found a slight decrease in employment rates (from 18.3% to 14.9%) and a slight increase in the rate of accessing welfare payments (from 54% to 57%) at the end of the trial. This discordance between subjective and objective measures has been found in other GET studies (Stouten, 2017). Thus, whilst subjective measures may reflect a change in an individual's *perception* of what they are able to do (which is subject to bias), objective measures tend to highlight a discrepancy between this perception and the individual's *actual* functional capacity.

The fear-avoidance/deconditioning model of ME/CFS, though already largely discredited (Bazelmans, Bleijenberg, Van Der Meer, & Folgering, 2001; Goudsmit & Howes, 2017; Schmalings, Fiedelak, Bader, & Buchwald, 2005; Scroop & Burnet, 2004; Twisk & Maes, 2008), is further undermined by these results from objective outcome measures in GET intervention studies. If deconditioning were indeed a significant perpetuating factor in ME/CFS (which, arguably, it is not (Bazelmans et al)), then undergoing an exercise intervention should result in more improvement in objectively measured physical functioning than has been found. The use of subjective measures likely results in an overestimation of the effectiveness of GET interventions. These results also highlight the inadequacy of subjective measures in such non-blinded trials, and the need for objective measures to adequately assess the effectiveness of GET interventions (Edwards, 2017; Kewley, 2013; Lilienfeld, Ritschel, Lynn, Cautin, & Latzman, 2014; Stouten, 2017; Vink, 2017).

## 5. GET studies - harm inadequately reported

### Summary:

GET studies have been criticised for inadequate reporting of harm experienced from the intervention. Such inadequate reporting has led to the conclusion that GET is safe for people with ME/CFS, however patient reports tell a different story. Doctors and patients should be aware of the risk of GET worsening ME/CFS. Blanket recommendations of GET for ME/CFS are likely to be harmful.

GET studies have been criticised for failing to adequately report harm from exercise interventions (Agency for Healthcare Research and Quality, 2014; Kindlon, 2011, 2017; Vink, 2017). Additionally, the intervention protocols themselves are likely to discourage research participants from reporting harm, as participants are often encouraged to interpret symptom flares experienced during the study as a normal exercise response and reconditioning, rather than PEM. For example, the PACE trial GET manual (Bavinton, et al., 2004) indicates that “Participants are encouraged to see symptoms as temporary and reversible, as a result of their current physical weakness, and not as signs of progressive pathology. A mild and transient increase in symptoms is explained as a normal response to an increase in physical activity” (p. 20), that a “central concept of GET is to MAINTAIN exercise as much as possible during a CFS/ME setback” (p.51, emphasis in original) and that it “is important to explain that although they have an increase in difficult symptoms, ‘hurt does not equal harm’” (p. 51).

However, patient surveys routinely report adverse experiences from GET, suggesting that very often hurt does equal harm for people with ME/CFS. In such surveys, GET frequently ranks low on lists of treatments which patients have found helpful, and high on lists of treatments which patients have found harmful (Kirke, 2017). For example, the UK's ME Association's patient survey found that 74% of survey respondents reported harm from GET (Geraghty, Hann, & Kurtev, 2017; ME Association, 2015), a Norwegian survey reported two thirds of patients' surveyed reported harm from GET (as cited in Johnson, 2014), and preliminary analysis of an unpublished Australian study undertaken by Federation University (in partnership with Emerge Australia) in 2015, found that 89% of the 555 respondents indicated that increasing their level

of exercise/activity resulted in a worsening of their symptoms. It is worth noting that these percentages are similar to the prevalence estimates of PEM in the ME/CFS population.

Patients' stories of their experience with GET can be found [here](#) (#MEAction, 2015a) and [here](#) (Stop GET, 2017), as well as the story of a [professional ballet dancer's](#) experience with GET (van der Zee, 2017), (someone who could hardly be considered either deconditioned, or activity averse). Australian patients describe similar experiences:

*"The staff were lovely and worked very hard for me, so I always feel guilty saying anything negative about it. But my health declined while I was there. I was told during one appointment to maintain 4,000 steps a day and I thought it was too much. I said so at my next appointment and was told that whilst I may feel like it was too much and would make me worse, actually they have found that there aren't negative consequences if I push through. I did push through, and I think that has negative consequences."*

*"In 2010, I was diagnosed with CFS from [my doctor]. He sent me to [an exercise physiology clinic] and I saw [an exercise physiologist]. At that stage I was able to drive to appointments (often over 45 minutes each way). I was told to walk for 20 minutes per day. I went from being able to get out of the house, attend appointments and do my shopping to being completely housebound in two months. I ended up having to do Skype consults and it was then that [the exercise physiologist] realised I also had the symptoms of POTS [Postural Orthostatic Tachycardia Syndrome]. While I am no longer completely housebound, I have only regained 20% of my pre GET activity level. I can walk 50-100 meters, shower every 2-3 days and drive five minutes to our local shop for a coffee 2-3 times a week"*

*"I completed GET as an outpatient with an exercise physiologist claiming to be a specialist in CFS and POTS at [exercise physiology clinic] for 9 months. I was not recommended a heart rate monitor or to track my daily step count- it was me that decided on this. Over the 9 months my health progressively worsened from being told I should do more exercise and push myself. I wanted to believe I could exercise my way to full health like all the doctors kept telling me but this was not the case. I have been unable to work for 2.5 yrs now despite desperately wanting to work. And I have been predominantly house/couch bound and sometimes bed bound."*

*"Each time I have tried to increase my aerobic fitness, my fatigue and muscle pain increases. I have tried doing this incrementally, carefully and under appropriate supervision. Each time, at some point, although I manage to gain a small amount of muscle I don't increase my cardiac capacity and it has been followed by a crash that generally involves months in bed unless I back right off and rest."*

For this reason, several ME/CFS organisations (ME Association, 2008; The Grace Charity for ME, n.d.), international treatment recommendations (Franklin, n.d.; International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, 2014), the [New York State Health Department](#), as well as clinicians and researchers (Pierce & Pierce, 2008; Speight, 2011; Twisk & Maes, 2008; Twisk, 2017; Vink, 2017) have warned of the potential harm from GET for people with ME/CFS. In addition, in July 2017, the Centers for

Disease Control removed GET from its list of treatment recommendations for ME/CFS (Centers for Disease Control and Prevention, 2017). Whilst GET may be helpful for some, it is clearly harmful for a significant percentage of people with ME/CFS, as are blanket recommendations of GET as a treatment for this condition.

## 6 Consequences: ME/CFS is seen as treatable, and GET is the primary treatment

### Summary:

The fear-avoidance/deconditioning model of ME/CFS has been dominant for decades, despite the flaws in the research on which it is based. As a result, ME/CFS is often seen as a non-permanent condition, that is treatable with GET, despite recovery rates from the condition being low, and there being no evidence of reversal of the condition following GET interventions. All of this has implications for people seeking to access support services like Disability Support Pension (DSP) and National Disability Insurance Scheme (NDIS). GET studies include only participants with mild forms of ME/CFS, but GET interventions are recommended to patients, regardless of illness severity.

The dominance of the fear-avoidance/deconditioning model of ME/CFS persists, despite the mounting evidence that the condition is physiologically driven (National Academy of Medicine, 2015a). The flaws in GET research are beginning to be noticed in the broader scientific community (#MEAction, 2015b; Coyne, 2015; Edwards, 2017; Geraghty, 2016, 2017; Kerr, 2015; Laws, 2015; Lubet, 2017; Sense about Science USA, 2016; Tuller, 2015; Vink, 2017), including an open letter to Psychological Medicine signed by more than 140 ME/CFS scientists and organisations around the world calling for the retraction of one of the PACE trial papers due to the significance of its flaws (Ablashi et al., 2017). However, the model continues to form the basis of medical treatment for ME/CFS in many countries, including Australia. This is in spite of strong objections and criticism from ME/CFS researchers (Goudsmit & Howes, 2017; Twisk & Maes, 2008), clinicians ("*The whole idea that you can take a disease like this and exercise your way to health is foolishness. It is insane.*" Dr Paul Cheney, Invest in ME Conference, 2010), patient advocates (Mar, 2015) and ME/CFS organisations (ME Association, 2008),

GET is one of two primary treatments offered to people with ME/CFS (the other being CBT), here in Australia (Royal Australian College of General Practitioners, 2015), in the UK (National Institute for Health and Care Excellence, 2007; Turnbull et al., 2007) and elsewhere. Whilst most GET studies only include participants with mild forms of the illness (and often exclude those who are more severely ill) (Turnbull, et al., 2007), GET interventions are often recommended to people with ME/CFS, regardless of their illness severity. The evidence to support GET for people with even mild forms of the illness has been deemed insufficient (Agency for Healthcare Research and Quality, 2016), however 25% of people with ME/CFS are housebound or bedbound (National Academy of Medicine, 2015a), and there has been very little study of this more impaired cohort with regards to the effectiveness of (or harm from) GET interventions. Thus, the evidence to support the use of GET as an intervention with people with moderate to severe forms of the illness is almost non-existent. Any recommendations for GET for this more severely ill cohort, are not evidence-based.

Despite the fact that unemployment rates in the ME/CFS population are high (National Academy of Medicine, 2015a), and recovery rates are very low (Cairns & Hotopf, 2005; Hill, Tiersky, Scavalla, Laviertes, & Natelson, 1999; Jason, et al., 2011), ME/CFS is seen as a non-permanent condition by many in both the medical profession, as well as government agencies such as Centrelink and the National Disability Insurance Agency (NDIA). There are numerous anecdotal reports of people with ME/CFS being rejected from support services (such as the Disability Support Pension (DSP) or National Disability Insurance Scheme (NDIS)) because their condition is deemed to be treatable with exercise. There are also anecdotal reports of

individuals having to indicate that they had undertaken GET in order for their condition to be regarded as fully treated and stable, for purposes of eligibility for the DSP.

The following anonymous patient quotes highlight this issue:

*"My DSP was rejected as I hadn't done a program of support/seen a specialist and therefore I couldn't be considered as having my condition stabilised. It was mentioned to me by one Centrelink staff member that I could do a GET program... I started a new claim after doing the UNSW Fatigue Clinic GET CBT program and that helped a lot as it ticked their boxes about treatment requirements for considering your condition stabilised."*

*"My application was knocked back by the NDIS because they said the PACE trial proved that CFS was not "permanent."... At the time of my application I had suffered with CFS for 18 years straight."*

*"I was told by my [NDIS] assessor that he was knowledgeable about Down syndrome, autism and cerebral palsy and yet he was to assess me. Told me that CFSers didn't usually qualify. I happened to mention... not in answer to a question but just in passing that I am only well enough to shower once every three days and that I had walked to the end of my street maybe 3 times in the last 18 months. He was stunned and said incredulously "Wow, that's really serious"!!! At that point I knew I was in trouble... I am dependent on my 76 year old mother to be my full time carer, to cook, clean, shop and do everything else... drive me to appointments and she has no respite options. Honestly it's outrageous!! She is paying for my physio, chiro, doctor's fees, specialists, medicine, supplements etc and I've been sick for 17 years. I asked how disabled you have to be and [assessor] said "Well, we have paraplegics and blind people"."*

*"I just heard from the NDIA who have denied my claim based on the fact they have 'overwhelming evidence' that ME/CFS is not a permanent condition and can be effectively treated with 'sleep, proper diet, CBT and GET."*

*"I have been rejected by NDIS on the grounds that they didn't think ME is permanent, despite my doctors assuring them that it is. My doctor had ticked that I had done GET but I actually had only gone to a Physio for some stretching exercises that would leave me debilitated for 3 days and significantly worsened me for weeks. I could only attend every 3 weeks. I appealed my NDIS refusal and they are wanting more information from a rheumatologist who straight out said he couldn't help me with treatment at all. I'm hoping he will write me a supporting letter. Meanwhile this process has taken me over a year!"*

## 7. ME/CFS & 'safe' exercise

### Summary:

Exercise may be possible with ME/CFS, provided the program is based on an understanding of PEM, and includes appropriate safety measures as outlined. Very few (if any) GET programs include the sort of safeguards which are recommended.

There are some researchers & clinicians who are examining ways to address the need for exercise (to improve functional strength and counter any effects of secondary deconditioning which may occur in ME/CFS), in a way that is safe for people with ME/CFS, such that it doesn't trigger PEM (Klimas, 2014; Snell, Vanness, & Stevens, 2004; Vanness, 2014; VanNess, Snell, & Stevens, 2014).

This approach to safe exercise consists of:

- Wearing a heart rate (HR) monitor, to ensure that the HR stays within safe limits (below either the anaerobic threshold (if a CPET has been undertaken) or 50-60% maximum heart rate).
- Focusing on recumbent, anaerobic exercise (to build functional strength), rather than aerobic exercise (which is more likely both to result in the HR exceeding safe limits, and to trigger PEM).
- Exercising for very short sessions (initially no longer than 30 seconds), with significant rest afterwards (3-6 times the duration of the exercise session). Session duration may be even shorter, depending on illness severity (eg: for individuals who are severely ill, exercise may consist of lifting the head off the pillow, or rotating wrists, or even less, as necessary).
- Rest, which is an integral part of this approach to exercise. Rest is encouraged both during and after exercise sessions. Exercise is initially undertaken only twice weekly, to ensure several rest days between sessions.
- Unlike GET, where symptom exacerbation is often framed as a normal part of reconditioning, with this approach, the emphasis is for the individual to experience no symptom exacerbation after exercise. The amount of exercise (& frequency of sessions) is tailored to the individual's physical capacity and to ensure that PEM is not triggered.
- Unlike GET, pushing through is not advised with this approach to exercise. Morning Resting Heart Rate (MRHR) can be used as a proxy measure of PEM. When the MRHR is more than 10% above or below the individual's usual MRHR, the individual is advised to not exercise that day, but to rest instead.

This safe approach to exercise differs from GET in key ways:

- It assumes that deconditioning is a consequence (not cause) of the condition.
- It is an adjunctive treatment, a management approach to help improve functional strength, rather than an active treatment to address the underlying dysfunction.
- It is based on an understanding of PEM, with the intention of building functional strength whilst avoiding triggering PEM, by remaining within the limits of a dysfunctional energy production system.
- It encourages adequate rest both within and between exercise sessions. HR monitoring is used within the session to ensure the patient stays below their anaerobic threshold and avoids PEM.

## Conclusion & Recommendations:

Whilst PEM is considered the cardinal feature of ME/CFS, proponents of GET for ME/CFS instead tend to focus on fatigue, utilise broad diagnostic criteria (which do not require the presence of PEM) in their studies, and often conflate ME/CFS with chronic fatigue states. GET studies have been criticised for their reliance on subjective measures and inadequate reporting of harm. Objective outcome measures, when used, generally do not support the effectiveness of GET for ME/CFS. GET studies mostly only include participants with mild forms of the illness, and exclude those who are more severely affected. Despite this, GET has been routinely recommended to ME/CFS patients, regardless of illness severity, and continues to influence medical treatment of ME/CFS. This has contributed to the widespread notion that ME/CFS is non-permanent and treatable with GET, which impacts the ability of people with this debilitating condition to access support services such as DSP and NDIS.

Given the evidence to support the physiological nature of PEM as a core feature of the condition, the risk of harm for people with ME/CFS from GET interventions, and the lack of evidence to support the effectiveness of the treatment, GET programs should not be considered an appropriate treatment for ME/CFS.

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