Rapid Response

Graded exercise therapy (GET) for people with chronic fatigue syndrome / myalgic encephalomyelitis (CFS/ME)

Rapid Responses are brief summaries of the best available evidence prepared to inform time-sensitive decision-making. Rapid Responses are not peer reviewed, are current only at time of publication, and do not constitute recommendations. They should be considered alongside existing guidance applicable to NHS Scotland.

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<table>
<thead>
<tr>
<th>Topic</th>
<th>Graded exercise therapy (GET) as a treatment for people with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME)</th>
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<tr>
<td>Date of search</td>
<td>21-23 July 2020</td>
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<tr>
<td>Referrer</td>
<td>Leanne McCardle, Policy Manager, Scottish Government</td>
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<tr>
<td>Report published</td>
<td>04 August 2020</td>
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</table>

HIS Evidence Conclusions:

The validity, applicability and certainty of positive findings around the effectiveness and safety of graded exercise therapy (GET) for symptom management in people with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) are extensively debated. Patient experience surveys indicate that over half of respondents find the intervention ineffective or detrimental.

A Cochrane systematic review and a NICE Guideline are currently being revised and updated and caution should be noted on the use of GET for CFS/ME until the updates are published.

No published evidence on the use of GET for people experiencing persisting fatigue following COVID-19 was identified. NICE has made a statement cautioning against assuming CFS/ME recommendations apply to this patient group.
What were we asked to look at?

We were asked to look at the efficacy and safety of graded exercise therapy (GET) as a treatment for people with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) and for people experiencing persisting fatigue following COVID-19 infection.

CFS - also referred to as systemic exertion intolerance disease (SEID), CFS/SEID or CFS/ME - is a long-term condition characterised by chronic disabling fatigue, post-exertional (physical, emotional, or cognitive) malaise, and an array of other possible symptoms including neurologic and/or cognitive impairment, orthostatic intolerance, non-refreshing sleep, musculoskeletal pain, and altered immune or autonomic responses.

Diagnosis is made clinically, based on symptoms and by ruling out other conditions. There is no universally agreed diagnostic reference standard. There are a range of case definitions in use across trials with different combinations of signs and symptoms.

Some viruses (and/or antibodies targeting them) are reported to be more common in affected patients but no specific infectious agent has been uniquely linked to the onset of CFS/ME.

Treatment for CFS/ME aims to relieve the symptoms; outcomes in studies include fatigue, physical functioning, improvement/recovery, pain, sleep quality, quality of life, and adverse effects.

GET is characterised by establishment of a baseline of achievable exercise or physical activity, followed by a negotiated, incremental increase in the duration of time spent physically active followed by an increase in intensity. It usually involves exercise that raises your heart rate, such as swimming or walking.

Overview of the evidence

Two literature searches were conducted by an information scientist between 21 and 23 July for (1) the effectiveness and safety of GET in patients with CFS/ME and (2) patient experiences of GET. Standard rapid review checklists were used. Search terms are outlined in Appendix 1.

To facilitate a rapid response, a health services researcher selected guidelines, systematic reviews and publications directly associated with these secondary sources, from the search results.

Guidelines

A 2007 NICE guideline recommended:

Cognitive behavioural therapy (CBT) and/or graded exercise therapy (GET) should be offered to people with mild or moderate CFS/ME and provided to those who choose these approaches, because currently these are the interventions for which there is the clearest research evidence of benefit.

The recommendation was based on review of five randomised controlled trials, four of which found that GET led to improvements in fatigue when compared to control groups. Although the
recommendation relates to mild or moderate CFS/ME, some of the more detailed recommendations around tailoring the GET intervention to individuals refer to people with severe CFS/ME.

A NICE guideline surveillance process in 2017 examined new evidence including the largest trial to date, the UK PACE trial (Pacing, graded Activity, and Cognitive behaviour therapy; a randomised Evaluation) trial (n=641), the findings of which were in line with guideline recommendation. The surveillance report summarises numerous published criticisms of the PACE trial, the responses by the trial authors and ongoing debate. The report also notes the findings and limitations of a survey conducted by the ME Association in 2012 which concluded that GET could not be seen as safe and effective for the majority of people with CFS/ME. This conclusion is in-line with survey findings provided during the initial guideline development in 2005 and also a more recent survey commissioned by Forward ME following discussions between the Chair and Vice-Chair of the NICE Guideline Development Group, Members of Parliament and the Chair of Forward-ME. The surveillance report also mentions a 2011 patient survey on NHS specialist services which reported that 48% of respondents selected GET as one of the treatment options which should be available on the NHS for people with ME. GET was the treatment least frequently selected (adaptive pacing therapy [referred to as ‘pacing’], fatigue management and medication were each selected by over 90% of respondents).

Although initial assessment of the report indicated no clear signal that the identified new evidence would result in changes to the recommendations, subsequent consultation with stakeholders identified broader issues that called into question the guideline scope and its current relevance.

Issues brought to NICE during the consultation process included:

- Interventions recommended in the guideline are based on the biopsychosocial model. Stakeholders raised that, since 2007, much has changed with respect to biomedical knowledge. Biological models based on measurable abnormalities may need greater consideration.
- Severe ME is not well covered in the guideline and can cause profound issues.
- Oxford criteria (used to recruit many studies included in the guideline) and NICE criteria are too broad.
- The US Centers for Disease Control and Prevention have dropped CBT and GET from their list of recommended treatments for CFS/ME.
- Evidence was cited of harms of GET, and pacing should be considered as an option.
- Large randomised controlled trials such as PACE and GETSET (Graded Exercise Therapy Guided Self-Help Trial for Patients with Chronic Fatigue Syndrome), and Cochrane reviews, appear to support the guideline recommendations on CBT and GET. These key studies have

\(^a\) PACE trial publications are at [https://www.qmul.ac.uk/wolfson/research-/current-research-projects/projects/pace-trial.html](https://www.qmul.ac.uk/wolfson/research-/current-research-projects/projects/pace-trial.html)

been criticised for inflating the efficacy of interventions. Some studies only require fatigue in the case definition, which may incorporate other fatiguing conditions with the potential to complicate results.

- Patient surveys appear to contradict findings from randomised controlled trials and systematic reviews regarding the safety and efficacy of CBT, GET and pacing.

The guideline is presently under full review and scheduled for publication in April 2021.

In a statement issued in July 2020 about graded exercise in the context of COVID-19, NICE cautioned against assuming the 2007 guideline could apply to people with fatigue following COVID-19 and noted that:

The evidence for and against graded exercise therapy is one of the important issues the guideline committee is considering. NICE plans to consult on the updated guidance in November 2020.

Systematic Reviews

Effectiveness

A Cochrane systematic review (literature search up to May 2014) - the latest version of which was published in October 2019 - examined exercise therapy (defined more broadly than GET) for chronic fatigue syndrome. The review has undergone several amendments between 2016 and 2019 in response to feedback and receipt of a formal complaint around how trials were interpreted and how findings were described. Amendments largely express reduced certainty around conclusions. A statement prefacing the review reads:

...this Cochrane Review has been modified by the review’s authors and evaluated by independent peer reviewers and editors. It now places more emphasis on the limited applicability of the evidence to definitions of [...] ME/CFS used in the included studies, the long-term effects of exercise on symptoms of fatigue, and acknowledges the limitations of the evidence about harms that may occur.

The Cochrane review is to undergo a full update commencing in 2020. The conclusions for exercise therapy compared with passive control, taken directly from the review, are presented below:

Exercise therapy probably reduces fatigue at end of treatment (SMD$^c$ −0.66, 95% CI −1.01 to −0.31; 7 studies, 840 participants; moderate-certainty evidence). We are uncertain if fatigue is reduced in the long term because the certainty of the evidence is very low (SMD −0.62, 95% CI −1.32 to 0.07; 4 studies, 670 participants)

We are uncertain about the risk of serious adverse reactions because the certainty of the evidence is very low (RR 0.99, 95% CI 0.14 to 6.97; 1 study, 319 participants).

Exercise therapy may moderately improve physical functioning at end of treatment, but the long-term effect is uncertain because the certainty of the evidence is very low. Exercise

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$^c$ SMD standardised mean difference
therapy may also slightly improve sleep at end of treatment and at long term. The effect of exercise therapy on pain, quality of life and depression is uncertain because evidence is missing or of very low certainty.

Two critical reviews of the Cochrane document present specific concerns around methodological parameters of the included randomised controlled trials and overall issues around researcher allegiance, study selection, trial inclusion criteria and the focus on subjective outcomes\textsuperscript{13, 14}.

A systematic review (literature search up to April 2017) examined the methodology of trials on GET for patients with CFS/ME\textsuperscript{15}. Five randomised controlled trials were identified. The main outcomes assessed in the studies were fatigue (Chalder Fatigue Questionnaire), physical functioning and functional status (SF-36). The analysis summarised potential sources of bias in the trials, with particular issues as follows: the lack of use of objective outcome measures (especially when combined with a non-blinded intervention); trial entry criteria which may not encompass participants who experience post-exertional malaise (PEM - the worsening of symptoms following even minor physical or mental exertion); and a lack of assessment or reporting of adverse events.

A US systematic review (literature search up to 2014) included five trials and concluded, based on low to moderate strength of evidence, that:

GET improved measures of function (SF-36 physical function weighted mean difference, 10.68 (CI, 6.32 to 16.88); 3 trials), fatigue (4 trials, n = 619), global improvement as measured by the clinical global impression of change score (relative risk, 1.58 (CI, 1.24 to 2.47); 3 trials) and work impairment (1 trial, n = 475).

An addendum to the systematic review published in 2016 (following public comment) revised the strength of evidence to low (1 trial, n=49) based on a re-analysis reflecting that:

The Oxford CFS case definition is the least restrictive, and its use as trial entry criteria could have resulted in selection of participants with other fatiguing illnesses or illnesses that resolve spontaneously with time.

Patient experience surveys

A review presented the findings of nine patient surveys published between 2001 and 2015 where there was symptom change data for people with CFS/ME who had experienced GET. This review had a limited literature search and both the search and the inclusion/exclusion criteria used were only minimally described. The paper is included in this rapid response as a summary of patient surveys.

Surveys from the UK, Norway and The Netherlands were included. Survey size ranged from 77 to 1,214 respondents and the proportion noting symptom deterioration following GET ranged from 33% to 79% with, on average (based on n=4,652) 57% of respondents reporting symptoms slightly or much worse. Symptoms were slightly or greatly improved for 26% of respondents and 17% reported no change.

The limitations of surveys include the potential bias in the recruitment of respondents (for example, those who have recovered their health are less likely to take part in surveys, and for some the diagnosis may be incorrect) and the variability in specification, content and delivery of the intervention(s).
References

4. CG53 NG. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): Diagnosis and management of CFS. ME in adults and children. 2007.
## Appendix 1: literature search

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<tr>
<th>Resource</th>
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Database: Ovid MEDLINE(R) ALL <1946 to July 21, 2020>

Search Strategy:
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1 chronic fatigue syndrome/ (5471)
2 ((post-viral or "post viral") adj (syndrome or fatigue)).tw. (61)
3 chronic fatigue syndrome.tw. (5575)
4 post infectious fatigue syndrome.tw. (9)
5 Myalgic Encephalomyelitis.tw. (985)
6 fibromyalgia.tw. (10264)
7 fibromyalgia/ (8413)
8 ("post-exertional" or "post exertional") adj malaise).tw. (95)
9 or/1-8 (17813)
10 "graded exercise therapy".tw. (112)
11 "exercise therap$".tw. (3366)
12 or/10-11 (3366)
13 9 and 12 (162)

Database: APA PsycInfo <2002 to July Week 3 2020>

Search Strategy:
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1 chronic fatigue syndrome/ (1484)
2 "myalgic encephalomyelitis".tw. (238)
3 "chronic fatigue syndrome".tw. (1668)
4 or/1-3 (1806)
5 "graded exercise therapy".tw. (92)
6 4 and 5 (86)

Details of additional resources searched available on request.
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