

Myalgic encephalomyelitis/chronic fatigue syndrome patients' reports of symptom changes following cognitive behavioural therapy, graded exercise therapy and pacing treatments

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ME/CFS patients' reports of symptom changes following CBT, GET 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 paper 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=1,428) 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 CBT is of benefit to a small percentage of patients (8-35%); GET 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%).

1 Background

2 Epidemiological estimates suggest around 1 million people in the United States suffer from
3 Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS) (Green et al., 2015) and
4 around 250,000 in the United Kingdom (DoH, 2002). The World Health Organisation
5 classifies ME, sometimes differentiated from CFS, as a neurological disease (WHO, 2007).
6 The abbreviation 'ME/CFS' is often used in the literature to denote the illness, taking account
7 of controversies around aetiology and pathogenesis. Despite the relatively large number of
8 sufferers, the disease remains poorly understood. Doctors and scientists have yet to agree on a
9 cause, thus various treatments have been applied experimentally without reference to a
10 universally accepted model of disease pathogenesis. In 2015, the US Institute of Medicine
11 conducted an extensive review of scientific evidence and suggested renaming ME/CFS
12 'Systemic Exertion Intolerance Disease' to better reflect the profound physical disabilities
13 most sufferers endure; including prolonged relapses and symptom exacerbation after minimal
14 exertion (IOM, 2015). The illness has a major negative impact on quality of life, economic
15 and social status (Jason et al., 2008; Drachler et al., 2009).

16 A wide range of treatments have been tested on ME/CFS patients, ranging from drug
17 therapies, mainly antidepressants and immunological agents; to non-pharmacological
18 therapies, often psycho-behavioural therapies (Smith et al., 2015). Over the last two decades
19 two treatments, cognitive behavioural therapy (CBT) and graded exercise therapy (GET)
20 have gained prominence. CBT originates from the work of Aaron Beck, an intervention for
21 patients with depression (Beck, 1976). GET is an exercise therapy designed to increase
22 physical activity via gradual increasing of exercise tolerance levels. The role of CBT in
23 ME/CFS is to challenge patients' illness beliefs and unwanted cognitions (Sharpe, 2010;
24 Knoop et al., 2010), while GET is used to address fear activity avoidance behaviours and to

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2
3 25 prevent or reverse physiological deconditioning (Moss-Morris et al., 2005). The aim of CBT
4
5 26 and GET, often used in combination, is to alter ‘perpetuating’ or ‘maintaining’ factors within
6
7 27 a CBT-model of ME/CFS (Deary et al., 2007). This CBT-model of ME/CFS emerges in the
8
9 28 late 1980s (Wessely et al., 1989) with empirical testing during the 1990s by Sharpe et al.
10
11 29 (1991) and Surawy et al.(1995), with later refinements by Moss-Morris et al. (2003) and
12
13 30 others (Wiborg et al., 2010).

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16
17 31 CBT and GET are often compared against usual care provided by health care practitioners
18
19 32 (e.g. family doctors) or pacing, self-pacing used by sufferers to manage their physical activity
20
21 33 or pacing therapy guided by a therapist (we abbreviate as PT). However, a vigorous debate
22
23 34 has emerged concerning the appropriateness and efficacy of these treatment approaches. The
24
25 35 PACE trial is a randomised controlled trial that compared CBT, GET and PT, against
26
27 36 standard care (White et al., 2011) and reported a 59-61% improvement rate and a 22%
28
29 37 recovery rate following CBT-GET (White et al., 2013). However, a two-year follow-up study
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31 38 from PACE revealed that between group differences fell away as the standard medical care
32
33 39 and pacing therapy groups showed a similar level of improvement (Sharpe et al., 2015).
34
35 40 Recent reanalyses of data from the PACE trial suggests that the actual improvement and
36
37 41 recovery rates are much lower than first reported, improvement rates fall from 60% to circa
38
39 42 20% and recovery rates fall from 22% to 4% for GET and 7% for CBT, with 3% for PT
40
41 43 (Wilshire et al., 2016). A Cochrane Review of CBT for the treatment of ME/CFS found some
42
43 44 benefit for a small portion of sufferers with mild-to-moderate severity, but a lack of evidence
44
45 45 of long-term benefit and inconsistent evidence that CBT has a positive impact on physical
46
47 46 function in the disease (Price et al., 2008). The US Agency for Health Care Research and
48
49 47 Quality (AHRQ) recently down-graded their rating of CBT and GET for ME/CFS following
50
51 48 a review that showed that the effectiveness of varied according to the diagnostic criteria used
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53 49 in RCTs (Smith et al., 2016). In the UK, the National Institute for Health and Care Excellence
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2
3 50 recommends CBT and GET as evidenced-based treatments for ME/CFS (NICE, 2007). In
4
5 51 contrast, patient surveys suggest that these treatments lead to negative outcomes for a large
6
7 52 percentage of patients. The UK ME Association, a leading UK ME/CFS charity, conducted a
8
9 53 large patient survey to gauge sufferers' experiences and views of the three main
10
11 54 interventions, CBT, GET and PT (ME Association, 2015). This paper presents an
12
13 55 independent analysis of this large patient dataset and compares findings against similar
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15 56 previously published surveys (2000-2015).
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20 **Methods**

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23 58 An online survey was opened for 4 months and advertised nationally to anyone with ME/CFS
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25 59 (not only members of the ME Association). Respondents were asked a series of 228 questions
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27 60 and sub-questions regarding treatment, particularly CBT, GET or PT. The survey had 1428
28
29 61 respondents. Respondents were required to confirm an affirmative diagnosis of ME/CFS from
30
31 62 a qualified medical professional. Respondents also had to confirm that they had taken part in
32
33 63 either one-to-one or group course therapy (CBT, GET, PT). Respondents had to indicate the
34
35 64 severity of their illness and symptoms before and after their treatment course. We used this
36
37 65 data to explore the effect that delivered treatment courses (CBT, GET, and PT) had on
38
39 66 patients' reported changes in symptoms and illness severity. Of the 1428 respondents, only
40
41 67 954 indicated that they had a confirmed medical diagnosis of ME/CFS, had participated in at
42
43 68 least one of the three courses of treatment and completed questions on their symptoms and
44
45 69 illness severity status, pre- and post- treatment (our main analysis cohort). Using ordered
46
47 70 logistic regression, we first model the direct effect of course approach on change in
48
49 71 symptoms (post-course); second, we consider the effects of course composition after
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51 72 adjusting for demographic, condition-specific and course-specific variables. We also
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53 73 comment on the effect that these variables have on change in symptoms. (Appendix 1 for
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3 74 details of our methods). We compare our results against those of other comparable patient
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5 75 surveys.
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8 76 **Results**

9 77 *Respondents Demographics*

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12 78 In our survey, 72% of respondents reported having received a positive diagnosis of ME/CFS
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15 79 by a specialist, 22% from a general practitioner (family doctor) and 4.5% from other
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18 80 professional, while 17% reported that their ME/CFS symptoms started prior to age 18, the
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21 81 average age of ME/CFS onset fell around 35. This closely resembles epidemiological
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24 82 evidence that suggests an average age at onset of 33 years, with ME/CFS age distribution
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26
27 83 ranging from under-10 years to 70+ years (IOM, 2015). Klonoff (1992) reports average
28
29
30 84 illness duration to be 4.4 years. In our survey, the average illness duration was close to 6
31
32
33 85 years with 6% of respondents having the illness for less than 2 years (12% 3-4 years, 33% 5-
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35
36 86 10, 31% 11-20 years, and 18% 21+ years) suggesting a bias towards more long-term
37
38
39 87 sufferers. Most respondents were female (79%). This finding is consistent with other studies
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41
42 88 that find a female to male ratio of between 3:1 - 6:1 (Faro et al., 2016; Capelli et al., 2010).
43
44
45 89 Prognostic data on recovery in ME/CFS suggest a recovery rate of between 5-31% (Cairns,
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47
48 90 2005). Recovered sufferers are unlikely to be captured by a survey of this kind. The
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51 91 demographics of our survey sample appear representative of the general ME/CFS population
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54 92 (Nacul et al., 2011).
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94 *Patients' responses to treatment courses*

95 Table 1 depicts 'change in degree of severity of symptoms' by 'course composition'. A small
96 number of respondents are unused here ($n=21$ from 954) due to ambiguous answers to some

1
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3 97 questions regarding treatment overlap. 302 patients (32%) reported a worsening of their
4
5 98 symptoms post-therapy, 455 (49%) reported that they stayed the same and 176 (19%)
6
7 99 improved. When considering the main course content (ignoring other elements), Pacing
8
9
10 100 Therapy (PT) brought about a greatest improvement rate in symptoms (44%) versus just 8%
11
12 101 in CBT and 12%. GET recorded the largest negative response (74% of patients) versus 18%
13
14 102 in CBT and 14% in PT.

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16
17 103 INSERT TABLE 1 HERE

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20 104 Irrespective of composition, on average 64% of patients in CBT reported symptoms
21
22 105 remaining the same (with those remaining the same or worse totally 88%). Where CBT was
23
24 106 the main content, 91% of patients reported no positive change in symptoms (88% using any
25
26 107 treatment combination). The only real deviation from this figure was when both elements of
27
28 108 GET and PT were present alongside the main CBT content, roughly two-thirds reported no
29
30 109 change (65.0%) and roughly equal numbers reported worse symptoms (19.1%) or an
31
32 110 improvement (15.9%). Where GET was the main content or included in combination with
33
34 111 any other treatment course (CBT or PT), patients tended to state that their symptoms
35
36 112 worsened more frequently than they improved. In contrast, the addition of elements of PT
37
38 113 improved outcomes, relative to corresponding courses in which it was not present. These
39
40 114 observations were formally tested using ordered logistic regression. Table 2 depicts the
41
42 115 distribution of the demographic, condition-specific and course-specific independent variables
43
44 116 included in the model.

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50 117 INSERT TABLE 2 HERE

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53 118 *Ordered Logistic Regression Analysis of 'Patient Response to Treatment Courses' on*
54
55 119 *'Course Content' and 'Respondent Demographics'*

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3 120 Without controlling for any covariates, our model shows (Table 3) that a greater percentage
4
5 121 of CBT in the course has a non-significant negative effect on symptom change post-course
6
7 122 [$\beta_{\text{CBT}} = -0.0049$; 95% C.I. (-0.0795, 0.0697); $P = 0.897$]. A greater percentage of GET has a
8
9 123 significant negative effect on symptom change - patients report a worsening of symptoms
10
11 124 post-therapy [$\beta_{\text{GET}} = -0.3226$; 95% C.I. (-0.3932, -0.2519); $P < 0.001$], whilst a greater
12
13 125 percentage of PT has a significant positive effect on symptom change - patients report an
14
15 126 improvement in symptoms post-therapy [$\beta_{\text{PT}} = 0.2190$; 95% C.I. (0.1503, 0.2877); $P <$
16
17 127 0.001]. These conclusions were unchanged after controlling for the demographic, condition-
18
19 128 related and course-related variables (Table 3), although the strength of association between
20
21 129 symptom change and the percentage of GET or PT in the course substantially weakened
22
23 130 ($\beta_{\text{GET}} = -0.2247$; $\beta_{\text{PT}} = 0.1179$), whilst the association between symptoms and percentage of
24
25 131 CBT became positive ($\beta_{\text{CBT}} = 0.0591$).
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INSERT TABLE 3 HERE

133 The strongest independent association with change in symptoms was with appropriateness of
134 the course ($\chi^2_{(2)} = 164.9$; $P < 0.001$); patients who rated the course ‘not appropriate’ (or only
135 partially so) reported a significant worsening of symptoms post-therapy than patients who
136 thought the course wholly appropriate. Course attendance was also associated with symptom
137 change ($\chi^2_{(4)} = 17.9$; $P = 0.001$); patients who did not attend for the full course duration
138 reported a significant worsening of symptoms compared with patients attending the full
139 course. This was particularly true if attending less than half the course. ‘Course Dynamic’
140 was not associated with change in symptoms ($P = 0.711$). Age at ME onset was marginally
141 associated with change in symptoms ($\chi^2_{(5)} = 11.6$; $P = 0.041$); compared with 35-44 year olds,
142 all other age-groups reported some improvement in their symptoms post-therapy (apart from
143 patients aged 12 and under), with teenagers reporting the greatest improvement. Men reported

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3 144 a significantly better improvement in their symptoms post-therapy than women ($P = 0.018$).
4
5 145 Both duration of ME (significantly: $\chi^2_{(4)} = 13.7$; $P = 0.008$) and therapist's beliefs (weakly:
6
7 146 $\chi^2_{(3)} = 6.6$; $P = 0.086$) were associated with reported changes in symptoms, but not the health
8
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10 147 professional who gave the diagnosis. In the former case, compared to patients who had had
11
12 148 ME for less than 12 months, patients who had had ME for more than 12 months reported a
13
14 149 significant worsening of symptoms post-therapy (esp. patients who had had ME for >2
15
16 150 years). The belief that ME was psychological (vs. physical) resulted in some reported
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18 151 worsening of symptoms post-therapy (but not for mixed beliefs).
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21 152 *Comparing Results with Previous Patient Surveys*

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25 153 We conducted a search of common scientific literature databases (PubMed and others) and
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27 154 patient organisation websites (grey literature) to identify similar published patient surveys to
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29 155 compare our primary results with previous ME/CFS patient surveys (2000-2015) that offered
30
31 156 data on patients' symptom profile following CBT, GET and PT. Our search revealed more
32
33 157 than 15 relevant surveys. We excluded 5 due to lack of clarity regarding treatment approach,
34
35 158 leaving 10 included comparable surveys. Table 4 summarises results from crude analysis of
36
37 159 these secondary surveys. We present aggregate scores concerning whether or not
38
39 160 interventions improved symptoms, had no change, or worsen/deteriorate symptoms. CBT
40
41 161 brings about improvement in symptoms for approximately 35% of respondents (65%
42
43 162 unchanged/worse). 25% of GET reported improvement in symptoms (17% unchanged/54%
44
45 163 worse), while 82% report benefit following PT with only 4% deterioration. These findings
46
47 164 are better than our primary survey findings for CBT/GET benefit (1/10 v 3/10), but similarly
48
49 165 show a pattern that GET brings about a worsening in symptom experience for at least 5 out of
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51 166 every 10 patients, with Pacing benefiting far more patients by a large margin (8/10).
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57 167 INSERT TABLE 4 HERE
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3 168 **Discussion**
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6 169 CBT is offered to patients based on a model of dysfunctional illness beliefs (Sharpe, 2010;
7
8 170 Deary et al., 2007) and rests on a theory that ME/CFS is perpetuated by such factors (Moss-
9
10 171 Morris et al., 2003). In our primary survey, patients were split on the appropriateness of CBT,
11
12 172 with over half finding it inappropriate (46% appropriate/partly appropriate) to their needs.
13
14 173 Findings from our patient survey and secondary survey analysis show that CBT has little
15
16 174 impact on symptom improvement for approximately 70-90% of patients, raising questions
17
18 175 about the utility of the CBT model of ME/CFS. For those who benefit from CBT, CBT may
19
20 176 be an adjunct therapy that helps ME/CFS patients deal with the emotional distress of illness,
21
22 177 the anxiety generated by suffering troubling physical symptoms, and the secondary
23
24 178 depression that is associated with most chronic illnesses (Harris, 2012). Our data indicates
25
26 179 that CBT therapists whom regard ME/CFS as a physical illness are more likely to have a
27
28 180 better chance of helping patients improve symptoms and relieve distress, compared to those
29
30 181 that view the illness as psychological.
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36 182 GET fails to help the majority of ME/CFS patients improve symptoms and has a marked
37
38 183 negative impact on approximately 50% of patients. GET also had a marked negative impact
39
40 184 on perceived degree of illness severity, particularly for those with severe-to-very severe
41
42 185 presentations, with 21% more patients reporting being more severely afflicted after GET. Not
43
44 186 surprisingly, 78% of patients in our survey reported GET not to be appropriate to their needs.
45
46 187 The beliefs of GET therapists have an effect on outcomes, with 80% of patients reporting no
47
48 188 benefit if the therapist believed ME/CFS to be a psychological illness. This evidence
49
50 189 contrasts with randomised controlled trials that report benefits using GET in CFS (Moss-
51
52 190 Morris et al., 2005; White et al., 2011). The high rate of adverse symptom reactions to GET
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54 191 observed in our survey and secondary survey analysis may well be connected to the advice of
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3 192 therapists to continue exercising even if symptoms worsen, with pushing ‘beyond limits’ a
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5 193 key feature of GET (Bavinton et al., 2016). While physiological deconditioning is important
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7 194 to combat in chronic illness, alternative physical rehabilitative therapies may need to be
8
9 195 developed and tested that take account of ME/CFS-specific features, including orthostatic
10
11 196 intolerance (Frith et al., 2014) and symptom flare post-exertion (Twisk and Geraghty, 2015).

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15 197 Pacing alone brought about the greatest positive impact on symptom experience with 44% of
16
17 198 patients reporting improvement, compared with 8% in CBT and 12% in GET treatment.
18
19 199 Following PT, 14% reported worsening symptoms, compared with 18% in CBT and 74% in
20
21 200 GET, making pacing the least negative treatment approach. Much more detailed empirical
22
23 201 research is needed to qualify these findings. PT is overwhelmingly favoured by patients (84%
24
25 202 finding it appropriate/partly appropriate) and has a moderate impact on reducing the degree
26
27 203 of illness severity. Secondary surveys show that 82% of patients report improvement with
28
29 204 PT, compared with 35% in CBT or 28% in GET. The beneficial outcomes of pacing were
30
31 205 strongly correlated with the beliefs of the therapists, with 53% of patients reporting benefit if
32
33 206 the therapist believed ME/CFS to be a physical illness, compared to just 5% if the therapist
34
35 207 believed ME/CFS to be psychological. Unlike CBT and GET, that are interventions to
36
37 208 emerge from a theoretical model of ME/CFS (Deary et al., 2007; Surawy et al., 1995), pacing
38
39 209 is less of a formal therapy and more of a personal approach to energy management practised
40
41 210 by ME/CFS sufferers. The benefit of PT may relate to the way in which it allows a sufferer to
42
43 211 adapt to the illness and work within-limits, while testing boundaries. This approach is less
44
45 212 invasive than CBT or GET programmes and may be more appropriate for the most severely
46
47 213 afflicted. It is worthwhile remembering that most RCTs of CBT/GET only recruit participants
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49 214 well enough to attend clinics (mild to moderate cases).

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56 215 *Benchmarking Key Findings*
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3 216 Findings from our primary and secondary survey analysis conflict with numerous randomised
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5 217 controlled trials that report CBT and GET to be superior and safe treatments for ME/CFS
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7 218 (e.g. PACE trial). However, the PACE trial has attracted much criticism (Kindlon, 2011a).
8
9 219 Reanalysis of data from PACE reveals alterations to methods that make CBT and GET
10
11 220 appear more beneficial than would have been the case if the original protocol had been
12
13 221 adhered to (Goldin, 2016). Detractors point to the way in which recovery was operationally
14
15 222 defined as not requiring return to normal, or near normal, levels of physical activity (Wilshire
16
17 223 et al., 2016; Geraghty, 2016). A Cochrane review of CBT in CFS found that 40% of CFS
18
19 224 patients report a reduction in self-rated fatigue following CBT, with 26% improving in usual
20
21 225 care, a differential of only 14% added benefit of CBT above standard care using subjective
22
23 226 measures (Price et al., 2008). Price et al. conclude that the benefits of CBT are not sustained
24
25 227 over the long term and that there is little evidence of improvements in physical function
26
27 228 following CBT. Moss-Morris et al. (2005) observed a decrease in self-rated fatigue in CFS
28
29 229 using CBT, but Wiborg et al. (2010) observed that reduced fatigue did not correlate with an
30
31 230 increase in physical activity measured objectively with actometers. Other RCTs have found
32
33 231 no substantive benefits using CBT or GET (Núñez et al., 2011; Wearden et al., 2010). A
34
35 232 Cochrane review of non-pharmacological interventions for functional syndromes, including
36
37 233 CFS, noted multiple methodological concerns in psychotherapy trials, including high drop-
38
39 234 out rates and selective biases in sampling (Van Dessel et al., 2014). ME/CFS is difficult to
40
41 235 diagnose and it is speculated that clinical trials often involve volunteer bias and include
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43 236 patients with psychiatric illnesses and milder cases. These patients may respond better to
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45 237 CBT or GET than patients with more moderate-to-severe cases that are captured by surveys.
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53 238 *Negative Responses in Context*
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3 239 A Cochrane review of exercise therapy for CFS found that exercise therapy did not have a
4
5 240 detrimental impact on primary outcomes (Larun et al., 2016), but this finding is based on
6
7 241 limited reporting of serious adverse reactions (SARs), from just 1 study. The largest RCT
8
9 242 (PACE) found little evidence of serious adverse effects, with just 2 SARs reported in the
10
11 243 GET group (Dougall et al., 2014). The FINE trial (Wearden et al., 2010) also found no SARs
12
13 244 using CBT/GET. In contrast, a detailed report on harms in ME/CFS treatment (Kindlon,
14
15 245 2011b) finds that that 51% of patients surveyed (range 28-82%, $n=4338$) reported that GET
16
17 246 worsened their health, while 20% (range 7-38%, $n=1808$) reported some adverse reaction to
18
19 247 CBT. Our survey findings of high negative responses to GET are inconsistent with RCTs that
20
21 248 report no substantial adverse outcomes using CBT/GET to treat ME/CFS, but are consistent
22
23 249 with Kindlon (2011b) and mirror the findings from a detailed epidemiological study by Nacul
24
25 250 et al. (2011) that found that 81% of ME/CFS patients reported fatigue after exercise (>24
26
27 251 hours); 72% had an intolerance to exercise; 69% had malaise after exertion (>24 hours). A
28
29 252 recent meta-synthesis of 7 relevant clinical studies found that acute exercise increases fatigue
30
31 253 in ME/CFS patients, particularly post-4 hours (Loy et al., 2016). Physiological reasons for
32
33 254 exercise intolerance and post-exertional malaise in ME/CFS include cellular events and
34
35 255 immune activation events (Twisk and Geraghty, 2015).

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41 256 In clinical trials, certain treatment biases may partly account for differences in reports of
42
43 257 harms/negative responses in patient surveys that canvass sufferers from patient organisations
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45 258 and community settings (Lilienfeld et al., 2014). In RCTs, manualised CBT/GET instructs
46
47 259 patients to view negative experiences as unhelpful (White et al., 2007); thus the patient is
48
49 260 asked to ignore or dismiss adverse reactions to treatments. In addition, patients undertaking
50
51 261 treatments may be reluctant to report all harms to therapists, given the 'therapeutic
52
53 262 relationship', even if harms occur (Blease, 2015). Scott and Young (2016) state that current
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55 263 methods for recording the negative effects of psychotherapies are insufficient. A systematic
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3 264 review of treatments for ME/CFS (Smith et al., 2015) suggests harms in GET are poorly
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5 265 reported in exercise trials with little sub-group analysis. This might help explain why RCTs
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7 266 of CBT or GET for ME/CFS find no major adverse effects, yet patient surveys consistently
8
9 267 find sizeable negative responses to CBT and GET. Drop-out rates in CBT treatment for CFS
10
11 268 range from 20%-42% (Price et al., 2008; Malouff et al., 2008). These patients may make up
12
13 269 part of those responding to surveys of these treatments.
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18 270 *Limitations*

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21 271 Patient surveys are open to a range of biases, particularly sampling bias and response biases.
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23 272 In our primary survey sample, more than 70% of respondents reported having ME/CFS for
24
25 273 more than 4+ years. ME/CFS sufferers belonging to patient advocacy groups tend to have
26
27 274 more long-term or severe illness presentations. Many respondents reported undertaking
28
29 275 multiple overlapping treatments. Here recall bias is a concern. However, we isolated single
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31 276 treatment courses for analysis (e.g. CBT only) to minimise this bias; this greatly reduced
32
33 277 cohort sizes and subsequent analysis is likely to be unpowered. These factors must be
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35 278 considered in terms of generalising our results to a wider ME/CFS population. In addition,
36
37 279 patient survey evidence is considered inferior to evidence to methodological approaches such
38
39 280 as controlled clinical trials. In our survey analysis (primary and secondary) we could not
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41 281 attest that all treatments were carried out in a uniform manner; there may have been
42
43 282 variations in approach, however given there are few dedicated NHS CFS treatment centres in
44
45 283 the UK, this is not a surprise. In addition, few RCTs have explored pacing compared to CBT
46
47 284 or GET, thus patient surveys offer a valuable insight into the 'patient experience'. While
48
49 285 survey evidence may include several biases, this does not mean that survey evidence is
50
51 286 wholly unreliable. A study to compare unsolicited ratings of care from patients across 146
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53 287 acute general hospital trusts in England found that patients' unsolicited feedback correlated
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3 288 well with conventional research findings (Greaves et al., 2012). As such, patient survey
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5 289 evidence should be carefully considered.
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8 290 **Conclusions**

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10 291 Our paper presents results pertaining to ME/CFS patients reports of symptom changes
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12 292 following CBT, GET or pacing. While a small percentage of patients report some benefit
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14 293 from either CBT or GET, the majority experience no benefit. In contrast, pacing brings about
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16 294 the greatest positive impact with the least negative reactions. GET brings about a substantive
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18 295 deterioration in symptoms for almost half of patients and it is the least favoured treatment,
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20 296 compared with pacing, which is most favoured by patients. Adding GET in combination with
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22 297 other treatments worsens outcomes and contributes to increases in illness severity, whereas
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24 298 adding pacing in combination improves outcomes. These findings conflict with evidence
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26 299 from clinical trials that report CBT and GET to be superior treatments, but are consistent with
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28 300 findings from multiple patient surveys that span fifteen years and multiple countries.
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30 301 Therapists' views have an impact on patient outcomes, with views of ME/CFS being a
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32 302 physical illness associated with better outcomes than views of ME/CFS being psychological
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34 303 illness. Further research is needed to validate these findings and to investigate if pacing is a
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36 304 viable alternative treatment approach in ME/CFS.
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318

319 **List of abbreviations**

320 CBT – Cognitive Behavioural Therapy

321 GET – Graded Exercise Therapy

322 GP – General Practitioner

323 NHS – National Health Service

324 NICE - National Institute for Health and Care Excellence

325 PT – Pacing Therapy/Treatment

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515 **Table 1: Patients' Symptom Changes Post-Treatment**

Main Course Content	+Elements	N	Change in Symptoms after Treatment		
			Worse	Same	Improve
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%)

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517 **Table 2: Patients' Symptom Changes Post-Treatment by Demographic, Condition-Specific and**
518 **Course-Specific Variables**

Variable	N	Change in Symptoms after Treatment		
		Worse	Same	Improve
Age at Onset of ME	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	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 Prof	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%)

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520 **Table 3: Parameter Estimates from Ordered Logistic Regression Analyses**

Variable	Coefficient (95% C.I.)	P	Coefficient (95% C.I.)	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				
12 or under			0.03 (-0.57, 0.63)	
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	0.041
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				
<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 Prof			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)	
Partly			-1.42 (-1.85, -0.98)	
Yes			Reference	<0.001
Amount of Course Completed				
All			Reference	0.001

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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)

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522 **Table 4 Summary of Key Symptom Change Data from ME/CFS Patient Surveys (2000-2015)**

Organisatio n (Year)	Country	Year	N- responde nts	Inter- vention	Improvement (slightly of greatly improved)	No change	Deterioration (slightly or much worse)
ME Association	UK	(2015)	179	CBT	8%	73%	18%
			77	GET	12%	14%	74%
			69	Pacing	45%	41%	14%
Gunn et al., Norwegian ME Association	Norway	(2014)	368	CBT	15%	63%	22%
			328	GET	14%	20%	66%
			690	CBT	54%	34%	12%
Action for ME	UK	(2014)	471	GET	35%	18%	47%
			1352	Pacing	85%	12%	4%
			997	CBT	26%	55%	20%
ME Association	UK	(2010)	906	GET	22%	21%	57%
			2137	Pacing	71%	24%	5%
			311	CBT	57%	36%	7%
Bjorkum, Wang and Waterloo	Norway	(2009)	620	GET	13%	8%	79%
			804	Pacing	96%	2%	2%
			699	CBT	50%	38%	12%
Action for ME	UK	(2008)	722	GET	45%	21%	34%
			1750x	Pacing	82%	15%	3%
			100	CBT	32%	30%	38%
Koolhaas, de Boorder and van Hoof	The Nether- lands	(2008)	115	CBT	30%	43%	27%
			142	GET	43%	24%	33%
			172	Pacing	57%	34%	9%
De Veer and Francke	The Nether- lands	(2008)	160	CBT	39%	44%	18%
			172	GET	12%	14%	74%
			298	Pacing	86%	10%	4%
Action for ME	Scotland	(2007)	160	CBT	39%	44%	18%
			172	GET	12%	14%	74%
			298	Pacing	86%	10%	4%

Action for UK ME (2001)	(2001)	285	CBT	7%	67%	26%
		1,214	GET	34%	16%	50%
		2180	Pacing	89%	9%	2%
Totals (averages)						
		3,251	CBT	34%	47%	20%
		4,652	GET	26%	17%	57%
		8762	Pacing	80%	15%	5%
Weighted						
			CBT	35%	48%	17%
			GET	28%	17%	54%
			Pacing	82%	14%	4%

523

524 ±All percentages rounded to closest round number/some cross-over between respondent numbers.

525

526 **Appendix 1: Data Management and Analysis Plan**

527 *Data Management:* Five intervention types (or therapies) CBT only, GET only, Pacing only,
528 any two in combination, and all three combined, are examined on three outcomes (general
529 symptoms, appropriateness, specific symptoms). General symptoms refers to effect on
530 symptom improvement overall (recoded as 'better', 'same', 'worse'). Appropriateness refers
531 to perception of the course as appropriate to the patient's needs ('yes', 'partly', 'no').
532 Specific symptoms refers to the effect of an intervention on the following symptoms:
533 exercise-induced muscle fatigue, post-exertional malaise, muscle pain (myalgia) and
534 cognitive dysfunction, e.g. problems with memory and concentration. The role and purpose
535 of CBT, GET and PT are described in the introduction section. The dependent variable was
536 the outcome of the course of treatment, assessed via a Likert scale, with three possible
537 responses to indicate change, either improvement, no change or some worsening of
538 symptoms. We combined and collapsed answers that indicted improvement, either
539 'somewhat' or 'mostly' improved into 'improved', the same for worsening. Several
540 independent variables were examined for possible effects on the outcome variable in an
541 ordered logistic regression model. They are: Content of Course: Three courses of treatment,
542 namely CBT, GET and Pacing, were the subject of the current study. However, analysis was
543 complicated by the fact that a substantial number of patients received a combination of these
544 treatments, some partially and some in full. Due to the relatively small counts of cases in the
545 analysis it was necessary to simplify the composition of the course of treatment variable. In
546 the cases when patients reported receiving a course of treatment that contained elements of
547 other courses, we assigned weights to them as follows: the main course received a weighting
548 of 80%, a single additional course received 20%, and two additional courses received 10%
549 each. Although the weightings might appear subjective, our subsequent analysis showed that
550 varying them did not change the outcome of the analysis qualitatively. The alternative tests
551 were done with percentages of 60 and 40 in the single additional course case and 60, 20, 20 in
552 the case of two additional courses of treatment. In their current format, the triplet of variables
553 defining course composition are necessarily collinear (they sum to 100) and any regression
554 model would omit one of them as being redundant (i.e. it can be derived from the other two).
555 We therefore use a transformation of these variables in order to overcome this collinearity:
556 the inverse sine transformation has been shown to be applicable with data that is subject to
557 the restrictions herein. Demographics: Age at onset of ME was recorded as 12 or under, 13-
558 18, 19-24, 25-34, 35-44, 45-54, 55-64 and 65+: for analytical purposes, the last 3 categories

559 were combined because the numbers of cases in them were too small. Participant gender was
560 also controlled for in the analysis.

561 Condition-specific variables: Number of years with ME was recorded as <1, 1-2, 3-4, 5-6, 7-
562 10, 11-20 and 20+: We combined the 5-6 and 7-10 categories into 5-10, and 11-20 and 20+
563 into 11+. Other variables related to who set the diagnosis for the patient (Medical Specialist,
564 GP or Other Health Professional) and the participants' therapists' beliefs about ME (physical
565 illness, psychological illness, physical/ psychological mix, unsure).

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

569 *Statistical Methods:* Variables which were considered to have ordinal properties (general
570 symptoms, appropriateness) were modelled using ordered logit models (STATA version
571 13.1). These models are appropriate for dependent variables in which the categories are
572 assumed to be ordered. The *ologit* command in STATA makes the Proportional Odds
573 assumption (here, that the estimated coefficients for a model of 'worse symptoms' versus
574 'same'/ 'improved' would be the 'same' as for a model of 'worse'/ 'same' versus
575 'improved'). In order to confirm this, we also fitted a stereotype logistic model, appropriate
576 for variables which measure subjective assessments (such as symptom change). The
577 monotonicity of the scale parameters of the stereotype model confirm the ordered nature of
578 the dependent variable and, consequently, the validity of the ordered logits' proportional odds
579 assumption. The results of the stereotype model are not shown here. Specific symptoms (the
580 sum of selected symptoms) was considered to be interval scaled and thus analysed using
581 standard regression models. It is important to point out a number of caveats concerning
582 inferences. Using the appropriate adjustments we attempted to reduce any bias resulting from
583 the differential take up of interventions, and differences in therapist characteristics, all of
584 which might influence outcome.

585 *Analysis Plan:* Using ordered logistic regression, we firstly model the direct effect of course
586 composition on change in symptoms (post-course): secondly, we consider the effects of
587 course composition after adjusting for demographic, condition-specific and course-specific
588 variables. We also comment on the effect that these variables have on change in symptoms.

589 *Analysis Rationale:* Adjustments were made for the following four variables selected on the
590 basis of evidence of a relationship to course outcome: Therapist's belief about illness ('belief'
591 i.e. 'ME is a psychological illness' versus 'other' ('ME is a physical illness,'... a mix of a
592 physical and psychological illness', 'can't be sure') whether the course was completed ('not
593 complete' versus 'complete'), 'one to one' therapy or group therapy ('group' versus 'one to
594 one') and gender (male versus female). In each case, the second option was considered as the
595 default group. Adjustments were also considered for differences, where known, between the
596 sample who completed the courses section of the survey and the ME/CFS population in the
597 UK (age, sex). No differences were found so no further adjustment was necessary.
598 Adjustments are made to enable a comparison of treatments under similar circumstances with
599 comparable client groups, to increase the validity and interpretability of the findings. CBT
600 was chosen as the default or reference in all statistical comparisons. We compared our results
601 with epidemiological data, including a large survey of GP registered cases of ME/CFS in
602 three English regions by Nacul et al. (2011), indicating our sample to be of comparable
603 composition.