Depressive symptoms and pragmatic rehabilitation for chronic fatigue syndrome

A. J. Wearden, G. Dunn, C. Dowrick and R. K. Morriss

Background
Previous research has suggested that depressed mood may predict outcome and moderate response to treatment in chronic fatigue syndrome, although findings have differed between studies.

Aims
To examine potential moderators of response to pragmatic rehabilitation v. general practitioner treatment as usual in a recent randomised trial for patients with chronic fatigue syndrome in primary care (IRCTN74156610).

Method
Simple regressions, with weighting adjustments to allow for missing data, were calculated. Demographic, medical and psychological variables, and treatment arm, were entered separately and as an interaction term. The outcome variable in each case was change in Chalder Fatigue Scale scores, from baseline to 1-year follow-up, our primary outcome point.

Results
Longer illness durations predicted poorer outcome across the two treatment arms. For patients allocated to pragmatic rehabilitation compared with those allocated to treatment as usual, higher levels of depressive symptoms at baseline were associated with smaller improvements in fatigue ($P = 0.022$).

Conclusions
For patients in primary care with higher levels of depressive symptoms, either more intensive or longer pragmatic rehabilitation, or cognitive–behavioural therapy, may be required in order to show a significant improvement in fatigue.

Declaration of interest
None.
In addition to the potential moderators of response to pragmatic rehabilitation outlined earlier (illness severity and disability, comorbidities and illness duration), we considered factors that had been shown to moderate response to treatment in the previous secondary care study — that is, level of symptoms of depression and anxiety, being in receipt of benefits and membership of a local self-help group.17 We also examined the effect of disturbed sleep at the start of the trial, reasoning that sleepiness may have affected the patients’ ability to undertake graded activity and that spending therapy time regularising sleep patterns could have delayed the effect of other elements of pragmatic rehabilitation treatment. Finally, we examined the potential effects of age and gender. In our original report13 we noted that nurses encountered social barriers to treatment when delivering therapy in patients’ homes. Although we did not have a measure of social problems, in accordance with our protocol,16 we examined whether the level of social support available to patients moderated their response to treatment. The FINE study inclusion criteria required that patients fulfilled the Oxford research diagnostic criteria.1 In order to assess the possibility that different diagnostic criteria define different groups who may respond differently to pragmatic rehabilitation treatment, we also examined whether fulfilment of the Fukuda2 or London ME19 criteria moderated response to treatment. The choice of potential moderator variables for this study was guided by the literature and, with the exception of sleep scale scores, specified in our protocol and analysis plan.19

Method

Participants and trial design

Participants were referred to the trial by their GPs. In total, 296 patients aged 18 and over who fulfilled the Oxford criteria for chronic fatigue syndrome1 and other study criteria16 were randomly allocated to one of three treatment arms. Patients were randomised individually, after stratification on two factors – whether the patient was ambulatory or not, and whether the patient fulfilled London ME criteria or not. The three treatment arms were pragmatic rehabilitation or supportive listening, both patient fulfilled London ME criteria or not. The three treatment arms were pragmatic rehabilitation or supportive listening, both arms were pragmatic rehabilitation or supportive listening, both

The primary outcome point for the FINE trial was 70 weeks, and the present study focuses on this outcome point. The outcome measure was change in fatigue from baseline to 1-year follow-up. Fatigue was measured using the 11-item Chalder Fatigue Scale.31 For the present set of analyses, each item was scored 0, 1, 2 or 3, and the 11 items summed to produce a total scale score varying from 0 to 33. Change scores were calculated by subtracting 70-week scores from baseline scores.

Potential moderators

All potential moderator variables were measures taken at the baseline assessment. Measures of illness severity and disability were: patient-reported ambulatory status, defined as use of a mobility aid on most days (yes/no); scores on questions relating to mobility, self-care and usual activities (each scored 0 – no problems, 1 – some problems and 2 – severe problems, and treated as a categorical variable) from the EQ-5D,27 and scores on the Short-Form 36-item questionnaire (SF-36) physical functioning scale,23 calculated as a percentage. Sleep problems were measured using the four items of the Jenkins Sleep Scale.24 At baseline assessment, the number of medical comorbidities reported by patients was recorded. Illness duration in months at baseline was taken from patient report.

Patients were asked whether they were a member of a local CFS/ME support group (yes/no). Levels of anxiety and depressive symptoms were measured using the summed scores on the seven items of each of the two Hospital Anxiety and Depression Scale (HADS);25 in addition, the two scales were summed to produce a HADS total score. Fulfilment of diagnostic criteria for any depressive disorder was obtained from the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I).26 Social support was measured using the three-item Oslo Social Support Scale.27 The first question asks ‘How many people are so close that you can count on them if you have serious personal problems’ (none, 1 or 2, 3–5, more than 5 – treated as an ordinal scale), followed by two questions answered on five-point Likert-type scales, with higher scores indicating less support: ‘How much concern do people show in what you are doing?’ and ‘How easy is it to get practical help from neighbours if you should need it?’ We added a fourth question, answered on a similar five-point scale, ‘How easy is it to get practical help from relatives and friends if you should need it?’ Fulfilment of Fukuda2 and London ME19 diagnostic criteria were obtained using a standard checklist during baseline interview.

Statistical methods

All formal analyses were carried out using Stata version 10 on Windows XP. The sample in each case consisted of patients who had received either pragmatic rehabilitation or GP treatment as usual. Separate regression models were used to evaluate the effect of each potential moderator. First, in each regression analysis the model contained the main effects of treatment arm (coded 0 for GP treatment as usual and 1 for pragmatic rehabilitation), the putative moderator and the interaction between the moderator and the treatment arm (that is the analysis was carried out in a single step by fitting the full model with main effects and the interaction). Next, the regressions were run again with the interaction term dropped to determine the prognostic effect of the potential moderator that was common to the two groups. The outcome variable in each case was change in the Chalder Fatigue Scale scores from baseline to 1-year follow-up (70 weeks). Missing change scores were allowed for by the use of an inverse probability weight estimated through a prior logistic regression analysis using baseline information to predict which patients provided follow-up data,28,29 leading to the estimation of robust standard errors, confidence intervals and associated P-values. The HADS scores, SF-36 physical function, the four items of the Jenkins Sleep Scale, the social support question scores, the number of medical comorbidities and illness duration were all centred on

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their corresponding means prior to the moderator analyses, so that the main treatment effect is interpreted as the effect at the mean value of the putative moderator. However, in the moderator analyses, the main treatment effect is difficult to interpret, and it is the interaction term with pragmatic rehabilitation that is of interest in each analysis, with a statistically significant interaction term implying that the effect of pragmatic rehabilitation varies with the value of the moderator.

**Results**

Baseline scores or frequencies on the putative moderator variables for the entire sample are given in Table 1. Fatigue scores (Likert scores 0, 1, 2, 3) for patients in the pragmatic rehabilitation and treatment as usual arms, at 0, 20 and 70 weeks, are given in Table 2.13

Table 2 shows the results of regression analyses predicting change in fatigue at 70 weeks, our primary outcome point. For ease of reading, the table reports the regression coefficients and significance values of the interaction terms only (pragmatic rehabilitation compared with treatment as usual x predictor variable). See online Table DS1 for a more detailed version of Table 3 that also includes the estimates for the main effects.

There were three significant interaction terms, showing that two baseline measures significantly moderated change in Chalder Fatigue Scale scores at 70 weeks. First, the effect of pragmatic rehabilitation (in comparison with treatment as usual) was lower in those participants who had a higher HADS depression and total scores at baseline. Second, there was a highly significant interaction between EQ-5D self-care score at baseline and treatment allocation – the effect of pragmatic rehabilitation appearing to be detrimental in those participants with severe self-care problems. However, as can be seen in Table 1, only five patients in the entire sample categorised themselves as having severe self-care problems on this measure at baseline. The significant interaction is due to the recovery of the only patient with severe self-care problems at baseline who was allocated to treatment as usual, as compared with one patient with severe self-care problems allocated to pragmatic rehabilitation, and cannot therefore be generalised further.

In addition to the above findings, there were two trends towards significant interactions. The first of these was on the EQ-5D mobility variable, and relates to the comparison between patients self-categorised as having ‘no’ v. ‘some’ mobility problems. As shown in Table 4, there was a trend towards patients with no mobility problems showing greater improvements in fatigue than those with some mobility problems in the pragmatic rehabilitation arm. The opposite pattern was seen in the GP treatment as usual arm. The second trend towards a significant interaction was seen on the Oslo Social Support Scale, item 2, which is patients’ reports of the amount of concern that others showed in what they were doing. Higher scores on this item represent less concern. Compared with patients allocated to treatment as usual, those allocated to pragmatic rehabilitation who reported that people showed more concern and interest in them had larger improvements in Chalder Fatigue Scale scores than those reporting that people showed less concern and interest.

The final set of analyses, where the regressions were repeated without the interaction terms, showed that three variables predicted change in Chalder Fatigue Scale scores across both the pragmatic rehabilitation and GP treatment as usual arms. Patients who were older, those who had longer baseline illness durations and those who reported severe mobility problems at baseline showed smaller improvements in fatigue. The effect with respect to severe mobility problems at baseline is produced by only three cases, and should be interpreted with caution. Table 5 shows the regression coefficients and significance values for these three variables. None of the other variables included in the analyses produced significant effects on fatigue across the two treatment arms (data not shown).

**Discussion**

**Main findings**

This study examined moderators of the effect of pragmatic rehabilitation on fatigue, as compared with GP treatment as usual, in a large RCT in primary care. The main finding was that most of the potential moderators investigated did not moderate the effects of pragmatic rehabilitation. Only baseline levels of HADS depressive symptoms and baseline total HADS scores significantly moderated the effect of pragmatic rehabilitation on fatigue at...
1-year follow-up, the primary outcome point of the trial. Patients who had any SCID-I diagnoses of depression also did less well, but this interaction did not reach statistical significance. Our second analysis showed that older age, longer illness duration and having severe mobility problems at baseline each predicted smaller changes in fatigue across the two treatment arms. The HADS depression, anxiety and total scores did not predict change in fatigue in the combined sample.

In the previous secondary care trial of pragmatic rehabilitation, baseline HADS total scores (that is depression and anxiety scores summed) moderated change in physical functioning after treatment, although the moderating effect on change in fatigue was not examined, so a direct comparison cannot be made. In our study, we considered HADS depression and anxiety scores separately, and found that depression but not anxiety scores interacted significantly with the effect of pragmatic rehabilitation treatment on fatigue. Our finding that a diagnosis of depression was not a significant moderator is consistent with a report that treatment effects of CBT were equivalent for patients with and without psychiatric diagnoses.

It could be the case that patients with higher levels of depressive symptoms, although not necessarily diagnosed as...
Compared with the earlier secondary care trial, might have showed that longer illness duration was a predictor of poorer rehabilitation treatment, although our second set of analyses analysis, illness duration did not moderate the effect of pragmatic comorbidities. Contrary to our expectations, in the moderator duration, greater levels of disability and complicating medical mobility problems showed a smaller improvement in fatigue with patients who initially categorised themselves as having some ambulatory status, or those who belonged to self-help groups benefitted less from treatment. Finally, age and gender did not moderate the effect of pragmatic rehabilitation on fatigue.

**Table 4** Change in Chalder Fatigue Scale scores for patients allocated to pragmatic rehabilitation and general practitioner treatment as usual, by initial EQ-5D mobility categorisation

<table>
<thead>
<tr>
<th>Baseline EQ-5D mobility categorisation</th>
<th>Pragmatic rehabilitation Mean (s.d.)</th>
<th>Treatment as usual Mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No problems</td>
<td>7.4 (9.9)</td>
<td>0.8 (6.1)</td>
</tr>
<tr>
<td>Some problems</td>
<td>4.6 (6.8)</td>
<td>3.4 (8.5)</td>
</tr>
</tbody>
</table>

**Table 5** Regression coefficients for age, baseline illness duration and EQ-5D mobility scores, in regression analyses to predict change in Chalder Fatigue Scale scores at 70 weeks across both the pragmatic rehabilitation and general practitioner treatment as usual groups

<table>
<thead>
<tr>
<th>Effect (s.e.)a</th>
<th>95% CI P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.10 (0.05)</td>
</tr>
<tr>
<td>Illness duration</td>
<td>0.01 (0.004)</td>
</tr>
<tr>
<td>EQ-5D mobility</td>
<td></td>
</tr>
<tr>
<td>Some problems</td>
<td>-0.30 (1.47)</td>
</tr>
<tr>
<td>Severe problems</td>
<td>-2.96 (1.29)</td>
</tr>
</tbody>
</table>

*Unstandardised regression coefficient.*

depressed, are unable to benefit from pragmatic rehabilitation unless their depressive symptoms, particularly loss of interest, pleasure and motivation, are treated first. In such cases, it would be necessary to explain the rationale for the treatment approach carefully, so that patients were assured that their CFS/ME symptoms were understood and not being misdiagnosed as depression. Alternatively, these patients might require longer or more intensive treatment with pragmatic rehabilitation than was possible in our trial, or pragmatic rehabilitation may require some modifications, for example, by including a wider variety of behavioural activation or emotion regulation elements, to address the additional difficulties of patients who have higher levels of depressive symptoms. In line with this suggestion, a recent meta-analytic review of CBT and GET for CFS/ME found that, although both treatments are effective for CFS/ME, CBT, which contains components that might explicitly address emotional difficulties, is the more effective treatment for patients with comorbid anxiety or depressive disorders.

We previously suggested that the smaller effect of pragmatic rehabilitation seen in the primary care FINE trial when compared with the earlier secondary care trial, might have been due to the sample in the primary care trial having a longer illness duration, greater levels of disability and complicating medical comorbidities. Contrary to our expectations, in the moderator analysis, illness duration did not moderate the effect of pragmatic rehabilitation treatment, although our second set of analyses showed that longer illness duration was a predictor of poorer outcome at 70 weeks, across the two treatment arms.

The picture with respect to level of disability is more complicated. There was no moderating effect on response to pragmatic rehabilitation of baseline SF-36 physical functioning scores, nor of ambulatory status, defined as needing a mobility aid on most days. However, on the EQ-5D mobility question, patients who initially categorised themselves as having some mobility problems showed a smaller improvement in fatigue with pragmatic rehabilitation than did those who initially categorised themselves as having no problems. Our second analyses showed that, across the two treatment groups, three patients with severe mobility problems at baseline showed a smaller improvement in fatigue at 70 weeks. Finally, the number of medical comorbidities experienced by patients in our study did not moderate the effect of pragmatic rehabilitation on fatigue, nor did it significantly predict outcome across the two treatment groups combined.

Our perception that the patients in the FINE trial had complex social needs that might have hampered their ability to respond to treatment is borne out to some extent by the trend for those patients who perceived themselves as less well supported by others benefitting less from pragmatic rehabilitation. This tentative finding underlines the importance of considering social factors when GPs and primary care teams are working with patients with CFS/ME; for example, primary care clinicians may suggest referral for social care assessment or to a local community organisation for patients with complex needs. Our study did not replicate previous findings from secondary care studies that patients in receipt of benefits, or those who belonged to self-help groups benefitted less from treatment. Finally, age and gender did not moderate the effect of pragmatic rehabilitation on fatigue.

**Strengths and limitations**

The FINE trial was the first UK study of treatments for CFS/ME delivered by non-specialists in primary care. Pragmatic rehabilitation had a relatively modest, although, we would argue, still clinically significant effect on fatigue at the 1-year follow-up point, but not on other outcomes; this has limited the analyses we were able to carry out here. Our findings need to be interpreted with caution: we investigated the potential moderating effects of over 20 baseline variables, although most of these were prespecified in our protocol, and our two positive findings may be type 1 errors.

**Implications**

Further research to replicate the finding that level of depressive symptoms moderates the effect of pragmatic rehabilitation treatment on fatigue is needed before we can have confidence in the result. Additionally, our findings suggest that future research to determine the optimal length and intensity of pragmatic rehabilitation for those with different levels of depressive symptoms would be useful. The effect of including additional elements in the pragmatic rehabilitation programme to address mood or emotional difficulties should also be examined.

The overall conclusion from our study is that pragmatic rehabilitation delivered in primary care by non-specialists will be a helpful treatment, particularly for those patients who are well supported and not overwhelmed with emotional difficulties. For patients with more complex needs, it may be necessary to include additional elements in the pragmatic rehabilitation programme. Alternatively, patients with mood disorders or with high levels of depressive symptoms may require treatment with CBT.

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References


8 White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet 2011; 377: 823–36.


### Online Table DS1  Regression coefficients for main effects of pragmatic rehabilitation treatment and for the interaction between putative moderators and treatment in regression analyses to predict change in Chalder Fatigue Scale scores at 70 weeks

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Main effects</th>
<th>Treatment moderator interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pragmatic rehabilitation effect (s.e.)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>2.78 (1.26)</td>
<td>0.30 to 5.26</td>
</tr>
<tr>
<td>Gender</td>
<td>1.35 (2.00)</td>
<td>-2.50 to 5.20</td>
</tr>
<tr>
<td>Ambulatory status</td>
<td>0.26 (3.51)</td>
<td>-6.67 to 7.19</td>
</tr>
<tr>
<td>EQ-5D mobility</td>
<td>6.55 (2.46)</td>
<td>1.69 to 11.40</td>
</tr>
<tr>
<td>EQ-5D self-care</td>
<td>3.72 (1.73)</td>
<td>0.31 to 7.14</td>
</tr>
<tr>
<td>EQ-5D usual activities</td>
<td>2.44 (4.50)</td>
<td>-6.45 to 11.33</td>
</tr>
<tr>
<td>Fulfilled Fukuda criteria</td>
<td>2.60 (1.33)</td>
<td>-0.03 to 5.22</td>
</tr>
<tr>
<td>Fulfilled London ME criteria</td>
<td>3.84 (1.85)</td>
<td>0.19 to 7.49</td>
</tr>
<tr>
<td>Member of local ME support group</td>
<td>0.25 (2.98)</td>
<td>-5.63 to 6.14</td>
</tr>
<tr>
<td>In receipt of benefits</td>
<td>0.90 (1.35)</td>
<td>-1.77 to 3.57</td>
</tr>
<tr>
<td>Any depression diagnosis</td>
<td>4.06 (1.57)</td>
<td>0.96 to 7.16</td>
</tr>
<tr>
<td>Oslo Social Support Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of people</td>
<td>3.05 (1.22)</td>
<td>0.65 to 5.45</td>
</tr>
<tr>
<td>Concern</td>
<td>2.89 (1.22)</td>
<td>0.49 to 5.29</td>
</tr>
<tr>
<td>Neighbours</td>
<td>3.03 (1.22)</td>
<td>0.62 to 5.44</td>
</tr>
<tr>
<td>Relatives</td>
<td>3.01 (1.24)</td>
<td>0.57 to 5.45</td>
</tr>
<tr>
<td>Medical comorbidities, n</td>
<td>2.76 (1.28)</td>
<td>0.28 to 5.24</td>
</tr>
<tr>
<td>Illness duration, months</td>
<td>2.58 (1.25)</td>
<td>-0.11 to 5.04</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression score</td>
<td>2.64 (1.24)</td>
<td>0.20 to 5.09</td>
</tr>
<tr>
<td>Anxiety score</td>
<td>2.77 (1.29)</td>
<td>0.23 to 5.31</td>
</tr>
<tr>
<td>Total score</td>
<td>2.75 (1.27)</td>
<td>0.25 to 5.26</td>
</tr>
<tr>
<td>Short-Form 36-item, physical functioning</td>
<td>2.72 (1.23)</td>
<td>0.29 to 5.16</td>
</tr>
<tr>
<td>Sleep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Trouble falling asleep</td>
<td>2.61 (1.25)</td>
<td>0.13 to 5.09</td>
</tr>
<tr>
<td>2. Wake during night</td>
<td>2.69 (1.28)</td>
<td>0.16 to 5.22</td>
</tr>
<tr>
<td>3. Trouble staying asleep</td>
<td>2.73 (1.27)</td>
<td>0.23 to 5.23</td>
</tr>
<tr>
<td>4. Awake feeling tired</td>
<td>2.79 (1.27)</td>
<td>0.28 to 5.30</td>
</tr>
</tbody>
</table>

a. Effect of pragmatic rehabilitation when covariate (moderator) is zero (after centering when appropriate).
b. Treatment moderator interactions omitted from analysis owing to insufficient cases available.
c. Centred on corresponding mean.
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**Supplementary Material**

Supplementary material can be found at:
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