Assessment of the Cochrane review into Exercise Therapy for Chronic Fatigue Syndrome

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Abridged Overview

The Cochrane review into exercise therapy for chronic fatigue syndrome relied on studies that used the Oxford and Fukuda Criteria to diagnose ME/CFS [1]. However, these criteria no longer provide a valid ME/CFS diagnosis in 2023 [4,5,6,7,8]. Furthermore, the Cochrane review and the reviewed studies are demonstrably compromised by inadequate ME/CFS diagnostic criteria, bias, low certainty evidence, methodological errors, statistical errors and misreporting [1,7]. Therefore, we strongly recommend that the RACGP disregard the Cochrane review and any study that uses the Oxford or Fukuda Criteria to diagnose ME/CFS.

This document explains how ME/CFS has been confused with depression and somatisation disorders and provides some guidance for differential diagnosis. It describes the defining feature of ME/CFS, post exertional symptom exacerbation, and explains how, by definition, graded exercise therapy is likely to harm people with ME/CFS [7,8,14,15,16,17,18,19].

The recommendations section offers principles and suggestions that will improve outcomes for Australians with ME/CFS. Key recommendations include the updating of the RACGP's diagnostic criteria to reflect more recent research, in line with the World Health Organisation and the US CDC Criteria [19,,23]; contraindication of graded exercise therapy for ME/CFS, as in the United States and the United Kingdom [16,17,19]; development and adoption of questionnaires and scales that will help GPs to diagnose ME/CFS; delivery of training and online resources for GPs; equitable research funding; and updated guidelines to ensure that people who have been severely disabled by ME/CFS receive acknowledgement and disability supports.

Overview

The RACGP is currently evaluating the *Exercise Therapy for Chronic Fatigue Syndrome* Cochrane review (Cochrane review). The RACGP's evaluation will influence RACGP policy on graded exercise therapy in ME/CFS. The current RACGP policy recommending graded exercise therapy in ME/CFS is controversial and the RACGP has received complaints stating that graded exercise therapy is harmful in ME/CFS. This document pinpoints the following flaws in the Cochrane review:

- The Cochrane review assesses eight studies of graded exercise therapy in people with chronic fatigue syndrome (CFS) [1]. Five of the studies used the Oxford Criteria, which do not exclude other sources of fatigue, such as heart disease, chronic obstructive pulmonary disease and cancer [1,2,4,7]. The Oxford Criteria have a false positive rate of over

90% [4]. Therefore, the results of Oxford Criteria studies are not relevant to people with ME/CFS.

- The remaining three reviewed studies used the Fukuda Criteria, or a questionnaire based on the Fukuda Criteria [1,27,28,29]. The Fukuda Criteria do not require the presence of the defining feature of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), post exertional symptom exacerbation [3,7,8,15,18,19]. Furthermore, the Fukuda Criteria allow the diagnosis of CFS in all people who have fibromyalgia or depression, but not ME/CFS [3] (see appendices A and B of this document). The Fukuda Criteria have a false positive rate of 42% [5,6]. Therefore, the results of these studies cannot validly be applied to people with ME/CFS.
- The International Consensus Criteria for ME/CFS diagnosis (ICC), Canadian Consensus Criteria, US Institute of Medicine's CDC Criteria and UK NICE guidelines recognise that **all people with ME/CFS experience post exertional symptom exacerbation** [5,8,15,16,18,19]. The Australian ME/CFS criteria also acknowledge post exertional symptom exacerbation [9]. Post-exertional symptom exacerbation is triggered by minimal physical or cognitive exertion, including the daily activities of life [8]. Post-exertional symptom exacerbation represents “extreme, prolonged exhaustion and sickness”, cognitive dysfunction and incapacity lasting days, weeks or more [8,9].
- By definition, post exertional symptom exacerbation predicts that people with ME/CFS will respond poorly to exercise, to the point of harm. Few graded exercise therapy studies have reported harm [1]. However, in those that have, between a third and 81% of participants reported adverse reactions to exercise [10,11,12,13].
- The Cochrane review did not acknowledge that post exertional symptom exacerbation has been found to be the defining feature of ME/CFS [1,2,7,8,15,18,19]; indicate that trials did not ensure that all participants had post exertional symptom exacerbation; or explain how participants with post exertional symptom exacerbation could possibly engage in exercise without being harmed.
- The Cochrane review's hypotheses did not consider the possibility that ME/CFS is indeed a neurological disorder, as specified by the World Health Organisation [23]. Neither did the Cochrane review consider that ME/CFS might be a systemic disease of physiological origin, as recognised by the International Consensus Criteria and the US Institute of Medicine's CDC Criteria [8,19], with cascades of abnormalities in neurological, immune, gastro-intestinal, genitourinary, cardiovascular and metabolic systems [8,43,44]. Consequently, the Cochrane review failed to identify and consider research papers that contradicted the premises of the graded exercise therapy studies or reported harms.
- The Cochrane review failed to recognise the selection bias that would inevitably arise when recruiting people with ME/CFS who, by definition, had post exertional symptom exacerbation [5,8,15,16,18], yet were willing to submit themselves to graded exercise therapy;

from a population of which 25% are housebound or bedridden [8]; in the presence of diagnostic criteria that did not uniquely select people who truly had ME/CFS.

- One of the Fukuda Criteria trials, Wallman et al., did not study graded exercise therapy, but, rather, pacing [29]. Therefore, Wallman et al. [29] cannot be used to support the use of graded exercise therapy in ME/CFS.

- A second Fukuda Criteria trial, Jason et al., studied graded exercise therapy combined with cognitive therapy [27]. Given that any experimental effects could have been due to the cognitive therapy, rather than the exercise therapy, this trial should not be used as evidence to support graded exercise therapy. As it happens, the exercise with cognitive therapy group showed no statistically significant improvements in fatigue, quality of life, pain interference or distance covered on a six-minute walking test; showed less improvement in depression, anxiety and self-efficacy than the relaxation condition; and failed to show a statistically significant improvement in physical functioning, compared to the relaxation group [27].

- The third Fukuda Criteria trial, Moss-Morris et al., misreported their results, claiming improvements in the graded exercise therapy group despite a deterioration in their objective measure, VO_2 peak [28].

- The Cochrane review acknowledged that all studies had a high risk of performance and detection bias 1. Given the reviewed studies' reliance on subjective measures, rather than the available physiological measures, the studies were also highly vulnerable to response bias and allegiance bias.

- Graded exercise therapy actively encourages people to disregard their physical symptoms [9]. It follows, therefore, that participants' subjective self-report symptom scores will improve after graded exercise therapy. Indeed, some studies' outcome measures showed these improvements [1]. However, physical functioning and objective measures showed no effects or a decline in functioning [1,27,29]. Nevertheless, study authors used the improvement in subjective measures to recommend graded exercise therapy, despite objective evidence to the contrary. This selective, misleading interpretation of results suggests bias and misreporting. Indeed, the Cochrane review acknowledged that reporting bias may have been a problem in six of the eight reviewed studies, including all three Fukuda Criteria studies (p24) [1].

- The reviewed papers did not adjust for type one error inflation. Had they done so, it is unlikely that post-treatment improvements in the outcome variables would have been statistically significant.

Therefore, the Cochrane Review [1] cannot be considered to support graded exercise therapy for people with ME/CFS [7]. Furthermore, given the harm reported by people with ME/CFS in response to exercise [10,11,12,13], the RACGP cannot justifiably or ethically recommend graded exercise therapy for ME/CFS. Rather, the evidence indicates that the RACGP should follow the example of the UK's NICE guidelines [16,17] in contraindicating graded exercise therapy for people with ME/CFS.

This document outlines problems in the diagnosis and management of ME/CFS in Australia and makes recommendations to improve outcomes for people with ME/CFS.

The importance of diagnostic criteria

Diagnostic criteria reflect the current understanding of a disease. Until 2003, ME/CFS was poorly understood, such that the diagnostic criteria did not require the presence of the key feature of the disease, post exertional symptom exacerbation [7,8,14,15,18,19].

ME was first mis-labelled as hysteria by McEvedy in 1970, on the basis of “only the most cursory examination of medical records” [14,25]. Despite the poor quality of evidence to support his judgement, McEvedy's opinion was influential [14,25,43].

The introduction of “fatigue” to the chronic fatigue syndrome case definition in 1988 launched several decades of confusion [14]. Mistakes were circulated in documents for general practitioners and policy makers, and this led to the diagnosis of CFS in any patient with long-term fatigue, including patients with cancer, chronic obstructive pulmonary disease and depression [14].

Oxford Criteria

The 1991 Oxford Criteria [2] reflected the confusion of long-term fatigue with CFS. The Oxford criteria did little more than to identify long-term fatigue of any origin [2,4,5]. Baraniak [4] found that “...Studies using the Oxford Criteria have investigated largely mild fatigue and recruited fewer than 10% of 'true' CFS subjects. In Baraniuk's 2017 study, “over 90% of Oxford CFS subjects were false positives” (p6, paragraph 4) [4]. Furthermore, one quarter of Oxford-defined ME/CFS cases have been found to be healthy adults [4].

False positives occur because the Oxford Criteria require only fatigue, without the necessary presence of additional symptoms such as cognitive dysfunction or pain [2]. Importantly, the Oxford Criteria do not require post exertional symptom exacerbation, which is the defining feature of ME/CFS [2,7,8,15,18,19]; and do not exclude other fatiguing health conditions, such as depression, anxiety, fibromyalgia. autoimmune conditions, cancer or chronic obstructive pulmonary disease [2,8].

To demonstrate the inability of the Oxford Criteria [2] to distinguish between ME/CFS and other conditions, the tables in appendices A and B cross reference the symptoms of depression and fibromyalgia, respectively, with CFS as defined by the Oxford Criteria. The tables show that people with depression and fibromyalgia qualify for a CFS diagnosis under the Oxford Criteria. To be clear, the Oxford Criteria do little more than to identify people with long-term fatigue. Given the Oxford Criteria's false positive rate of over 90% [4], studies that rely on the Oxford Criteria cannot be applied to people with ME/CFS. Therefore, five of the eight studies reviewed by the Cochrane review [1] must be disregarded. This removes Fulcher and White (1997), Powell (2001), Wearden (1998), Wearden (2010) and White (2011) from consideration [1].

Fukuda Criteria

The 1994 Fukuda Criteria acknowledged that people with CFS may experience prolonged recovery from minimal exercise, known as post exertional malaise or post exertional symptom exacerbation [3]. However, the Fukuda Criteria did not require the presence of this symptom[3,15]. Consequently, like the Oxford Criteria, the Fukuda Criteria failed to differentiate between CFS and several other sources of long-term fatigue. For example, the Fukuda Criteria do not exclude non-psychotic, non-melancholic major depressive disorder or fibromyalgia [3].

Canadian Consensus Criteria, International Consensus Criteria, CDC Criteria and Post-exertional Symptom Exacerbation

In 2003, the Canadian Consensus Criteria acknowledged “post exertional malaise” as the defining feature of ME/CFS, making it a mandatory criteria for diagnosis [15,18]. In confirmation, the 2011 International Consensus Criteria (ICC) [8] and 2015 US National Academy of Medicine, previously called the Institute of Medicine, CDC Criteria [19] recognised post exertional symptom exacerbation as the cardinal feature of ME/CFS. Symptom exacerbation includes “acute, flu-like illness, pain and worsening of other symptoms” lasting for days, weeks or longer, that may occur in response to mild physical or cognitive exertion, including the daily activities of living [8].

Post exertional symptom exacerbation decreases functional ability and forces individuals with ME/CFS to restrict, reduce, and/or modify activities to avoid suffering amplified symptoms [8,15]. For many people, post exertional symptom exacerbation is incapacitating [8,15]. On average, symptom exacerbation lasts for 14 days [18]. However, about 10% of people with ME/CFS take longer than three weeks to recover [18]. In contrast, age- and gender-matched sedentary controls without ME/CFS recover within two days [18].

The US National Institutes of Health have directed researchers to use diagnostic criteria that require post exertional malaise [15]. However, many researchers have failed to do this.

In the last 20 years, research has identified cascades of physiological abnormalities in the immune, cardiovascular, aerobic, metabolic, gastrointestinal and neurological systems of people with ME/CFS [14,20,43]. Notably, these abnormalities cannot be explained by deconditioning [14,21,22].

Consequently, in addition to post exertional symptom exacerbation, diagnosis under the ICC requires the presence of neurological impairments; immune, gastro-intestinal and genitourinary Impairments; and energy production⁄ transportation impairments [8]. Other fatiguing illnesses are excluded, together with primary psychiatric disorders, somatoform disorder and substance abuse [8].

The disease specified by the ICC [8] is clearly very different to the fatigue of any origin as described by the Oxford Criteria [2,4]. Furthermore, the ICC are more specific than the Fukuda Criteria [3,5,6].

False Positive Rates in the Fukuda Criteria

The Fukuda Criteria have been criticised for ambiguity in the symptom severity required for diagnosis [6]. In fact, the Fukuda Criteria have been found to diagnose CFS in 15% of healthy adults[5]. Comparing the prevalence rates under different diagnostic criteria, 0.19% of the UK population meet the Fukuda Criteria, while 0.11% meet the stricter Canadian Consensus Criteria[6]. This suggests that only 58% of Fukuda-defined CFS cases meet ME/CFS criteria that require the presence of post exertional symptom exacerbation.

Similarly, Brown et al. found that only 74 of 114 Fukuda-defined cases (65%) met the stricter ICC[5], which require the presence of post exertional symptom exacerbation. However, due to the use of incomplete historical data, Brown et al.'s participants were only required to meet two criteria, rather than the three criteria required by the ICC [5]. Therefore, the percentage of Fukuda-defined cases that also meet the ICC criteria is likely to be closer to Baraniuk's 58% [6]. In other words, it has now become clear that around 42% of Fukuda-defined cases are false positives.

Having excluded the five Oxford criteria studies, only three Cochrane reviewed studies remain (Jason et al. (2007)[27], Moss-Morris et al. (2005) [28] and Wallman (2004)) [29]. Two of these studies used the Fukuda Criteria [28,29] and the remaining study used a questionnaire based on the Fukuda Criteria [27]. Given the Fukuda Criteria's 42% false positive rate [6], the results of these three remaining studies cannot validly be applied to people with ME/CFS. Consequently, the Cochrane review cannot justifiably be used as the basis for recommending graded exercise therapy in ME/CFS.

It is worth noting that all of the Cochrane reviewed studies predated the 2011 International Consensus Criteria and the Institute of Medicine's recognition of post exertional symptom exacerbation as the cardinal feature of ME/CFS in 2015 [1,8,19]. Presumably, most researchers have recognised that it makes no sense to recommend graded exercise therapy in the presence of post exertional symptom exacerbation. Furthermore, informed ethics boards would not approve such research, due to obvious risk of harm.

Australian Criteria

In 2018, the Australian Medical Association (AMA) updated Australia's ME/CFS diagnostic criteria from the Fukuda CFS Criteria to the US National Academy of Medicine's CDC criteria [19]. However, the RACGP's graded exercise therapy web page still refers to the Fukuda Criteria [9]. As explained above, the Fukuda Criteria show a false positive rate of 42% [6]. As shown in Appendix B, the Fukuda Criteria are not specific enough to separate true ME/CFS patients with post exertional symptom exacerbation from people with fibromyalgia, depression and a range of other conditions.

Unlike the Fukuda Criteria, the CDC Criteria require the presence of post exertional symptom exacerbation [3,9,19]. Post exertional symptom exacerbation, the defining feature of ME/CFS, separates ME/CFS from other illnesses [7,8,15,18,19]. This is important, because, as explained below, ME/CFS, fibromyalgia and depression require markedly different management. Therefore, it is vital that the RACGP update their website to refer to the CDC Criteria, rather than the Fukuda Criteria.

Post Exertional Malaise and Graded Exercise Therapy

Fibromyalgia is a pain disorder with debilitating fatigue. Patients respond well to exercise [31].

Major depressive disorder is a mood disorder. Patients respond well to exercise [32].

ME/CFS is a systemic neurological disorder (ICD-11) [23]. The defining feature of ME/CFS is post exertional symptom exacerbation [7,8,15,18,19]. By definition, post exertional symptom exacerbation predicts a negative response to graded exercise therapy in people with ME/CFS.

Moore et al. observed that post exertional symptom exacerbation lasts for an average of two weeks in ME/CFS [18]. The paper concluded that “graded exercise therapy would almost certainly cause harm.” [18] Furthermore, studies that have measured harm have reported that between a third and 81% of participants with CFS experienced extended, adverse responses to exercise [7,11,12,13,16,17,18,24]. Consequently, the UK's NICE guidelines and the CDC have already withdrawn graded exercise therapy as a treatment for ME/CFS [15,16,17].

The RACGP's web page (https://www.racgp.org.au/clinical-resources/clinical-guidelines/handi/handi-interventions/exercise/graded-exercise-therapy-chronic-fatigue-syndrome) acknowledges the presence of “post exertional malaise, where physical or mental exertions bring on ‘extreme, prolonged exhaustion and sickness'” [9]. By definition, therefore, it is nonsensical to recommend graded exercise therapy to people with ME/CFS. To be clear, patients who show only “a mild and transient increase in symptoms” [9] in response to exercise do not have ME/CFS [8,15,18,19].

Differential Diagnosis

Fibromyalgia, major depressive disorder and ME/CFS have a large symptom overlap. However, Australian GPs are not trained to perform a differential diagnosis [25]. Around a third to a half of GPs do not recognise ME/CFS as a genuine clinical entity, and most of the remainder lack confidence in diagnosing or managing it [25]. Furthermore, 82% of doctors believe that ME/CFS is partly or wholly a psychological condition [26]. Given that the rigorous ICC specifically exclude primary psychiatric conditions [8], this indicates a great problem in Australia's health care system.

By sometimes using the Fukuda Criteria, which do not require the presence of post exertional symptom exacerbation, an Australian ME/CFS diagnosis does not select a homogenous set of patients [3,5,6]. “Patient sets that include people who do not have the disease lead to biased research findings, inappropriate treatments and waste scarce research funds” (ICC, p 328) [8]. It is, therefore, important to update the ME/CFS diagnostic criteria on the RACGP website [9], in line with the last two decades of research, to the AMA-validated CDC Criteria, which require the presence of post exertional symptom exacerbation.

Updated diagnostic criteria would help to address the disbelief and lack of diagnosis experienced by almost 40% of ME/CFS patients from their GPs [25]. Pheby et al. reported that “uninformed, negative, or hostile attitudes to people with ME/CFS from healthcare professionals were… detrimental to health and well-being, and could deter them from seeking treatment.” [25]. Updated diagnostic criteria would support GPs in acknowledging the severity of ME/CFS and differentiating ME/CFS from depression, fibromyalgia and psychosomatic problems. To this end, GPs would benefit from the development, validation and adoption of ME/CFS questionnaires and scales, such as the DePaul Symptom Questionnaire's Post-Exertional Malaise subscale [33], combined with assessment of increased immune abnormalities, sleep dysfunction and pain after exercise [45].

Three-quarters of GPs recognise the need for better information and training about the diagnosis and treatment of ME/CFS, and the availability of local services [25]. This suggests that there is a great need for an active education campaign for GPs, and the development of online resources [34].

Critical Analysis of the 2019 *Exercise Therapy for Chronic Fatigue Syndrome* Cochrane Review

Introduction

The following sections identify methodological errors and many sources of bias in the 2019 *Exercise Therapy for Chronic Fatigue Syndrome* Cochrane Review and the reviewed papers; and assess whether the Cochrane review does truly support exercise therapy in ME/CFS.

Diagnostic Criteria in the Papers Reviewed by the Cochrane review

Five of the eight studies in the Cochrane review relied on the Oxford Criteria to diagnose ME/CFS [1]. As stated above, the Oxford Criteria do little more than to identify people with long-term fatigue [2,4]. Over 90% of the participants in the Oxford Criteria trials are unlikely to have had ME/CFS [4]. Therefore, the results of these studies cannot be considered to apply to people with ME/CFS, and the results should be disregarded. Removing the Oxford Criteria trials from consideration reduces the number of participants in the Cochrane Review's graded exercise therapy trials from 870 to 200, 82 of which underwent graded exercise therapy, with or without pacing [1,27,28,29].

The Cochrane review states that two of the eight reviewed studies used the CDC Fukuda Criteria[1,28,29]. In fact, the remaining study, Jason et al., used a questionnaire based on the Fukuda Criteria [27]. As stated above, 42% of Fukuda-defined CFS cases are unlikely to have ME/CFS [6]. Therefore, the Fukuda studies should also be disregarded.

Furthermore, the Cochrane review included studies if at least 90% of the participants had been diagnosed with ME/CFS [1]. Even if we were to overlook the inadequate diagnostic criteria used in the trials, there is a risk that the undiagnosed 10% of participants skewed the results. To be clear, it is essential that 100% of ME/CFS trial participants have been diagnosed using stringent criteria, such as the ICC, that require the presence of post exertional symptom exacerbation.

In summary, over 90% of the 670 Oxford Criteria participants and 42% of the 200 Fukuda Criteria participants in the Cochrane review are **unlikely to have had ME/CFS** [4,6]. The conflation of ME/CFS, long-term fatigue, depression and other fatiguing disorders confounds the reviewed studies. It is vital that studies using the Oxford and Fukuda Criteria be excluded from future ME/CFS reviews. Any unpublished data from Oxford and Fukuda Criteria trials should also be disregarded.

Definition of Graded Exercise Therapy

As stated by the RACGP's own web page [9], graded exercise therapy encourages patients to “see symptoms as temporary and reversible, as a result of the 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.” However, one of the Fukuda Criteria trials, Wallman et al., reduced or ceased physical activity in response to increased symptoms [29]. Graded exercise therapy encourages patients to disregard increased symptoms and continue exercising [7,9]. Therefore, despite the paper's title - *Randomised controlled trial of graded exercise in chronic fatigue syndrome* - Wallman et al. was **not** a study of graded exercise therapy[29]. It was, rather, a study of pacing. Consequently, Wallman et al.'s results cannot be taken as evidence to support graded exercise therapy in people with ME/CFS. The Wallman trial contained 61 particpants [29]. Excluding these participants from the Fukuda Criteria sample leaves 139 participants, 50 of whom underwent graded exercise therapy.

Jason et al.'s graded exercise therapy group underwent a combination of graded exercise and cognitive therapy [27]. Jason et al.'s results cannot be taken to support graded exercise therapy alone, because any change in outcome measures may have been due to the cognitive therapy rather than the graded exercise therapy. Excluding these participants from the Fukuda Criteria sample leaves the 49 participants in the Moss-Morris et al. study, 25 of whom underwent graded exercise therapy [28].

Likely Affects on Results in Mixed Participants With and Without ME/CFS

Participants without ME/CFS are likely to show improvements with graded exercise therapy. However, post exertional symptom exacerbation predicts that participants with ME/CFS will deteriorate or fail to improve with graded exercise therapy.

The combination of participants with and without true ME/CFS is unlikely to have had a large affect on the Oxford Criteria trial results, because fewer than 10% of the Oxford Criteria trial participants are likely to have had true ME/CFS [4]; participants with post exertional symptom exacerbation are likely to have shown a high dropout rate; and the remaining true ME/CFS participants are likely to have remained hidden in the tails of a normal distribution, or been excluded from the analysis as outliers.

However, around half of the Fukuda Criteria trial participants may have had true ME/CFS [5,6]. Therefore, we would expect to see bimodal distributions in the graded exercise therapy groups' results. Most statistical tests require that the data are normally distributed, and it is important that researchers report whether their data showed a normal distribution. Neither Jason et al. nor Moss-Morris et al. did this [27,28]. Therefore, their results may have been statistically invalid.

Wallman et al. reported that all continuous variables were normally distributed (p446) [29]. However, the resting heart rate, depression, anxiety, fatigue, Stroop test and clinical global impression change scores were not continuous variables [29]. If the assumptions of the statistical tests on these variables were violated, their results for these variables were statistically invalid.

When distributions are adequately reported, standard deviation may give a clue as to whether graded exercise therapy caused both deterioration and improvement. A high standard deviation indicates a high variability in outcomes. Jason et al. did not report post-treatment standard deviations [27]. However, their graded exercise therapy with cognitive therapy group showed increased standard deviations at one year, compared to pre-treatment, on all measures [27]. Notably, the standard deviation for the distance walked in a six minute walking test was twice as high twelve months after the treatment (M = 1542.60, SD = 634.11) compared to before the treatment (M = 1346.35, SD = 296.76) [27]. Moss-Morris et al. reported increased standard deviations for fatigue, physical functioning and heart rate in the paced exercise group [28]. Wallman et al. did not report standard deviations [29].

Given the inadequate reporting of distributions and standard deviations, it is unclear whether the three Fukuda Criteria trials' results and conclusions were valid.

Selection Bias

On page 2 of the Cochrane review, the authors state, “most studies had a low risk of selection bias" [1]. However, this cannot be true. One quarter of people with ME/CFS are housebound or bedridden [19,30]. It follows, therefore, that one quarter of the ME/CFS population was excluded from the trial; and that the results of graded exercise therapy trials cannot be generalised to people with severe ME/CFS.

Furthermore, it is likely that many people with moderate ME/CFS (mostly housebound) refused to participate, understanding post exertional symptom exacerbation and the risks of exposing themselves to exercise programs run by people who do not understand post exertional symptom exacerbation.

Doctors who understand ME/CFS, and post exertional symptom exacerbation in particular, are unlikely to recommend their patients for a graded exercise therapy trial.

Researchers who understand ME/CFS will not conduct graded exercise therapy trials, due to the high risk of harm from post exertional symptom exacerbation.

The above sources of selection bias, together with the high false positive rates of the Oxford and Fukuda Criteria [4,5,6], suggest that few of the reviewed study participants are likely to have had ME/CFS, and none are likely to have had severe or very severe ME/CFS.

Performance and Detection Bias

The Cochrane review reported that "All [studies] had a high risk of performance and detection bias", because they were unblinded [1]. In unblinded studies, it is common for the experimental group to receive different care than the control group. Difference in care can influence the outcome measurements. For example, the Moss-Morris et al. control group appears to have had no contact with the researchers, apart from filling in the outcome measurement scales [28]. However, the Moss-Morris treatment group met weekly to "assess progress, provide encouragement and set new exercise goals." (p 249) [28]. It is entirely possible that the support provided to the treatment group influenced the outcomes.

Response Bias

Although the Cochrane review did not explicitly mention response bias [1], the reviewed studies were all vulnerable to response bias. Response bias can occur when participants are eager to give the response desired by the experimenters [38]. The participants in many of the studies had regular contact and guidance from nursing staff and therapists [27,28,29]. The development of positive ongoing relationships between participants and staff increases the risk of response bias[38]. Given that many of the reviewed studies' treatment groups had regular contact with therapists, while the control groups did not, the improvement in treatment group scores may reflect positive relationships with the researchers and therapists, rather than an improvement in CFS symptoms.

Graded exercise therapy encourages participants to dismiss their symptoms [9]. Therefore, the studies encouraged participants report an improvement, regardless of symptom exacerbation. Given that the reviewed studies relied on subjective measures, improvements in outcome measurements may simply suggest that the studies induced participants to report differently.

Reporting Bias

Page 24 of the Cochrane review suggests that 6 out of the 8 included studies may have reported their results selectively, in order to confirm their hypothesis [1]. This includes the three Fukuda Criteria studies [1].

Some trials under-reported results that did not support their hypothesis. For example, Moss-Morris et al. briefly stated that there was no statistically significant change in SF-36 physical functioning scores during the trial [28]. The authors then focused on retrospective self-rated improvement scores, using these to claim that graded exercise therapy was an effective treatment for ME/CFS [28]. Clearly, if this were true, the participants' physical functioning would have improved. Rather, the contrast between the physical functioning and retrospective self-rated improvement scores frames this study as a demonstration of response bias and misreporting.

Publication Bias

The Cochrane review may have failed to find graded exercise therapy trials that did not support graded exercise therapy for people with ME/CFS, due to the widely recognised unwillingness of journals to publish null results. The Cochrane review acknowledged that publication bias might affect their review, but found too few relevant studies to run an analysis that might identify publication bias [1].

Confirmation Bias

Confirmation bias was evident in the Cochrane review on p17 [1]: The hypotheses favoured the view that ME/CFS is essentially a psychological condition, caused by deconditioning; and excluded from consideration the hypothesis that ME/CFS is indeed a neurological condition, as per the World Health Organisation's ICD-11 [1,23]. This problem may have occurred because the authors focused the literary search on ME/CFS, exercise and relaxation (p 19) [1]. Most exercise and CBT studies contain an implicit bias towards the belief that ME/CFS is caused by deconditioning [7]. This bias may have been transferred to the Cochrane review because the authors failed to research the nature and physiological markers of ME/CFS. Had they done so, they would have learnt about post exertional symptom exacerbation, broken ATP cycles, neuroimmune activation, autoimmunity, T cell exhaustion, inflammation, impeded calcium flux in and out of cells, mitochondrial damage, reduced oxygen uptake by muscle cells, orthostatic intolerance and much more. It is essential that future reviewers fully research ME/CFS. This will give them a better understanding of the true nature of ME/CFS and the flaws in most graded exercise therapy studies.

Allegiance bias describes the influencing of subjective outcome measures by researcher bias [7]. Seven of the eight reviewed studies were run by researchers with an alliance to graded exercise therapy [7]. Notably, Jason et al., the only study run by researchers with no allegiance, found that graded exercise therapy failed to exceed relaxation at a level that was both statistically and clinically significant(p289) [27].

The Cochrane review did consider the possibility of adverse reactions to exercise (p2) [1]. However, the reviewed studies did not measure or report adverse reactions [1]. Furthermore, the Cochrane review did not look for studies that reported harm [1]. This oversight constitutes a major failure on the part of the Cochrane review to ensure the safety of people with ME/CFS.

The Cochrane review's authors observed that Jason et al.'s relaxation group reported greater physical functioning improvements than their exercise group [1]. The authors then excluded Jason et al.'s physical functioning scores from meta analysis, due to “very large baseline differences in physical functioning between the exercise and relaxation groups (39/100 versus 54/100)” (p27)[1]. However, the low 39/100 anaerobic exercise score was of no interest to the Cochrane review, because graded exercise therapy (46/100) was the subject of the review, not anaerobic exercise. Perhaps the decision to exclude Jason et al.'s physical functioning scores was still justified. However, in comparison, Moss-Morris et al.'s results were confounded by a 9-year mean age difference between the exercise and relaxation groups (p250) [28]. Moss-Morris et al. acknowledged correlations between age and physical functioning, mental fatigue and physical fatigue [28]. Yet, the Cochrane review did not exclude the Moss-Morris et al. results from meta-analysis [1]. This differential treatment of studies that supported graded exercise therapy, compared to those that did not, may suggest bias on the part of the Cochrane review's authors.

Unreliable Fatigue Measures

The defining feature of ME/CFS is post exertional symptom exacerbation. Yet no studies used post exertional symptom exacerbation as an outcome measure [1]. Rather, studies favoured self-report fatigue scales, which are vulnerable to demand bias, acquiescence bias and allegiance bias [38]; show ceiling and floor effects in people with ME/CFS [46]; and have questionable reliability and validity in people with ME/CFS [46]. Furthermore, the Chalder Fatigue Scale used by several of the reviewed studies makes time-based comparisons such as “Do you have less strength”, “Do you think as clearly as usual” and “Do you find it more difficult to find the correct word?” [1,39]. These comparisons are meaningless for people who have had ME/CFS for many years – or decades – because it is normal to feel weak and fatigued, and to have difficulty thinking or finding words. Therefore, these scales are likely to underestimate fatigue.

Non-measurement of Harm

The current diagnostic criteria for ME/CFS require the presence of post exertional symptom exacerbation. Post-exertional symptom exacerbation is a long-lasting, disproportionate increase in symptoms in response to exertion; exertion may be minimal. Therefore, it is essential for graded exercise therapies in people with ME/CFS to measure harm. Yet, none of the studies reviewed by the Cochrane review did this [1]. The lack of harm measurement represents a blind spot in graded exercise therapy research. It is important that ethics boards do not approve such studies in people with ME/CFS unless harm is measured; and treatment is reduced or ceased in response to post exertional symptom exacerbation. Without these measurements, people with ME/CFS remain unvalidated by the medical community [48]; disadvantaged by research bias [47]; exposed to stigma, discrimination, gaslighting and abuse [47,48]; and denied financial, medical and disability support [48].

WHODAS 2.0

The World Health Organisation's Disability Assessment Schedule (WHODAS 2.0) [49] is the most accurate measure of incapacitation caused by ME/CFS. However, none of the studies used it. Most functional scales measure ability to perform a task. However, the WHODAS 2.0 takes into account the consequences of performing a task, including increased pain, fatigue, cognitive problems and a reduced capacity to perform other tasks [49]. Given that post exertional symptom exacerbation is the defining feature of ME/CFS, scales that do not take post exertional symptom exacerbation into account cannot measure the disability caused by ME/CFS and cannot validly measure improvement during a graded exercise therapy trial. The WHODAS 2.0 [49] stands out in its ability to measure the functional effects of post exertional symptom exacerbation. Therefore, if ME/CFS treatment trials require a self-report functional capacity measure, the WHODAS 2.0 [49] is the measure to choose.

A Further Look at the Reviewed Studies

Given that under 10% of Oxford-defined CFS cases have ME/CFS, the five Oxford Criteria studies can be disregarded from further consideration, namely Fulcher(1997), Powell (2001), Wearden (1998), Wearden (2010) and White (2011) [1]. The remaining (Fukuda Criteria) studies are examined below. If required, a more detailed analysis of the Cochrane Review and reviewed studies is provided by Vink and Vink-Neise [7].

Jason et al.

Jason et al. compared cognitive therapy; anaerobic activity; active relaxation; and graded exercise therapy combined with cognitive behavioural therapy in people with ME/CFS [27]. According to Vink and Vink-Niese, Jason et al. were the only researchers with studies reviewed by the Cochrane review who had no bias towards graded exercise therapy [7].

- The study screened participants with a questionnaire that was based on the Fukuda (1994) criteria. As explained above, the Fukuda Criteria do not require the presence of post exertional symptom exacerbation [3], the defining feature of ME/CFS [7,8,15,18,19]. Therefore, participants may not have had ME/CFS as defined by the stricter ICC [8] and more recent research [7,8,15,18,19].
- The researchers did not exclude participants with non-melancholic, non-psychotic depression and fibromyalgia [27]. As explained earlier, there is large overlap between the symptoms of depression, fibromyalgia and ME/CFS, and it is easy to confuse the conditions. However, ME/CFS reacts differently to exercise than fibromyalgia and depression [7,11,12,13,16,17,18,24,31,32]. Therefore, it is essential that graded exercise therapy researchers exclude people who have depression and fibromyalgia, and not ME/CFS, from ME/CFS studies.
- Jason et al.'s graded exercise group underwent graded exercise therapy in combination with cognitive therapy [27]. Therefore, experimental effects could be due to the cognitive therapy rather than than the exercise therapy. Consequently, Jason et al. cannot be used to support graded exercise therapy in ME/CFS.

- The study excluded people in wheelchairs and people who were bedridden or housebound [27]. Therefore, the results cannot be generalised to people with severe ME/CFS.
- The dropout rate of 25% may suggest that the therapies were ineffective or harmful for some participants [27]. However, harm was not measured [27].
- The changes in fatigue, quality of life, pain interference and distance covered on a six-minute walking test were not statistically significant between groups at the end of the trial [27].
- It is of concern that Jason et al. did not report whether their data were normally distributed [27]. If they were not, then the assumptions of their statistical tests were violated and their results were statistically invalid.
- Compared to the other treatment conditions – cognitive therapy, anaerobic exercise and relaxation – graded exercise therapy performed poorly [27]. In fact, the relaxation condition showed greater improvements in depression, anxiety and self-efficacy than graded exercise therapy [27]. Graded exercise therapy performed better than the other treatment conditions on only one measure – pain severity on the 10-point Brief Pain Inventory [27]. The improvement was tiny (graded exercise therapy plus cognitive therapy -0.04; cognitive therapy -0.03; anaerobic exercise -0.02; relaxation .02) [27]. These changes are unlikely to have been clinically meaningful.
- The Cochrane review acknowledged that Jason et al.'s graded exercise therapy condition failed to exceed relaxation in increasing physical functioning at a clinically significant level (p287) [1,27].

Therefore, this study did not support the hypothesis that graded exercise therapy with cognitive therapy would improve symptoms, fatigue, or fitness in people with ME/CFS. Furthermore, this study cannot be used to recommend graded exercise therapy without cognitive therapy in ME/CFS.

Moss-Morris (2005)

Moss-Morris (2005) used the Fukuda Criteria as inclusion criteria for their trial [28]. Crucially, people with fibromyalgia, depression and anxiety were not excluded; and 56% of participants were “possible or probable” cases of psychiatric disorder [28]. Given the Fukuda Criteria's 42% false positive rate [6] and the high incidence of psychiatric disorders, it is unclear whether the participants genuinely had ME/CFS. Furthermore:

- The study briefly mentioned that there was no change in physical functioning during the trial [28]. Instead, the authors focused on an improvement in self-rated improvement scores and claimed that graded exercise therapy was an effective treatment for ME/CFS[28]. Clearly, if this were true, the participants' physical functioning scores would have shown a statistically significant improvement. However, they did not [28]. Furthermore, VO_2 peak **deteriorated** by 15% in the treatment group (p252) [28]. Therefore, rather than supporting graded exercise therapy as a treatment for ME/CFS, this study is a demonstration of the vulnerability of subjective measures to bias. In other words, the study aimed to change the participants' subjective reports and it was successful in doing this. However, the study failed to demonstrate that graded exercise reduced disability. In fact, the objective measure - VO_2 peak - suggests that graded exercise may have increased disability [28].

- The Moss-Morris control group appears to have had less contact with the researchers than the treatment group [28]. Both groups underwent physiological measures and filled out self-report scales at the beginning and end of the trial [28]. However, the Moss-Morris treatment group met weekly to "assess progress, provide encouragement and set new exercise goals." (p 249) [28]. The reduced contact between the researchers and the control group, in comparison to the experimental group, introduces performance bias to the study.
- The control group had lower SF-36 physical functioning scores than the experimental group at baseline (45.65 versus 53.10) [28]. The authors did not indicate whether these differences were statistically significant [28]. It is possible that the study was confounded from the start by a differential level of disability between the experimental and control groups.
- Despite randomisation, the experimental group's mean age was almost 9 years lower than the control group's average age [28]. The authors admitted that age was correlated with physical fatigue, mental fatigue and the SF-13 physical functioning subscale scores[28]. Therefore, the study was confounded by statistically significant age differences between the experimental and control groups.
- The paper claimed global rating of improvement scores as the main outcome measure[28]. The score comprised a single question, "how would you rate the change in your CFS in the last three months?", rated from 1 to 7 [28]. Although pre- and post-treatment scores were reported for all other variables, the global rating of improvement scores were measured once, at the end of the trial [28]. Given the lack of pre- and post-treatment comparison and the reliance on subjective memory of the previous three months, this single question cannot be considered to be a reliable and valid measure of CFS symptom improvement.
- Moss-Morris et al. reported that 54.5% of the paced exercise participants reported themselves as "much" or "very much" better [28]. Presumably, the remaining 45.5% reported feeling a little better, no change, or worse. It is shocking that the authors did not report how many participants felt worse.
- The paper used the 14-item Fatigue Scale to measure fatigue [28,39]. However, this scale makes time-based comparisons, such as "Do you have less strength in your muscles", "Do you think as clearly as usual" and "Do you find it more difficult to find the correct word" [39]. As explained earlier, these comparisons are meaningless for people who have had ME/CFS for many years or decades. Therefore, this scale is likely to underestimate fatigue.
- The paper was based on one-way hypotheses [28]:

> "The first was that graded exercise would lead to a reduction in fatigue and disability through an increase in physiological fitness. The second was that

> graded exercise would lead to a reduction in fatigue and disability through decreasing patients' tendencies to focus on their symptoms."

A two way hypothesis would have been more appropriate. For example, "It was hypothesised that graded exercise therapy would have an effect on fatigue and disability." Compared to a two-way hypothesis, a one-way hypothesis doubles the likelihood of a result achieving statistical significance. In the Moss-Morris study, a two-way hypothesis would have dropped the change in mental fatigue below the level of significance at α=.05, and the change in physical fatigue is likely to have been statistically significant, but just under the chosen cut-off point. It is possible that the study's authors succumbed to p-hacking.

- The study did not control for type one error inflation. According to the Bonferroni correction, the statistical significance threshold (.05) should be divided by the number of comparisons made in the study [37]. Moss-Morris et al. ran four pre- and post-treatment regression analyses [28]. Therefore, the statistical significance threshold should have been .05 /4 = .0125 [37]. On this basis, the study showed no statistically significant improvements between the treatment and control groups.
- It is of concern that Moss-Morris et al. did not report whether their data were normally distributed [28]. If they were not, then the assumptions of their statistical tests were violated and their results were statistically invalid.
- Moss-Morris states that "the key aim of this research was to test mediation" (p 249) [28]. The Moss-Morris abstract states, "At the end of treatment the exercise group rated themselves as significantly more improved and less fatigued than the control group. A decrease in symptom focusing rather than an increase in fitness mediated the treatment effect. Graded exercise appears to be an effective treatment for CFS and it operates in part by reducing the degree to which patients focus on their symptoms." [28] However, this conclusion does not follow from the findings. Graded exercise therapy encourages patients to ignore their symptoms [9]. Participants then self-reported their symptoms [28]. Therefore, the study, indeed, succeeded in persuading participants to report their symptoms less severely. However, the absence of change in physical functioning shows the study did not succeed in reducing disability. Rather, it demonstrated that graded exercise therapy can influence how participants self-report their CFS symptoms. Therefore, the study failed to demonstrate that graded exercise therapy is an effective treatment for CFS.
- Post-exertional symptom exacerbation and harm were not measured [28].

In summary, this paper appears to have demonstrated only that the researchers were able to convince the participants to reduce their self-reported symptom ratings. The study showed no statistically significant improvements in SF-36 physical functioning subscale scores; and a deterioration in VO_2 peak [28]. Therefore, Moss-Morris et al. does not support graded exercise therapy in ME/CFS.

Wallman et al.

As stated earlier, Wallman et al. [29] did **not** use graded exercise therapy. Graded exercise encourages participants to disregard their symptoms, push through bad reactions and continue with the exercise program [9]. However, Wallman et al.'s participants paced their activity by shortening or cancelling exercise sessions after a bad reaction [29]. Therefore, this study cannot be used to support graded exercise therapy. Furthermore:

- Participant ages ranged from 16 to 74 [29]. Recovery rates are around 60-65% for children[36], but only 5% for adults [35]. It is unclear how many of the participants were teenagers. Therefore, the results may not be generalisable to adults.
- The majority of Australian GPs have little knowledge of ME/CFS [25] and often conflate ME/CFS with long-term fatigue. Doctors' appointments are usually around 10 minutes. Therefore, few GPs have time to run a detailed check of specific diagnostic criteria. Doctors are also unlikely to turn down free exercise therapy for their patients. Given that Wallman et al. did not verify the diagnoses [29], it is uncertain that their participants met the Fukuda Criteria, let alone displayed the defining feature of ME-CFS – post exertional symptom exacerbation.
- The study required weekly visits to the university [29]. One quarter of people with ME/CFS have are housebound or bedridden [19] and, therefore, unable to attend weekly appointments. It is likely, therefore, that the participants – those who had ME/CFS at all – had mild to moderate ME/CFS, and that the results cannot be generalised to people with severe or very severe ME/CFS.
- The study showed no statistically significant improvement in physical fatigue [29].
- Wallman et al. did not specify a minimum fatigue score as an inclusion criterion [29]. Had they done so, it is likely that participants would have continued to meet the inclusion criteria at the end of study [7]. Therefore, the study's exercise therapy cannot be claimed to have been an effective treatment for ME/CFS.
- Like Moss-Morris et al., this study did not control for type one error inflation. Wallman et al. made twelve comparisons [29]. Therefore, per the Bonferroni correction, the statistical significance threshold should have been .05 /12 = .004 [37]. On this basis, there would have been only one statistically significant improvement, i.e. oxygen uptake. The large overlap in the exercise group's pre-treatment confidence intervals (13.3 – 17.7) and post-treatment confidence intervals (14.9 – 19.2) [29] suggests that the effect size for oxygen uptake is likely to have been too small to be clinically significant.

Given the above points, and the fact that the participants underwent pacing rather than graded exercise therapy, this study cannot be considered to support graded exercise therapy for people with ME/CFS.

Does the Cochrane Review Truly Support Graded Exercise Therapy in ME/CFS?

The Cochrane review acknowledged that there is only low certainty evidence that graded exercise therapy improved physical functioning (p27) [1]. Five of the six studies that measured physical functioning were Oxford Criteria trials [1]. Therefore, their results must be disregarded. The remaining study, Moss-Morris et al., did not show a statistically significant change in physical functioning [28]. Furthermore, Jason et al. showed greater improvement in physical functioning in the relaxation group than the graded exercise therapy group [27]. Notably, Jason et al.'s physical functioning results were excluded from the meta-analysis [1].

The improvements in depression, anxiety and sleep were minimal and based on low certainty evidence (respectively, -1.63 on the 21-point HADS depression scale (p27); -1.48 on the HADS anxiety scale (p28); and -1.49 on the 21-point Jenkins sleep Scale (p29) [1]. It is doubtful that these improvements were reliable or clinically significant.

Moderate certainty evidence indicated that graded exercise improved fatigue (p 25) [1]. However, the improvement was quite small, representing a 3.4 improvement on the 33-point Chalder Scale[1]. Therefore, participants were likely to have continued to be diagnosed with ME/CFS at the end of the trials. Fatigue scales have shown low reliability, poor validity, vulnerability to bias and ceiling and floor effects in ME/CFS [38,46]. Therefore, the Cochrane review may have overrated the certainty of evidence. The review did not offer an unqualified recommendation for exercise therapy in improving fatigue, stating that “Exercise therapy **probably** reduces fatigue” (p2,p25). However, the authors failed to indicate that the effect size was small [1].

Furthermore, fatigue is not the defining feature of ME/CFS, but, rather, post exertional symptom exacerbation [7,8,15,18,19]. However, post exertional symptom exacerbation was not an outcome measure in the Cochrane review or the reviewed papers. Therefore, the review failed to assess the single most important symptom that might indicate a clinically significant improvement.

Furthermore, the entire aim of graded exercise therapy is to influence subjective awareness of symptoms [7,9]. Surely, therefore, the Cochrane review should have considered the lack of convincing evidence of improvement in physical functioning, depression, anxiety and sleep; discussed the influence of allegiance bias on subjective self-report scores; and concluded that graded exercise had no meaningful positive effect on ME/CFS. This conclusion is supported by the lack of improvement in quality of life (p27) or pain (p26) [1].

Conclusion

The Cochrane review assessed five studies that used the Oxford Criteria and three studies that used the CDC Fukuda Criteria [1]. The Oxford and Fukuda Criteria carry a 90% and 42% false positive rate, respectively [4,5,6]. Therefore, neither the Oxford or the Fukuda Criteria provide a valid ME/CFS diagnosis in 2023 [4,5,6,8]. The inability of the Oxford and Fukuda Criteria to accurately diagnose ME/CFS confounds the Cochrane review. Furthermore, the Cochrane-reviewed trials displayed methodological problems and many types of bias; most of the improvements in outcome variables were small and supported only by low-certainty evidence; and the moderate-certainty variables displayed poor reliability and validity [1,].

The Fukuda criteria acknowledge that people with CFS may experience post exertional symptom exacerbation [9]. Recent research, including the ICC, indicates that **all** people with ME/CFS experience post exertional symptom exacerbation [7,8,15,18,19]. As expected in the presence of post exertional symptom exacerbation, harm has been reported by ME/CFS patients undertaking graded exercise therapy[7,11,12,13,16,17,18,24]. It is unethical, therefore, to continue to recommend graded exercise therapy for ME/CFS – particularly on the basis of such flawed evidence. To safeguard the health and welfare of people with ME/CFS and post exertional symptom exacerbation, it is vital for the that the RACGP acknowledge the many flaws in graded exercise therapy trials for ME/CFS; recognise the research evidence of harm; and update guidelines to contraindicate graded exercise therapy for ME/CFS.

Recommendations

The following recommendations will improve the diagnosis and treatment of ME/CFS:

1. Change the RACGP web page (https://www.racgp.org.au/clinical-resources/clinical-guidelines/handi/handi-interventions/exercise/graded-exercise-therapy-chronic-fatigue-syndrome) to contraindicate graded exercise therapy in ME/CFS.
2. Update the ME/CFS diagnostic criteria on the RACGP website to the AMA-validated CDC Criteria [19], which require the defining feature of ME/CFS, post exertional symptom exacerbation.
3. Assess, develop and promote the adoption of scales to measure ME/CFS symptoms and post exertional symptom exacerbation in general practice.
4. Active education of GPs, specialists and allied health in the diagnosis and management of ME/CFS.
5. Discourage the use of 'CFS' with its incorrect emphasis on fatigue .
6. Emphasise the use of 'ME' and awareness of post exertional symptom exacerbation.
7. Request that GPs treat ME/CFS patients with respect. Discourage the dismissal, disparagement, gaslighting and minimisation of symptoms in people with ME/CFS.
8. Encourage the use of the WHODAS 2.0, rather than the ABAS 3.0 and other functional assessments, when assessing people with ME/CFS.
9. Ensure that people with ME/CFS have access to Medicare-funded video/phone consults with GPs.
10. Modify GP funding to allow for long consultations with ME/CFS patients.
11. Modify vaccination guidelines to provide free COVID and flu injections to people with ME/CFS. Specify ME/CFS in the inclusion criteria.
12. Create an in-home vaccination service for housebound people with ME/CFS.
13. Create an in-home pathology collection service for housebound people with ME/CFS.
14. Provide in-home GP care to housebound people with ME/CFS.
15. Create a new medical specialty for ME/CFS.

16. Create new centres for complex health conditions, with teams of specialists and allied health who work with each other and with patients.
17. Create faster pathways for the adoption of evidence-based treatments generated by new research in general practice.
18. Assist Centrelink and the NDIS in modifying their guidelines to recognise the severity of ME/CFS and ensure that people with ME/CFS have access to the disability support pension and NDIS supports.
19. Advocate for equitable research funding for ME/CFS.
20. Ensure that ethics boards understand post exertional symptom exacerbation and the risk of harm to people with ME/CFS undergoing exercise studies.
21. Ensure that ethics boards only approve ME/CFS research that uses strict diagnostic criteria such as the ICC.
22. Recommend the adoption of the WHODAS 2.0 in preference to other functional assessments when measuring disability in ME/CFS.

Appendix A: Comparison of Fibromyalgia Symptoms with ME/CFS Under the Oxford, Fukuda, and International Consensus Criteria (ICC)

The following table summaries the symptoms of fibromyalgia and the Oxford, Fukuda and International Census Criteria for ME/CFS [2,3,8]. It then cross-references fibromyalgia symptoms with ME/CFS under the Oxford, Fukuda and International Census Criteria [2,3,8]. The table shows that people with fibromyalgia will often qualify for an incorrect ME/CFS diagnosis under the outdated Oxford and Fukuda Criteria, but not the more recent ICC. criteria[2,3,8].

	Fibromyalgia [40]	**ME/CFS** **(Oxford Criteria)** [2]	**ME/CFS** **(CDC Fukuda Criteria)** [3]	**ME/CFS** **(ICC)** [8]
Diagnostic criteria summary	Symptoms must have been present for at least 3 months. Fibromyalgia is diagnosed on the basis of measurement scales. The scales measure: • Widespread pain • Fatigue • Cognitive problems • Environmental sensitivity • Sleep disturbance • Musculoskeletal stiffness • Pain or cramps in the lower abdomen • Headaches	Severe fatigue (for at least 6 months) that is disabling; significantly affects mental and physical functioning; represents a clear change from a previous state; is present at least 50% of the time; and is disproportionate to exertion. Other symptoms may be present, especially myalgia, mood disturbance and sleep disturbance. Exclusions: Medical conditions known to produce chronic fatigue (eg severe anaemia). Patients with a current diagnosis of schizophrenia, manic depressive illness, substance abuse, eating disorder or proven organic brain disease.	Chronic fatigue (of new or definite onset, that is not lifelong; is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities) Plus four or more of the following: • Impairment in short-term memory or concentration • Muscle pain • Multijoint pain • Headaches • Sore throat • Tender lymph nodes • Post-exertional symptom	Each of the following must be present: Postexertional neuroimmune exhaustion (pathological inability to produce sufficient energy on demand) Debilitating postexertional symptom exacerbation in response to minimal exertion, which may be immediate or delayed by hours or days, and can cause a relapse Recovery period is prolonged, usually 24 h or longer. A relapse can last days, weeks or months. Substantial reduction in pre-illness activity level. 50% reduction is mild ME/CFS. Very severe ME/CFS patients are bedridden and completely reliant on care.

	Fibromyalgia [40]	**ME/CFS** **(Oxford Criteria)** [2]	**ME/CFS** **(CDC Fukuda Criteria)** [3]	**ME/CFS** **(ICC)** [8]
	• Depression, anxiety and negative affect Exclusions: Other sources of widespread pain	Note: Other psychiatric disorders (including depressive illness, anxiety disorders, and hyperventilation syndrome) are not necessarily reasons for exclusion.	exacerbation	Symptoms may fluctuate. Neurological impairments, including pain, cognitive impairments, sleep disturbance, motor or perceptual disturbance. Immune, genitourinary or gastro-intestinal impairments Energy production/transportation impairments, including cardiovascular or respiratory problems, loss of thermostatic stability, or intolerance of temperature extremes
Severe, disabling fatigue present?	Yes	Yes	Yes	Yes
Cognitive problems	Yes	Yes	Yes	Yes
Muscle pain	Yes	Yes	Yes	Yes
Joint pain	Yes	Not listed or excluded	Yes	Yes
Headaches	Yes	Not listed or excluded	Yes	Yes
Mood disturbance	Yes	Yes	No. However, depression and anxiety are common in severe and very severe ME/CFS, due to high	No. However, depression and anxiety are common in severe and very severe ME/CFS, due to high

	Fibromyalgia [40]	**ME/CFS (Oxford Criteria)** [2]	**ME/CFS (CDC Fukuda Criteria)** [3]	**ME/CFS (ICC)** [8]
			pain levels, poor quality of life and loss of personal agency.	pain levels, poor quality of life and loss of personal agency.
Poor sleep	Yes	Yes	No	Yes
Post-exertional symptom exacerbation	**No**	**No**	**Optional**	**Yes** **(required)**
Based on the exclusion of other diseases?	Yes	Yes	Yes	Yes. However, ME/CFS is the only health condition that presents with high levels of post exertional symptom exacerbation.
Prevalence	2-4% [40]	20% [4]	2% [4,42]	0.11% [4,5]
Do people with fibromyalgia, and not ME/CFS, qualify for an ME/CFS diagnosis under these criteria?		**Yes**	**Yes**	**No** **ME/CFS is the only condition with post exertional symptom exacerbation**

Appendix B: Comparison of Major Depressive Disorder Symptoms with ME/CFS Under the Oxford, Fukuda, and International Consensus Criteria (ICC)

The following table summaries the symptoms of major depressive disorder (MDD) and the Oxford, Fukuda and International Census Criteria [8] for ME/CFS [2,3,8]. It then cross-references MDD symptoms with ME/CFS under the Oxford, Fukuda and International Census Criteria [2,3,8]. The table shows that people with MDD will often qualify for an incorrect ME/CFS diagnosis under the outdated Oxford Criteria, but not the more recent ICC criteria [2,8].

	MDD [41]	**ME/CFS** **(Oxford Criteria)** [2]	**ME/CFS** **(CDC Fukuda Criteria)** [3]	**ME/CFS** **(ICC)** [8]
Diagnostic criteria summary	Depressed mood; or diminished interest or pleasure. Plus, four or more of the following symptoms: • Fatigue • Insomnia or hypersomnia • Unexplained weight changes • Psychomotor agitation or retardation • Feelings of worthlessness or guilt • Recurrent thoughts of death	Severe fatigue (for at least 6 months) that is disabling; significantly affects mental and physical functioning; represents a clear change from a previous state; is present at least 50% of the time; and is disproportionate to exertion. Other symptoms may be present, especially myalgia, mood disturbance and sleep disturbance. Exclusions: Medical conditions known to produce chronic fatigue (eg severe anaemia). Patients with a current diagnosis of schizophrenia, manic depressive illness, substance abuse, eating disorder or proven organic brain disease. Note: Other psychiatric disorders (including depressive illness,	Chronic fatigue (of new or definite onset, that is not lifelong; is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities) Plus four or more of the following: • Impairment in short-term memory or concentration • Muscle pain • Multijoint pain • Headaches • Sore throat • Tender lymph nodes • Post-exertional symptom	Each of the following must be present: • Postexertional neuroimmune exhaustion (pathological inability to produce sufficient energy on demand) • Debilitating postexertional symptom exacerbation in response to minimal exertion, which may be immediate or delayed by hours or days, and can cause a relapse • Recovery period is prolonged, usually 24 h or longer. A relapse can last days, weeks or months. • Substantial reduction in pre-illness activity level.

	MDD [41]	ME/CFS (Oxford Criteria) [2]	ME/CFS (CDC Fukuda Criteria) [3]	ME/CFS (ICC) [8]
		anxiety disorders, and hyperventilation syndrome) are not necessarily reasons for exclusion.	exacerbation	50% reduction is mild ME/CFS. Very severe ME/CFS patients are bedridden and completely reliant on care. Symptoms may fluctuate. • Neurological impairments, including pain, cognitive impairments, sleep disturbance, motor or perceptual disturbance. • Immune, genitourinary or gastro-intestinal impairments • Energy production/transportation impairments, including cardiovascular or respiratory problems, loss of thermostatic stability, or intolerance of temperature extremes
Depressed mood; or diminished interest or pleasure	Yes	Yes	No. However, depression and anxiety are common, particularly in severe and very severe ME/CFS, due to high pain levels; struggling to perform simple, daily tasks; an inability to perform previously pleasurable activities; and a loss of relationships, personal agency and meaning in life.	
Fatigue	Yes	Yes	Yes	Yes

	MDD [41]	ME/CFS (Oxford Criteria) [2]	ME/CFS (CDC Fukuda Criteria) [3]	ME/CFS (ICC) [8]
	"Often insomnia or fatigue is the presenting complaint" (DSM-V, p 162)			
Sleep disturbance	Yes	Yes	No	Yes
Unexplained weight changes	Yes	No. Weight changes are common. However, they can be explained by inactivity or gastrointestinal dysfunction		
Psychomotor agitation or retardation	Yes	No	No	Yes
Feelings of worthlessness or guilt	Yes	Not in diagnostic criteria, but common. People with severe or very severe ME/CFS are unable to work or contribute to society. They are dependent on family and disability supports. Many people feel that they are a drain on society, and this leads to a sense of guilt and worthlessness. For people with mild to moderate ME/CFS, post exertional symptom exacerbation leads to periodic incapacitation. Patients often fail to maintain relationships and honour commitments. They feel unreliable, and experience criticism from family, friends, employers and health professionals. Their quality of life drops and they lose self esteem.		
Recurrent thoughts of death	Yes	Not in diagnostic criteria, but common. 12.5% of people with ME/CFS have a quality of life that is worse than death. Suicide rates are six times higher than those of the general population		
Post-exertional symptom exacerbation	**No**	**No**	**Optional**	**Yes** **(required)**
Based on the	No	Yes	Yes	Yes. However, ME/CFS is the only

	MDD [41]	**ME/CFS (Oxford Criteria)** [2]	**ME/CFS (CDC Fukuda Criteria)** [3]	**ME/CFS (ICC)** [8]
exclusion of other diseases?				health condition that presents with high levels of post exertional symptom exacerbation.
Prevalence	7% [41]	20% [4]	2% [4,42]	0.11% [4,5]
Do people with MDD, and not ME/CFS, qualify for an ME/CFS diagnosis under these criteria?		**Yes**	**No, although there is large symptom overlap**	**No** **ME/CFS is the only condition with post exertional symptom exacerbation**

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