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Myalgic encephalomyelitis/chronic fatigue syndrome patients' reports of symptom changes following cognitive behavioural therapy, graded exercise therapy and pacing treatments: Analysis of a primary survey compared with secondary surveys

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Abstract

Cognitive behavioural therapy and graded exercise therapy are promoted as evidence-based treatments for myalgic encephalomyelitis/chronic fatigue syndrome. This article explores patients' symptom responses following these treatments versus pacing therapy, an approach favoured by many sufferers. We analyse data from a large cross-sectional patient survey ($n = 1428$) and compare our findings with those from comparable patient surveys ($n = 16,665$), using a mix of descriptive statistics and regression analysis modelling. Findings from analysis of primary and secondary surveys suggest that cognitive behavioural therapy is of benefit to a small percentage of patients (8%–35%), graded exercise therapy brings about large negative responses in patients (54%–74%), while pacing is the most favoured treatment with the lowest negative response rate and the highest reported benefit (44%–82%).

Keywords

chronic fatigue syndrome, cognitive behavioural therapy, graded exercise therapy, patient satisfaction, treatment

Background

Epidemiological estimates suggest around 1 million people in the United States (Green et al., 2015) and around 250,000 in the United Kingdom (Department of Health, 2002) suffer from myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS). The World Health Organization (WHO) classifies ME, sometimes

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differentiated from CFS, as a neurological disease (WHO, 2007). The abbreviation 'ME/CFS' is often used in the literature to denote the illness, taking account of the controversies surrounding the aetiology and pathogenesis. Despite a relatively large number of sufferers, the disease remains poorly understood. Doctors and scientists have yet to agree on a cause; thus, various treatments have been applied experimentally without reference to a universally accepted model of disease pathogenesis. In 2015, the US Institute of Medicine conducted an extensive review of scientific evidence and suggested renaming ME/CFS 'Systemic Exertion Intolerance Disease' to better reflect the profound physical disabilities most sufferers endure, including prolonged relapses and symptom exacerbation after minimal exertion (Institute of Medicine, (IOM), 2015). The illness has a major negative impact on the quality of life, economic and social status (Drachler Mde et al., 2009; Jason et al., 2008).

A wide range of treatments have been tested on ME/CFS patients, ranging from drug therapies, mainly antidepressants and immunological agents, to non-pharmacological therapies, often psychobehavioural therapies (Smith et al., 2015). Over the last two decades, two treatments, cognitive behavioural therapy (CBT) and graded exercise therapy (GET), have gained prominence. CBT originated from the work of Beck (1976), an intervention for patients with depression. GET is an exercise therapy designed to increase the physical activity through gradual increasing of exercise tolerance levels. The role of CBT in ME/CFS is to challenge patients' illness beliefs and unwanted cognitions (Knoop et al., 2010; Sharpe, 2010), while GET is used to address fear activity avoidance behaviours and to prevent or reverse physiological deconditioning (Moss-Morris et al., 2005). The aim of CBT and GET, often used in combination, is to alter the 'perpetuating' or 'maintaining' factors within a CBT model of ME/CFS (Deary et al., 2007). This CBT model of ME/CFS emerged in the late 1980s (Wessely et al., 1989) with empirical testing during the 1990s by Sharpe et al. (1991) and Surawy et al. (1995) and with later refinements by Moss-Morris et al. (2003) and Wiborg et al. (2010).

CBT and GET are often compared against usual care provided by health care practitioners (e.g. family doctors) or pacing, self-pacing used by sufferers to manage their physical activity or pacing therapy (PT) guided by a therapist. However, vigorous debate has emerged concerning the appropriateness and efficacy of these treatment approaches. The PACE trial is a randomised controlled trial (RCT) that compared CBT, GET and PT, against standard care (White et al., 2011) with a 59–61 per cent improvement rate and a 22 per cent recovery rate following CBT-GET (White et al., 2013). However, a 2-year follow-up study from PACE revealed that between-group differences fell away as the standard medical care and PT groups showed a similar level of improvement (Sharpe et al., 2015). Recent reanalyses of data from the PACE trial suggest that the actual improvement and recovery rates are much lower than first reported, improvement rates fell from 60 per cent to circa 20 per cent and recovery rates fell from 22 to 4 per cent for GET and 7 per cent for CBT, with 3 per cent for PT (Wilshire et al., 2016). A Cochrane Review of CBT for the treatment of ME/CFS found some benefit for a small portion of sufferers with mild-to-moderate severity, but lack of evidence of long-term benefit and inconsistent evidence that CBT has a positive impact on physical function in the disease (Price et al., 2008). The US Agency for Health Care Research and Quality (AHRQ) recently downgraded their rating of CBT and GET for ME/CFS following a review that showed that the effectiveness varied according to the diagnostic criteria used in RCTs (Smith et al., 2016). In the United Kingdom, the National Institute for Health and Care Excellence (NICE; 2007) recommends CBT and GET as evidence-based treatments for ME/CFS. In contrast, patient surveys suggest that these treatments lead to negative outcomes for a large percentage of patients. The ME Association (2015) in the United Kingdom, a leading UK ME/CFS charity, conducted a large

patient survey to gauge sufferers' experiences and views of the three main interventions, CBT, GET and PT. This article presents an independent analysis of this large patient data set and compares findings against similar previously published surveys (2000–2015).

Methods

A survey was opened for 4 months and nationally advertised for anyone with ME/CFS to participate in the study (not only members of the ME Association). Respondents were asked a series of 228 questions and subquestions regarding treatment, particularly CBT, GET or PT. The survey had 1428 respondents. Respondents were required to confirm an affirmative diagnosis of ME/CFS from a qualified medical professional. Respondents also had to confirm that they had taken part in either one-to-one or group course therapy (CBT, GET and PT). Respondents had to indicate the severity of their illness and symptoms before and after their treatment course. We used these data to explore the effect that delivered treatment courses (CBT, GET and PT) had on patients' reported changes in symptoms and illness severity. Of the 1428 respondents, only 954 indicated that they had a confirmed medical diagnosis of ME/CFS, had participated in at least one of the three courses of treatment and completed questions on their symptoms and illness severity status, before and after treatment (our main analysis cohort). Using ordered logistic regression, we first model the direct effect of course approach on change in symptoms (post-course); second, we consider the effects of course composition after adjusting for demographic, condition-specific and course-specific variables. We also comment on the effect that these variables have on change in symptoms (see Appendix 1 for details of our methods). We compare our results against those of other comparable patient surveys.

Results

Respondent demographics

In our survey, 72 per cent of respondents reported having received a positive diagnosis of ME/CFS by a specialist, 22 per cent from a general practitioner (family doctor) and 4.5 per cent from other professionals; 17 per cent reported that their ME/CFS symptoms started prior to age 18 and the average age of ME/CFS onset fell around 35 years. This closely resembles the epidemiological evidence which suggests an average age at onset of 33 years, with ME/CFS age distribution ranging from less than 10 years to 70 years and older (IOM, 2015). Klonoff (1992) reported average illness duration to be 4.4 years. In our survey, the average illness duration was close to 6 years with 6 per cent of respondents having the illness for less than 2 years (12%, 3–4 years; 33%, 5–10 years; 31%, 11–20 years; 18%, 21+ years), suggesting a bias towards more long-term sufferers. Most respondents were women (79%). This finding is consistent with other studies that found female-to-male ratio of between 3:1 and 6:1 (Capelli et al., 2010; Faro et al., 2016). Prognostic data on recovery in ME/CFS suggest a recovery rate of between 5 and 31 per cent (Cairns, 2005). Recovered sufferers are unlikely to be captured by a survey of this kind. The demographics of our survey sample appear representative of the general ME/CFS population (Nacul et al., 2011).

Patients' responses to treatment courses

Table 1 depicts 'change in degree of severity of symptoms' by 'course composition'. A small number of respondents are unused here (*n* = 21 from 954) due to ambiguous answers to some questions regarding treatment overlap. A total of 302 patients (32%) reported worsening of their symptoms post-therapy, 455 (49%) reported that they stayed the same and in 176 (19%) the symptoms showed improvement. When considering the main course content (ignoring other elements), Pacing Therapy (PT) brought about a greater improvement rate in symptoms (44%), versus just 8% in CBT and 12%. GET recorded the largest negative response (74% of patients) versus 18 per cent in CBT and 14 per cent in PT.

Table 1. Patients' symptom changes post-treatment.

Main course content	+Elements	N	Change in symptoms after treatment		
			Worse	Same	Improved
CBT	GET + pacing	157	55 (35.0%)	77 (49.0%)	25 (15.9%)
CBT	GET	39	14 (35.9%)	23 (59.0%)	2 (5.1%)
CBT	Pacing	115	10 (8.7%)	87 (75.7%)	18 (15.7%)
CBT		179	33 (18.4%)	131 (73.2%)	15 (8.4%)
CBT	Any combination	490	112 (22.9%)	318 (64.9%)	60 (12.2%)
GET	CBT; pacing	81	48 (59.3%)	20 (24.7%)	13 (16.0%)
GET	CBT	22	17 (77.3%)	2 (9.1%)	3 (13.6%)
GET	Pacing	44	24 (54.5%)	11 (25.0%)	9 (20.5%)
GET		77	57 (74.0%)	11 (14.3%)	9 (11.7%)
GET	Any combination	224	146 (65.2%)	44 (19.6%)	34 (15.2%)
Pacing	CBT; GET	80	23 (28.8%)	37 (46.3%)	20 (25.0%)
Pacing	CBT	41	4 (9.8%)	14 (34.1%)	23 (56.1%)
Pacing	GET	28	7 (25.0%)	13 (46.4%)	8 (28.6%)
Pacing		70	10 (14.3%)	29 (41.4%)	31 (44.3%)
Pacing	Any combination	219	44 (20.1%)	93 (42.5%)	82 (37.4%)
Overall total		933	302 (32.4%)	455 (48.8%)	176 (18.9%)

CBT: cognitive behavioural therapy; GET: graded exercise therapy.

Irrespective of composition, on average 64 per cent of patients in CBT reported symptoms remaining the same (with those remaining the same or worse totally at 88%). Where CBT was the main content, 91 per cent of patients reported no positive change in symptoms (88% using any treatment combination). The only real deviation from this figure was when both elements of GET and PT were present alongside the main CBT content; approximately two-thirds reported no change (65.0%) and approximately equal numbers reported worse symptoms (19.1%) or an improvement (15.9%). Where GET was the main content or included in combination with any other treatment course (CBT or PT), patients tended to state that their symptoms worsened more frequently than improved. In contrast, the addition of elements of PT improved outcomes, relative to the corresponding courses in which it was not present. These observations were formally tested using ordered logistic regression. Table 2 depicts the distribution of the demographic, condition-specific and course-specific independent variables included in the model.

Ordered logistic regression analysis of 'patient response to treatment courses' on 'course content' and 'respondent demographics'

Without controlling for any covariates, our model shows (Table 3) that a greater percentage of CBT in the course has a non-significant negative effect on symptom change post-course ($\beta_{CBT}=-0.0049$; 95% CI (-0.0795, 0.0697); $p=0.897$). A greater percentage of GET has a significant negative effect on symptom change – patients report a worsening of symptoms post-therapy ($\beta_{GET}=-0.3226$; 95% CI (-0.3932, -0.2519); $p<0.001$), while a greater percentage of PT has a significant positive effect on symptom change – patients report an improvement in symptoms post-therapy ($\beta_{PT}=0.2190$; 95% CI (0.1503, 0.2877); $p<0.001$). These conclusions were unchanged after controlling for the demographic, condition-related and course-related variables (Table 3), although the strength of association between symptom change and the percentage of GET or PT in the course substantially weakened ($\beta_{GET}=-0.2247$; $\beta_{PT}=0.1179$),

Table 2. Patients' symptom changes post-treatment by demographic, condition-specific and course-specific variables.

Variable	N	Change in symptoms after treatment		
		Worse	Same	Improved
Age at onset of ME, years	954	307 (32.2%)	465 (48.7%)	182 (19.1%)
12 or under	71	33 (46.5%)	26 (36.6%)	12 (16.9%)
13–18	94	28 (29.8%)	47 (50.0%)	19 (20.2%)
19–24	115	42 (36.5%)	61 (53.0%)	12 (10.4%)
25–34	241	71 (29.5%)	116 (48.1%)	54 (22.4%)
35–44	254	85 (33.5%)	127 (50.0%)	42 (16.5%)
45 and over	179	48 (26.8%)	88 (49.2%)	43 (24.0%)
Gender	957	309 (32.3%)	467 (48.8%)	181 (18.9%)
Female	758	255 (33.6%)	363 (47.9%)	140 (18.5%)
Male	199	54 (27.1%)	104 (52.3%)	41 (20.6%)
Duration of ME at start of course, years	938	298 (31.8%)	460 (49.0%)	180 (19.2%)
<1	111	30 (27.0%)	51 (45.9%)	30 (27.0%)
1–2	258	75 (29.1%)	118 (45.7%)	65 (25.2%)
3–4	157	51 (32.5%)	81 (51.6%)	25 (15.9%)
5–10	217	78 (35.9%)	106 (48.8%)	33 (15.2%)
>10	195	64 (32.8%)	104 (53.3%)	27 (13.8%)
Who diagnosed you?	957	310 (32.4%)	466 (48.7%)	181 (18.9%)
Medical specialist	688 (71.9%)	225 (32.7%)	336 (48.8%)	127 (18.5%)
General practitioner	227 (23.7%)	77 (33.9%)	102 (44.9%)	48 (21.1%)
Other health professional	42 (4.4%)	8 (19.0%)	28 (66.7%)	6 (14.3%)
Therapists' beliefs about ME	953	307 (32.2%)	466 (48.9%)	180 (18.9%)
Physical illness	190	36 (18.9%)	92 (48.4%)	62 (32.6%)
Psychological illness	178	97 (54.5%)	77 (43.3%)	4 (2.2%)
Physical/psychological mix	301	95 (31.6%)	140 (46.5%)	66 (21.9%)
Unsure	284	79 (27.8%)	157 (55.3%)	48 (16.9%)
Course dynamic	959	310 (32.3%)	467 (48.7%)	182 (19.0%)
1 to 1	667	211 (31.6%)	333 (49.9%)	123 (18.4%)
Group based	292	99 (33.9%)	134 (45.9%)	59 (20.2%)
Was the course appropriate?	947	307 (32.4%)	458 (48.4%)	182 (19.2%)
No	460	256 (55.7%)	199 (43.3%)	5 (1.1%)
Partly	238	39 (16.4%)	153 (64.3%)	46 (19.3%)
Yes	249	12 (4.8%)	106 (42.6%)	131 (52.6%)
Amount of course completed	947	305 (32.2%)	460 (48.6%)	182 (19.2%)
All	589	130 (22.1%)	305 (51.8%)	154 (26.1%)
More than half	115	43 (37.4%)	57 (49.6%)	15 (13.0%)
Roughly half	51	27 (52.9%)	24 (47.1%)	0 (0.0%)
Less than half	105	59 (56.2%)	44 (41.9%)	2 (1.9%)
Unsure	87	46 (52.9%)	30 (34.5%)	11 (12.6%)

ME: myalgic encephalomyelitis.

while the association between symptoms and percentage of CBT became positive ($\beta_{CBT} = 0.0591$).

The strongest independent association with change in symptoms was with appropriateness of the course ($\chi^2_{(2)} = 164.9$; $p < 0.001$); patients who

Table 3. Parameter estimates from ordered logistic regression analyses.

Variable	Coefficient (95% CI)	p	Coefficient (95% CI)	p
Inverse sine (% of CBT in course)	−0.00 (−0.08, 0.07)	0.897	0.06 (−0.03, 0.15)	0.190
Inverse sine (% of GET in course)	−0.32 (−0.39, −0.25)	<0.001	−0.22 (−0.31, −0.14)	<0.001
Inverse sine (% of PT in course)	0.22 (0.15, 0.29)	<0.001	0.12 (0.03, 0.20)	0.006
Age at onset of ME, years				
12 or under			0.03 (−0.57, 0.63)	0.041
13–18			0.80 (0.27, 1.32)	
19–24			0.29 (−0.21, 0.79)	
25–34			0.44 (0.05, 0.84)	
35–44			Reference	
45 and over			0.40 (−0.03, 0.83)	
Gender				
Female			Reference	0.018
Male			0.42 (0.07, 0.77)	
Duration of ME at start of course, years				
<1			Reference	0.008
1–2			−0.57 (−1.06, −0.07)	
3–4			−0.79 (−1.34, −0.24)	
5–10			−0.86 (−1.38, −0.34)	
>10			−0.88 (−1.41, −0.35)	
Who diagnosed you?				
Medical specialist			Reference	0.617
General practitioner			0.03 (−0.31, 0.37)	
Other health professional			0.34 (−0.34, 1.03)	
Beliefs about ME				
Physical illness			Reference	0.086
Psychological illness			−0.48 (−0.99, 0.02)	
Physical/psychological mix			0.01 (−0.41, 0.43)	
Unsure			0.05 (−0.38, 0.49)	
Course dynamic				
1 to 1			Reference	0.711
Group based			−0.06 (−0.39, 0.26)	
Was the course appropriate?				
No			−3.13 (−3.62, −2.65)	<0.001
Partly			−1.42 (−1.85, −0.98)	
Yes			Reference	
Amount of course completed				
All			Reference	0.001
More than half			−0.59 (−1.04, −0.13)	
Roughly half			−0.58 (−1.24, 0.07)	
Less than half			−0.82 (−1.32, −0.33)	
Unsure			−0.58 (−1.13, −0.04)	

CBT: cognitive behavioural therapy; GET: graded exercise therapy; ME: myalgic encephalomyelitis; PT: pacing therapy; CI: confidence interval.

rated the course 'not appropriate' (or only partially so) reported a significant worsening of symptoms post-therapy than patients who thought the course wholly appropriate. Course attendance was also associated with symptom change ($\chi^2_{(4)} = 17.9$; $p = 0.001$); patients who did not

attend the full course reported a significant worsening of symptoms compared with patients who attended the full course. This was particularly true if attending less than half the course. 'Course Dynamic' was not associated with change in symptoms ($p=0.711$). Age at ME onset was marginally associated with change in symptoms ($\chi^2_{(5)}=11.6$; $p=0.041$); compared with 35–44 year olds, all other age groups reported some improvement in their symptoms post-therapy (apart from patients aged 12 years and under), with teenagers reporting the greatest improvement. Men reported a significantly better improvement in their symptoms post-therapy than women ($p=0.018$). Both duration of ME (significantly: $\chi^2_{(4)}=13.7$; $p=0.008$) and therapist's beliefs (weakly: $\chi^2_{(3)}=6.6$; $p=0.086$) were associated with reported changes in symptoms, but not the health professional who gave the diagnosis. In the former case, compared to patients who had had ME for less than 12 months, patients who had had ME for more than 12 months reported a significant worsening of symptoms post-therapy (especially patients who had had ME for >2 years). The belief that ME was psychological (vs physical) resulted in some reported worsening of symptoms post-therapy (but not for mixed beliefs).

Comparing results with previous patient surveys

We conducted a search of common scientific literature databases (PubMed and others) and patient organisation websites (grey literature) to identify similar published patient surveys to compare our primary results with previous ME/CFS patient surveys (2000–2015) that offered data on patients' symptom profile following CBT, GET and PT. Our search revealed more than 15 relevant surveys. We excluded 5 surveys due to lack of clarity regarding treatment approach, leaving 10 included comparable surveys. Table 4 summarises results from crude analysis of these secondary surveys. We present aggregate scores concerning whether or not interventions improved symptoms, had no change or worsen/deteriorate symptoms. CBT brought about improvement in symptoms for

approximately 35 per cent of respondents (65% unchanged/worse). In total, 25 per cent of GET reported improvement in symptoms (17% unchanged/54% worse), while 82 per cent reported benefit following PT with only 4 per cent deterioration. These findings are better than our primary survey findings for CBT/GET benefit (1/10 vs 3/10), but similarly show a pattern that GET brings about a worsening in symptom experience for at least 5 out of every 10 patients, with PT benefiting far more patients by a large margin (8/10).

Discussion

CBT is offered to patients based on a model of dysfunctional illness beliefs (Deary et al., 2007; Sharpe, 2010) and rests on a theory that ME/CFS is perpetuated by such factors (Moss-Morris et al., 2003). In our primary survey, patients were split on the appropriateness of CBT, with over half finding it inappropriate (46% appropriate/partly appropriate) to their needs. Findings from our patient survey and secondary survey analysis show that CBT has little impact on symptom improvement for approximately 70–90 per cent of patients, raising questions about the utility of the CBT model of ME/CFS. For those who benefit from CBT, CBT may be an adjunct therapy that helps ME/CFS patients deal with the emotional distress of illness, the anxiety generated by suffering troubling physical symptoms, and the secondary depression that is associated with most chronic illnesses (Harris, 2012). Our data indicate that CBT therapists who regard ME/CFS as a physical illness are more likely to have a better chance of helping patients improve symptoms and relieve distress, compared to those who view the illness as psychological.

GET fails to help the majority of ME/CFS patients improve symptoms and has a marked negative impact on approximately 50 per cent of patients. GET also had a marked negative impact on perceived degree of illness severity, particularly for those with severe to very severe presentations, with 21 per cent more patients reporting being more severely afflicted after GET. Not surprisingly, 78 per cent of patients in

Table 4. Summary of key symptom change data from ME/CFS patient surveys (2000–2015).

Organisation (year)	Country	Year	N-respondents	Intervention	Improvement (slightly or greatly improved)	No change	Deterioration (slightly or much worse)
ME Association (2015)	United Kingdom	2015	179	CBT	8%	73%	18%
			77	GET	12%	14%	74%
			69	PT	45%	41%	14%
Gunn et al. (2014) Norwegian ME Association	Norway	2014	368	CBT	15%	63%	22%
			328	GET	14%	20%	66%
Action for ME (2014)	United Kingdom	2014	690	CBT	54%	34%	12%
			471	GET	35%	18%	47%
			1352	PT	85%	12%	4%
ME Association (2010)	United Kingdom	2010	997	CBT	26%	55%	20%
			906	GET	22%	21%	57%
			2137	PT	71%	24%	5%
Bjørkum et al. (2009)	Norway	2009	311	CBT	57%	36%	7%
			620	GET	13%	8%	79%
			804	PT	96%	2%	2%
Action for ME and The Association of Young People with ME (2008)	United Kingdom	2008	699	CBT	50%	38%	12%
			722	GET	45%	21%	34%
			1750	PT	82%	15%	3%
Koolhaas et al. (2008)	The Netherlands	2008	100	CBT	32%	30%	38%
De Veer and Francke (2008)	The Netherlands	2008	115	CBT	30%	43%	27%
			142	GET	43%	24%	33%
			172	PT	57%	34%	9%
Action for ME (2007)	Scotland	2007	160	CBT	39%	44%	18%
			172	GET	12%	14%	74%
			298	PT	86%	10%	4%
Action for ME (2001)	United Kingdom	2001	285	CBT	7%	67%	26%
			1214	GET	34%	16%	50%
			2180	PT	89%	9%	2%
Total (averages)			3251	CBT	34%	47%	20%
			4652	GET	26%	17%	57%
			8762	PT	80%	15%	5%
Weighted				CBT	35%	48%	17%
				GET	28%	17%	54%
				PT	82%	14%	4%

CBT: cognitive behavioural therapy; GET: graded exercise therapy; ME: myalgic encephalomyelitis; PT: pacing therapy.
All percentages rounded to closest round number/some crossover between respondent numbers.

our survey reported GET not to be appropriate to their needs. The beliefs of GET therapists have an effect on outcomes, with 80 per cent of patients reporting no benefit if the therapist believed ME/CFS to be a psychological illness. This evidence contrasts with RCTs that report benefits using GET in CFS (Moss-Morris et al., 2005; White et al., 2011). The high rate of adverse symptom reactions to GET observed in our survey and secondary survey analysis may well be connected to the advice of therapists to continue exercising even if symptoms worsen, with pushing 'beyond limits' a key feature of GET (Bavinton et al., 2004). While physiological deconditioning is important to combat in chronic illness, alternative physical rehabilitative therapies may need to be developed and tested that take account of ME/CFS-specific features, including orthostatic intolerance (Frith et al., 2014) and symptom flare post-exertion (Twisk and Geraghty, 2015).

Pacing alone brought about the greatest positive impact on symptom experience with 44 per cent of patients reporting improvement, compared with 8 per cent in CBT and 12 per cent in GET treatment. Following PT, 14 per cent reported worsening symptoms, compared with 18 per cent in CBT and 74 per cent in GET, making pacing the least negative treatment approach. Much more detailed empirical research is needed to qualify these findings. PT is overwhelmingly favoured by patients (84% finding it appropriate/partly appropriate) and has a moderate impact on reducing the degree of illness severity. Secondary surveys show that 82 per cent of patients report improvement with PT, compared with 35 per cent in CBT or 28 per cent in GET. The beneficial outcomes of pacing were strongly correlated with the beliefs of the therapists, with 53 per cent of patients reporting benefit if the therapist believed ME/CFS to be a physical illness, compared to just 5 per cent if the therapist believed ME/CFS to be psychological. Unlike CBT and GET, that are interventions to emerge from a theoretical model of ME/CFS (Deary et al., 2007; Surawy et al., 1995), pacing is less of a formal therapy and

more of a personal approach to energy management practised by ME/CFS sufferers. The benefit of PT may relate to the way in which it allows a sufferer to adapt to the illness and work within limits, while testing boundaries. This approach is less invasive than CBT or GET programmes and may be more appropriate for the most severely afflicted. It is worthwhile remembering that most RCTs of CBT/GET only recruit participants well enough to attend clinics (mild to moderate cases).

Benchmarking key findings

Findings from our primary and secondary survey analysis conflict with numerous RCTs that report CBT and GET to be superior and safe treatments for ME/CFS (e.g. PACE trial). However, the PACE trial has attracted much criticism (Kindlon, 2011b). Reanalysis of data from PACE reveals alterations to methods that make CBT and GET appear more beneficial than would have been the case if the original protocol had been adhered to (Goldin, 2016). Detractors point to the way in which recovery was operationally defined as not requiring return to normal, or near normal, levels of physical activity (Geraghty, 2016; Wilshire et al., 2016). A Cochrane review of CBT in CFS found that 40 per cent of CFS patients report a reduction in self-rated fatigue following CBT, with 26 per cent improving in usual care, a differential of only 14 per cent added benefit of CBT above standard care using subjective measures. Price et al. (2008) concluded that the benefits of CBT are not sustained over the long term and that there is little evidence of improvements in physical function following CBT. Moss-Morris et al. (2005) observed a decrease in self-rated fatigue in CFS using GET, but Wiborg et al. (2010) observed that reduced fatigue did not correlate with an increase in physical activity measured objectively with actometers. Other RCTs have found no substantive benefits using CBT or GET (Núñez et al., 2011; Wearden et al., 2010). A Cochrane review of non-pharmacological interventions for functional

syndromes, including CFS, noted multiple methodological concerns in psychotherapy trials, including high drop-out rates and selective biases in sampling (Van Dessel et al., 2014). ME/CFS is difficult to diagnose and it is speculated that clinical trials often involve volunteer bias and include patients with psychiatric illnesses and milder cases. These patients may respond better to CBT or GET than patients with more moderate-to-severe cases that are captured by surveys.

Negative responses in context

A Cochrane review of exercise therapy for CFS found that exercise therapy did not have a detrimental impact on primary outcomes (Larun et al., 2016), but this finding is based on limited reporting of serious adverse reactions (SARs), from just one study. The largest RCT (PACE) found little evidence of serious adverse effects, with just two SARs reported in the GET group (Dougall et al., 2014). The FINE trial (Wearden et al., 2010) also found no SARs using CBT/GET. In contrast, a detailed report on harms in ME/CFS treatment (Kindlon, 2011a) found that 51 per cent of patients surveyed (range, 28%–82%; $n = 4338$) reported that GET worsened their health, while 20 per cent (range, 7%–38%; $n = 1808$) reported some adverse reaction to CBT. Our survey findings of high negative responses to GET are inconsistent with RCTs that report no substantial adverse outcomes using CBT/GET to treat ME/CFS, but are consistent with Kindlon (2011a) and mirror the findings from a detailed epidemiological study by Nacul et al. (2011) who found that 81 per cent of ME/CFS patients reported fatigue after exercise (>24 hours), 72 per cent had an intolerance to exercise and 69 per cent had malaise after exertion (>24 hours). A recent meta-synthesis of seven relevant clinical studies found that acute exercise increases fatigue in ME/CFS patients, particularly after 4 hours (Loy et al., 2016). Physiological reasons for exercise intolerance and post-exertional malaise in ME/CFS include cellular events and immune activation events (Twisk and Geraghty, 2015).

In clinical trials, certain treatment biases may partly account for differences in reports of harms/negative responses in patient surveys that canvass sufferers from patient organisations and community settings (Lilienfeld et al., 2014). In RCTs, manualised CBT/GET instructs patients to view negative experiences as unhelpful (White et al., 2007); thus, the patient is asked to ignore or dismiss adverse reactions to treatments. In addition, patients undertaking treatments may be reluctant to report all harms to therapists, given the 'therapeutic relationship', even if harms occur (Blease, 2015). Scott and Young (2016) stated that current methods for recording the negative effects of psychotherapies are insufficient. A systematic review of treatments for ME/CFS (Smith et al., 2015) suggests harms in GET are poorly reported in exercise trials with little subgroup analysis. This might help explain why RCTs of CBT or GET for ME/CFS find no major adverse effects; yet, patient surveys consistently find sizeable negative responses to CBT and GET. Drop-out rates in CBT treatment for CFS range from 20 to 42 per cent (Malouff et al., 2008; Price et al., 2008). These patients may make up part of those responding to surveys of these treatments.

Limitations

Patient surveys are open to a range of biases, particularly sampling bias and response biases. In our primary survey sample, more than 70 per cent of respondents reported having ME/CFS for more than 4 years. ME/CFS sufferers belonging to patient advocacy groups tend to have more long-term or severe illness presentations. Many respondents reported undertaking multiple overlapping treatments. Here, recall bias is a concern. However, we isolated single treatment courses for analysis (e.g. CBT only) to minimise this bias; this greatly reduced cohort sizes and subsequent analysis is likely to be unpowered. These factors must be considered in terms of generalising our results to a wider ME/CFS population. In addition, patient survey evidence is considered inferior to evidence to methodological approaches

such as controlled clinical trials. In our survey analysis (primary and secondary), we could not attest that all treatments were carried out in a uniform manner, there may have been variations in approach; however, given there are few dedicated NHS CFS treatment centres in the United Kingdom, this is not a surprise. In addition, few RCTs have explored pacing compared to CBT or GET; thus, patient surveys offer a valuable insight into the 'patient experience'. While survey evidence may include several biases, this does not mean that survey evidence is wholly unreliable. A study to compare unsolicited ratings of care from patients across 146 acute general hospital trusts in England found that patients' unsolicited feedback correlated well with conventional research findings (Greaves et al., 2012). As such, patient survey evidence should be carefully considered.

Conclusion

This article presents results pertaining to ME/CFS patient reports of symptom changes following CBT, GET or PT. While a small percentage of patients report some benefit from either CBT or GET, the majority experience no benefit. In contrast, pacing brings about the greatest positive impact with the least negative reactions. GET brings about a substantive deterioration in symptoms for almost half of patients and it is the least favoured treatment, compared with pacing, which is most favoured by patients. Adding GET in combination with other treatments worsens outcomes and contributes to increases in illness severity, whereas adding pacing in combination improves outcomes. These findings conflict with evidence from clinical trials that report CBT and GET to be superior treatments, but are consistent with findings from multiple patient surveys that span 15 years and multiple countries. Therapists' views have an impact on patient outcomes, with views of ME/CFS being a physical illness associated with better outcomes than views of ME/CFS being psychological illness. Further research is needed to validate these findings and to investigate if pacing is a viable alternative treatment approach in ME/CFS.

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Appendix I

Data management and analysis plan

Data management. Five intervention types (or therapies), cognitive behavioural therapy (CBT) only, graded exercise therapy (GET) only, Pacing only, any two in combination and all three combined, are examined on three outcomes (general symptoms, appropriateness and specific symptoms). General symptoms refers to effect on symptom improvement overall (recoded as 'better', 'same', 'worse'). Appropriateness refers to perception of the course as appropriate to the patient's needs ('yes', 'partly', 'no'). Specific symptoms refer to the effect of an intervention on the following symptoms: exercise-induced muscle fatigue, post-exertional malaise, muscle pain (myalgia) and cognitive dysfunction, for example, problems with memory and concentration. The role and purpose of CBT, GET and pacing therapy (PT) are described in the 'Background' section. The dependent variable was the outcome of the course of treatment, assessed via a Likert scale, with three possible responses to indicate change – improvement, no change or some worsening of symptoms. We combined and collapsed answers that indicted improvement, either 'somewhat' or 'mostly' improved into 'improved', the same for worsening. Several independent variables were examined for possible effects on the outcome variable in an ordered logistic regression model. They are as follows.

Content of course. Three courses of treatment, namely CBT, GET and Pacing, were the subject of this study. However, analysis was complicated by the fact that a substantial number of patients received a combination of these

treatments, some partially and some in full. Due to the relatively small counts of cases in the analysis, it was necessary to simplify the composition of the course of treatment variable. In the cases when patients reported receiving a course of treatment that contained elements of other courses, we assigned weights to them as follows: the main course received a weighting of 80 per cent, a single additional course received 20 per cent and two additional courses received 10 per cent each. Although the weightings might appear subjective, our subsequent analysis showed that varying them did not change the outcome of the analysis qualitatively. The alternative tests were done with percentages of 60 and 40 in the single additional course case and 60, 20, 20 in the case of two additional courses of treatment. In their current format, the triplet of variables defining course composition are necessarily collinear (they sum to 100) and any regression model would omit one of them as being redundant (i.e. it can be derived from the other two). We therefore use a transformation of these variables in order to overcome this collinearity: the inverse sine transformation has been shown to be applicable with data that is subject to the restrictions herein.

Demographics. Age at onset of myalgic encephalomyelitis (ME) was recorded as 12 years or under, 13–18, 19–24, 25–34, 35–44, 45–54, 55–64 and 65+: for analytical purposes, the last three categories were combined because the numbers of cases in them were too small. Participant gender was also controlled for in the analysis.

Condition-specific variables. Number of years with ME was recorded as <1, 1–2, 3–4, 5–6, 7–10, 11–20 and 20+: We combined the 5–6 and 7–10 categories into 5–10, and 11–20 and 20+ into 11+. Other variables related to who set the diagnosis for the patient (medical specialist, general practitioner (GP) or other health professional) and the participants' therapists' beliefs about ME (physical illness, psychological illness, physical/ psychological mix, unsure).

Course-specific variables. Data were available on the course dynamic (one-to-one, group based), appropriateness of the course (wholly, partially, not appropriate) and the amount of the course completed (all, more than half, about half, less than half, unsure).

Statistical methods. Variables that were considered to have ordinal properties (general symptoms, appropriateness) were modelled using ordered logit models (STATA version 13.1). These models are appropriate for dependent variables in which the categories are assumed to be ordered. The *ologit* command in STATA makes the Proportional Odds assumption (here, that the estimated coefficients for a model of 'worse symptoms' vs 'same'/'improved' would be the 'same' as for a model of 'worse'/'same' vs 'improved'). In order to confirm this, we also fitted a stereotype logistic model, appropriate for variables which measure subjective assessments (such as symptom change). The monotonicity of the scale parameters of the stereotype model confirms the ordered nature of the dependent variable and, consequently, the validity of the ordered logits' proportional odds assumption. The results of the stereotype model are not shown here. Specific symptoms (the sum of selected symptoms) were considered to be interval scaled and thus analysed using standard regression models. It is important to point out a number of caveats concerning inferences. Using the appropriate adjustments we attempted to reduce any bias resulting from the differential take up of interventions, and differences in therapist characteristics, all of which might influence outcome.

Analysis plan. Using ordered logistic regression, we first model the direct effect of course composition on change in symptoms (post-course); second, we consider the effects of course composition after adjusting for demographic, condition-specific and course-specific variables. We also comment on the effect that these variables have on change in symptoms.

Analysis rationale. Adjustments were made for the following four variables selected on the

basis of evidence of a relationship to course outcome: therapist's belief about illness ('belief', that is, 'ME is a psychological illness' vs 'other' ('ME is a physical illness, … a mix of a physical and psychological illness', 'can't be sure') whether the course was completed ('not complete' vs 'complete'), 'one-to-one' therapy or group therapy ('group' vs 'one to one') and gender (male vs female). In each case, the second option was considered as the default group. Adjustments were also considered for differences, where known, between the sample who completed the courses section of the survey and the ME/CFS population in the United Kingdom (age, sex). No differences were found, so no further adjustment was necessary. Adjustments are made to enable a comparison of treatments under similar circumstances with comparable client groups, to increase the validity and interpretability of the findings. CBT was chosen as the default or reference in all statistical comparisons. We compared our results with epidemiological data, including a large survey of GP registered cases of ME/CFS in three English regions by Nacul et al. (2011), indicating our sample to be of comparable composition.