The ME Association Review:
The GETSET Randomised Controlled Trial for CFS | 28 June 2017

Introduction

GETSET was published in The Lancet on 22 June 2017. It was a randomised controlled trial in secondary care of a new approach for people with ME/CFS that used the principles of graded exercise therapy, delivered in a self-help booklet, with up to four sessions of assistance offered remotely by trained physiotherapists via phone or Skype.

The results from the two primary outcome measures suggest that Guided graded Exercise Self-help (GES) plus specialist medical care (SMC) improved fatigue to a greater extent than physical function when compared to the control group (SMC alone). Publication attracted little media attention in the UK although The Telegraph managed to roll-out an article with the headline, 'Exercise can help chronic fatigue syndrome, study shows'.

ME Association trustees were unimpressed by the trial results or by media and other reports that focused on the main improvement in fatigue – made no mention of other symptoms including PEM – and did not seem to question why there was no significant improvement in the original outcome measure of physical function. However, we were pleasantly surprised by the mixed reaction from those experts assembled by the Science Media Centre, in particular the comments from Prof. Chris Ponting and Dr Simon Day.

Had the trial authors included objective measures - for example, actometers to record actual physical activity – it might have convinced more people that GES/GET plus SMC had been a largely ineffective approach even for people who were sufficiently able to take part. But despite the lessons from the PACE Trial (or perhaps because of them) these authors chose a continued reliance on subjective measures.

“We did not measure any objective outcomes, such as actigraphy, which might have tested the validity of our self-rated measures of physical activity.”

Our cautionary advice to anyone who is recommended graded exercise therapy (GET) - or its' derivatives - remains the same. In our opinion GET is all too often applied in an inappropriate 'one-size-fits-all' generalised way, and delivered in a regimented and inflexible manner. It is based largely on the deconditioning theory for which there is now even less evidence. GES/GET in our opinion is an ineffective approach to management.

We continue to be extremely concerned by the many reported experiences of people with ME/CFS who have been persuaded by specialists to embark on courses of GET only to find it was inappropriate and triggered significant worsening of their health. And we maintain that GET should be withdrawn with immediate effect as a primary intervention for everyone with ME/CFS.

Trial Basics

This was a 12 week trial that recruited 211 eligible patients who expressed a willingness to take part from two CFS/ME specialist clinics. Once they had been assessed, they were randomly assigned to either specialist medical care (SMC) which served as the control group, or SMC with additional guided graded exercise self-help (GES). Results are based on 12-week outcomes compared to data

collected at entry (baseline). The authors will also publish a follow-up study examining outcomes at 12 months.

All those recruited met the NICE guideline criteria which requires 'at least 4 months of clinically evaluated, unexplained, persistent, or relapsing fatigue with a definite onset that has resulted in a substantial reduction in activity and that is characterised by post-exertional malaise or fatigue, or both', plus at least 1 of 10 other relevant symptoms.

The trial measured outcomes using 2 primary self-report measures, the 11-item Chalder Fatigue Scale (CFQ) (range 0–33; higher scores represent more fatigue) and the Short-Form-36 (range 0–100; higher scores represent better function). The SF-36 was originally the only primary outcome measure, and relates to generic physical function. Other secondary outcome self-report questionnaires were used, and future publications from the trial authors will reveal additional findings.

At 12 weeks, compared with the control group, mean fatigue score was 19·1 (SD 7·6) in the GES group and 22·9 (6·9) in the control group (adjusted difference −4·2 points, 95% CI −6·1 to −2·3, p<0·0001; effect size 0·53) and mean physical function score was 55·7 (23·3) in the GES group and 50·8 (25·3) in the control group (adjusted difference 6·3 points, 1·8 to 10·8, p=0·006; 0·20).

Fatigue therefore improved by 12.7% and physical function by 6.3% in the GES group when compared with the control group. The improvement in fatigue was described as being a 'moderate' effect size, while the improvement in physical function was less impressive and of small effect size. Limiting the analysis to those participants who met either Oxford or CDC/Fukuda criteria did not alter the headline results.

There were also considered to be no reported adverse events, leading the authors to claim that:

“GES is a safe intervention that might reduce fatigue and, to a lesser extent, physical disability for patients with chronic fatigue syndrome.”

The full details of the trial are open access and can be read in The Lancet.

Our concerns and observations:

1. Despite one commentator claiming that the protocol was published in advance of the trial beginning – it appears that in fact the protocol was published in 2016 – a year after the trial ended and a year before the trial was published
2. Perhaps more worrying, a completely new primary outcome measure – the Chalder Fatigue Scale (CFQ) – was added to the protocol after the trial began and 5 months before it concluded on 01 December 2015. It is not clear whether the subsequent update to the primary outcome measures will actually mean the CFQ and therefore fatigue will not be a focus of the 12 month follow up study, but that is the implication. Originally physical function was to be the only primary outcome, measured subjectively using the SF-36 (see below)
3. While the authors claim the NICE guideline is most commonly used to diagnose people with ME/CFS in the NHS, a study from McDermott et al. (2014) determined that significantly more clinics were using CDC/Fukuda:
   “Twenty-three of 30 (77%) used the Centers for Disease (CDC) 1994 (Fukuda) criteria making this the most common case definition for diagnosis. Ten services used the CDC 1994 criteria and the recent NICE 2007 criteria. Five services used the NICE 2007 criteria only. Three services offered no diagnostic service and only accepted referrals from patients with prior diagnosis.”

4. Table 1 demonstrated that not all participants recruited using the NICE criteria met the CDC/Fukuda or the Oxford criteria: 68% of GES-group met CDC/Fukuda (74% of control group), 78% of GES-group met Oxford (84% of control group). CDC/Fukuda does not have PEM as a required characteristic (unlike the NICE criteria, although PEM is an option), but it does insist on 4 symptoms in addition to fatigue (rather than at least 1 symptom from the NICE list of symptoms)
5. Our preferred criteria would be the London criteria (2014), but we would have been more comfortable with CDC/Fukuda (1994) and Canadian Consensus Criteria (2005) to determine diagnoses and make comparisons rather than NICE and Oxford which we believe are not fit for purpose
6. We would have liked to see the DePaul Symptom Questionnaire used in this study as it is a validated tool highly relevant to ME/CFS and capable of capturing symptom/illness severity and frequency. It could have demonstrated, for example, the extent to which the range of symptoms – including PEM – were affected by GES/GET and it would also have enabled participants to be compared between CDC/Fukuda, Canadian Consensus, and International Consensus criteria
7. We would also have favoured use of the WHO Disability Assessment Schedule, a 36 item questionnaire that we feel is more relevant to ME/CFS functionality and far more useful than the SF-36. Although WHODAS 2.0 is not as recognised a tool in ME/CFS research of this type, we feel it should be as it offers a much fairer picture of mental and physical function
8. Table 1 revealed that 9% of the GES group (11% of the control group) had a current diagnosis of major depressive disorder. This might have adversely affected those able to include and maintain an exercise plan – as exercise is generally recognised as being good for depression and an elevation of mood could have led to higher scores on self-report questionnaires – while it could have impacted those in the control group and resulted in lower scores
9. Use of the Hospital Anxiety and Depression Scale (HADS) is unfortunate but we recognise there is little recognised alternative. It is disappointing that a suitable tool has yet to be developed that is more relevant to ME/CFS and other chronic diseases where depression and anxiety can develop as co-morbid conditions, and yet is also capable of determining primary psychiatric conditions for exclusion purposes
10. Table 1 also provided some further insight into how much physical activity participants felt they undertook in a week. This average allows us to consider just how able-bodied participants might have been, but as there is no accompanying definition for 'physical activity' and no similar outcome data we cannot take any conclusions too far: GES group (mean per participant): 120 mins per week (range: 30-360) and SMC-only control group: 185 mins per week (75-570). It may be that this is one area future publications will address
11. We were astonished to read that the author's recruited people with a high SF-36 physical function score (described in the protocol as being a 'significant minority' and scoring close to normal function). These participants were included as they 'had substantial reductions in functioning in other domains, such as mental or social activity levels', but their inclusion was also given as the reason for the introduction of the Chalder fatigue scale (CFQ) as a new primary outcome measure. This effectively altered the purpose of the trial and turned the focus of the study towards fatigue, which of course came out on top in terms of improvement. It should be noted that if people were being diagnosed using a properly applied NICE criteria, their illness would have caused a "substantial reduction in activity" which would imply – to us at least – a low SF-36 score at baseline. It suggests to us that the NICE criteria were not properly applied and

we do not agree with the decision to introduce the CFQ based on scores from a minority of participants who should not have been included

12. The above concern and the case studies given in the GES/GET booklet lead us to believe that the trial recruited an unrepresentative number of people who might best be considered mildly affected and/or who were ambulatory and able to exercise. Thus we feel that any results could not and should not be generalised to the wider patient population or to those moderately affected (as per the current NICE guideline)
13. We were amused by a comment from Dr Daniel Clauw (an advocate for GET and supporter of the trial), that seemed to validate both the ineffectiveness of GES on physical function, while making the point if it hadn't been for the late addition of CFQ and the focus on fatigue, this study would be about as effective as some 'alternative therapies':
    "In fact, although one might argue that some alternative pharmacological and non-pharmacological therapies might yield similarly small improvements in physical function or mood to those noted in the GETSET trial, far fewer available alternative therapies have this magnitude of effect on fatigue."
    A good job the authors added the CFQ then as a primary outcome measure, wasn't it?
14. Despite this the authors felt able to say, "We suggest that these findings show that a guided self-help intervention, when added to SMC, is a moderately effective intervention for fatigue, but has less effect on physical functioning, for people with chronic fatigue syndrome waiting for clinic therapy." But, had fatigue and the CFQ not been introduced as primary subjective outcome measures, this trial would have been a failure
15. What remains unclear from this trial and other similar studies involving GET is whether or not people actually did more activity, or reorganised existing activities (e.g. by removing non-urgent ones, or delegating etc. and resting more) in order to take on activities relating to exercise and invest their time and energy in this trial. In our experience it seems likely that unless people with ME/CFS have attained a relative plateau in terms of symptom stability and are confident they can take on more, it is far more likely that new activities are attempted at the expense of others. This would also be the case when people are attempting to avoid the post-exertional malaise that is a characteristic part of this disease and/or the so-called 'boom and bust'. The time and energy participants invested in this trial may also have led to bias when making self-reports
16. We are also concerned that cost considerations are the driving force behind this remote-delivered therapy rather than a desire to deliver the most appropriate and relevant clinical care. Although we recognise that patients with ME/CFS do have difficulty accessing secondary care, we feel remote services should be tailored to individual needs and allow experienced therapists greater freedom to work with those under their care to deliver more appropriate illness management and support. We would not want remote services to replace good quality physician-led specialist clinics
17. We feel that examining data at 12 weeks is too short a timescale to adequately measure the effects of this intervention, and may indeed reflect a peak in outcomes. And we don't understand why the authors could not also publish the 12 month outcome data rather than making us wait
18. The trial authors said they '...recruited adult patients (aged 18 years and older) attending these clinics who were diagnosed with chronic fatigue syndrome and placed on a waiting list for therapy'. This implies participants already had a diagnosis of ME/CFS and yet when assessing participants for the trial, the authors managed to exclude 236 (out of 683) for *not* meeting the NICE criteria. This is very worrying and implies a significant proportion of patients awaiting

therapy in the CFS/ME specialist clinics, do not in fact meet what should be a minimum UK clinical standard for diagnosis

19. We would also like to know what this might mean: 'Patients were excluded if they... had physical contraindications to exercise.' Only 9 patients were excluded for this reason, but if a definition were forthcoming it might provide useful insight into the kind of suitability that the authors regarded as necessary for people enrolled in a trial testing the efficacy of a therapy that employs the principles of GET
20. Table 2 demonstrated participant satisfaction with GES: 85% moderately or very satisfied, 10% minimally satisfied or dissatisfied, 1% moderately or very dissatisfied, 3% reported not receiving help. It is reasonable to say that participants were willing to take part in the trial and that those who found themselves in the GES group might have felt gratitude, and could have been biased by the investment of time and energy. But we also think it likely these results are a fair representation. When people don't have to leave their own homes but can remain in touch with therapists from the NHS by phone or on Skype, we think it likely there will be a higher degree of satisfaction than if people were left to get on with it by themselves. We would like to see more information revealing the proportion of people who felt they actually followed the protocol, and it would have been useful had objective measures been used allowing a comparison to be made with what had been reported i.e. was the protocol actually helping people to do more physical activity and exercise on a regular (daily) basis or were participants just claiming that it did?
21. Table 5 reveals that 20 people in the GES group (21%) downgraded their physical function scores by 10 or more points at 12 weeks compared to when they began the trial. It is unclear why and it would obviously be interesting to know. Was this because GES was not working for them? Had it led to them being unable to follow any plan as rigorously as it was meant to be? Or was it because of the very nature of ME/CFS and a result of illness fluctuation? A similar number of people in the control group also reported such a downgrade, but again we don't know the rationale and it would seem presumptive draw any conclusions
22. Table 6 demonstrated that in terms of Overall Health, 81% of those in the GES group felt there had been minimal change (87% in the SMC-only group), and only 18% felt there had been a positive change (5% in the SMC-only group). This doesn't seem to compare well with the satisfaction scores revealed in Table 2 and perhaps goes some way to explain that satisfaction with GES had little to do with how effective GES was as a therapy. Again, use of actometers would have helped us to better determine how effective GES had actually been, as might a re-assessment at 12 weeks to see if any participant still met the entry criteria, and/or use of the DePaul Symptom Questionnaire and WHODAS 2.0. But perhaps the authors will provide more data when they publish the 12 month follow-up study
23. Likewise when participants were asked to rate overall change in their Chronic Fatigue Syndrome: 86% of the GES group recorded minimal change (85% in the SMC-only group), and only 14% of the GES group recorded a positive change (6% in the SMC-only group). It really doesn't seem that GES/GET was seen by the majority of participants as having a significant effect on their primary health complaint and it made little difference if you were receiving GES or only specialist medical care. As before, actometers and the other measures mentioned above, might have allowed us to see more clearly where any improvements were made – and allowed us to better judge if efficacy had been achieved
24. Secondary outcomes (in the main paper) did show how well participants followed GES. However, it should be noted that these figures come from the physiotherapists who were only in contact with participants up to 4 times via phone or Skype during the 12 weeks and not from the

participants themselves:
"The physiotherapists reported that 43 participants (42%) adhered to GES completely or very well, 31 (30%) moderately well, and 30 (29%) slightly or not at all."
We don't know why participants were not asked to self-rate on this aspect of the trial – it would have made more sense. But what we don't yet know is why the physiotherapists felt participants adhered e.g. only slightly or not at all. It would also have be useful to compare participant ratings of adherence with the scores from physiotherapists to perhaps better understand any bias

25. Finally, we are concerned these results will to be used by NICE to support their seriously flawed recommendations that everyone with mild or moderate ME/CFS should be offered GET – despite the validity of our main criticism that use of GES/GET had little to no effect on physical function and did not result in participants claiming it had any significant effect on their overall health or primary disease

So what is the potential risk if GES is implemented as a therapy in secondary care? GES is a new approach to an existing therapy, albeit one that relies largely on the patient implementing the principles of GET in their own home. It seems to have been well accepted by those who took part in trial – although they were not representative of the wider patient population (it would have been useful if the study had recorded illness severities at point of recruitment and after 12 weeks and then at follow up in 12 months for example).

There can be little doubt that eliminating the personal cost of travel to and from clinic would also be welcomed by some people with ME/CFS who could also remain in touch with specialists by phone or Skype. However, we don't believe GES should replace what ought to be a tailored approach to more appropriate and flexible illness management delivered on a one-to-one basis by a specialist practitioner experienced in ME/CFS care who works with the patient to enable them to better cope and understand their condition.

Our concern is that GES will be applied as a 'one-size-fits-all' approach similar to both GET and CBT with the potential risk of long-term deteriorations to health and that it could replace existing specialist clinics or see funding reduced. We don't believe the results from this trial justify implementation of this approach despite the reported satisfaction expressed by participants. As with GET patients are coerced into believing that they should 'push through' or tolerate any increase in symptoms following the adoption of a new exercise plan and/or increase in exercise intensity and ignore what their own body is telling them; and we believe this is fundamentally wrong.

One of the characteristic features of ME/CFS is PEM (post-exertional malaise) and yet this trial and others like it pay scant regard to the implications for PEM and other ME/CFS symptoms when patients are encouraged to increase the time spent exercising and to increase intensity. The risk to patients is therefore that instead of being alerted that doing more is potentially triggering a setback in their health, and being advised to rest and recuperate when symptoms flare and then to rethink or abandon this particular management approach; they could be pushed into a situation that causes a more comprehensive relapse.

While we were initially encouraged by one report in a blog from QMUL indicating that the kind of exercise GES might involve did reflect the seriousness of this illness e.g. walking for 1 minute each day, or walking for 5 minutes each day, these examples assumed walking was a reasonable exercise

when for many e.g. those in a wheelchair, it is not. It was also noted that these particular examples were not reflected in the GES booklet.

Even the adoption of regular unguided and unsupervised stretching could be too much for some people particularly if attempted when standing. And the character, 'Julie' (GES booklet, page 11) – showering daily, travelling to and from work, working almost full-time each day of the week, doing the housework, socialising, cooking, even regularly watching TV and reading – strongly suggest that GES is aimed at high-functioning individuals and certainly not the vast majority of those the ME Association seeks to represent.

We remain concerned that practitioners can plan and deliver therapies with minimal regard to individual patient ability or available support, and that the therapies themselves have become far too standardised and inappropriate. We are also of the opinion that even if GES and CBT were delivered appropriately in clinic or at home remotely and tailor-made to the individual, they are not really suited for study in randomised controlled trials – particularly ones that only use subjective outcome measures.

You cannot standardise therapies or necessarily blind them like you can a drug for example, especially when therapeutic delivery should depend very much on understanding the needs and abilities of the individual and the ability and freedom of the practitioner to work with patients on a one-to-one basis and tailor their advice accordingly. People with ME/CFS have a variety of abilities and the condition itself is fluctuating, and while the people in this trial might have been mildly affected, applying the same standard approach to everyone with this disease would be wrong, and highly likely to not only lead to worse outcomes, but also to dire consequences for the individual.

Trials such as this one are giving some secondary care clinics carte-blanche to apply standardised, cost-effective approaches to people who cannot achieve what is expected because of the disease mechanisms underlying ME/CFS. Had we seen results from the employment of objective measures we might have better evidence indicating just how well participants actually managed to adhere to their exercise plans and goals. As it is we are not convinced by the results and can only fall back on the comprehensive patient-testimony provided by those who have actually tried GET in secondary care.

The ME Association continue to recommend the use of more suitable activity management strategies that take much better account of the disease and incorporate the principles applied in pacing – principles that allow patients the freedom to judge for themselves when to embark on appropriately tailored and suitable forms of activity.