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Cognitive-behaviour therapy for chronic fatigue syndrome: Comparison of outcomes within and outside the confines of a randomised controlled trial

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Abstract

Outcomes for cognitive-behaviour therapy (CBT) in randomised controlled trials (RCTs) have rarely been compared to those in routine clinical practice. Taking the case of CBT for chronic fatigue syndrome (CFS), we evaluated the results of a successful RCT against those of the same treatment given in the same setting as part of routine practice. Fatigue and social adjustment scores were compared for patients who received CBT for CFS as part of a RCT ($N = 30$) and patients who received CBT as part of everyday clinical practice ($N = 384$).

The results in the RCT were superior to those in routine clinical practice. Between pre-treatment and 6-month follow-up, the RCT showed a larger reduction in fatigue and greater improvement in social adjustment than those in routine treatment. The changes in fatigue scores were similar for both groups during treatment but were greater in the RCT between post-treatment and follow-up.

Potential reasons for the superior results of the RCT include patient selection, therapist factors and the use of a manualised treatment protocol. Practitioners need to pay particular attention to relapse prevention and ensuring adequate follow-up in addition to encouraging patients to continue with cognitive-behavioural strategies once treatment has ended.

Keywords: Clinical trials; Routine clinical practice; Cognitive-behaviour therapy; Chronic fatigue syndrome

Introduction

Three randomised controlled trials (RCTs) of cognitive-behaviour therapy (CBT) for chronic fatigue syndrome (CFS) have shown that therapy led to substantial improvements in physical functioning and reductions in levels of fatigue (Deale, Chalder, Marks, & Wessely, 1997; Prins et al., 2001; Sharpe et al., 1996).

As RCTs, the results from the aforementioned studies are given substantial import. However, while it is recognised that RCTs yield high-quality data, objections have been raised about the extrapolation of their

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findings to everyday clinical settings (e.g., Rothwell, 1995). Crucially, it has been argued that the outcomes of a RCT may exceed those of usual clinical care and therefore misrepresent the effectiveness of the intervention under study (Weijer et al., 1996). The greater effect size in RCTs may stem from the fact that trial clinicians follow a thoroughly researched protocol that is manualised to ensure replicability across time and therapist. This can be contrasted with clinic therapists who tend to rely upon their own training and experience when carrying out an intervention (Garfield, 1996). The former, more systematised, approach arguably produces a higher quality of care than that characteristic of routine practice (Braunholtz, Edwards, & Lilford, 2001). For example, a study of phobic disorders identified that the application of a treatment protocol was linked to improved outcome when compared to the use of a therapeutic schedule determined by the individual clinician (Schulte, Kunzel, Pepping, & Schulte-Bahrenberg, 1992). Furthermore, the therapists taking part in a trial may receive specific training and supervision and may have resources available to them that it is unrealistic to expect of everyday clinicians (Shadish et al., 1997; Wilson, 1998).

The "general air of optimism" which pervades the testing of an intervention has also been noted as a potential factor which may influence patient expectations of treatment efficacy (Everitt & Wessely, 2004, p. 28), while the screening processes involved in an RCT may "maximise the patience and perseverance" of participants (Havik & VandenBos, 1996). These effects on the motivation and expectations of patients, coupled with an increased enthusiasm among trial therapists, may be associated with better treatment outcomes and may inevitably limit a trial's external validity.

Furthermore, the application of restrictive exclusion criteria may under represent the more varied referrals to routine care and may limit the generalisability of treatments tested in RCTs (Hofer et al., 2000). For example, in a meta-analysis of therapies for depression, panic and generalised anxiety disorder, it was noted that potential participants are frequently excluded from RCTs and that the criteria such trials apply eliminate "more troubled and difficult to treat patients" (Westen & Morrisson, 2001). The authors further identified a positive correlation between the percentage of patients improved with therapy and the percentage excluded from the study of that therapy. This led them to argue that empirical support for a treatment that is validated through a RCT should be qualified by a description of the sample used.

Although CBT is an intervention used for a wide variety of conditions, the outcomes from RCTs have rarely been compared to those in routine clinical practice. Specifically, no previous studies have compared RCT and routine clinical outcomes of CBT for CFS. With the above issues in mind, the aim of this study is to compare the CBT treatment outcomes of a RCT (Deale et al., 1997) conducted in the CFS research and treatment unit at King's College Hospital with the CBT outcomes collected in routine clinical practice in the same unit. On the basis of the aforementioned literature, it is hypothesised that the 6-month outcome of patients treated in the RCT will be better in terms of both fatigue and social adjustment.

Method

This study compares the results of a RCT (Deale et al., 1997) performed between 1993 and 1994 at King's College CFS Research and Treatment Unit with the routine outcomes gathered in relation to patients attending that same unit between 1995 and 2000.

Participants

RCT: Patients in this trial were recruited from consecutive GP and consultant referrals. The diagnosis of CFS was made by an experienced consultant psychiatrist (SW) according to Oxford (Sharpe et al., 1991) and US Centre for Disease Control (Fukuda et al., 1994) case definitions. Patients were excluded if they took anti-depressant or anxiolytic medication of greater than 10 mg/day/diazepam or equivalent, or if their dose changed during the trial or within the 3 months prior. Patients with somatisation disorder, severe depression, ongoing physical investigations, concurrent treatment and/or an inability to attend all therapy sessions were also excluded (Deale et al., 1997).

Routine clinical practice: As with the RCT, patients in routine clinical practice were taken from consecutive GP and consultant referrals to the CFS specialist unit. All patients were assessed by either the aforementioned consultant psychiatrist or one of a number of other specialists in CFS. Treatment was offered to those who

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fulfilled the Centre for Disease Control Criteria for CFS (Fukuda et al., 1994). Unlike the RCT patients, those in routine clinical practice were not excluded for reasons related to medication and the importance of their making an initial commitment to attend all therapy sessions was not emphasised. All patients were screened by their GP to exclude alternative medical causes and, as with the RCT, patients with somatisation disorder, severe depression, ongoing physical investigations and concurrent treatment were referred elsewhere.

Procedure and treatment

RCT: All trial patients were randomised to either CBT or relaxation using a table of random numbers that was stratified by source of referral. Participants received 13 sessions on a weekly or fortnightly basis for an average of 15 h. CBT delivery was based on a treatment manual and proceeded through a number of stages including development of a rationale, creation of a schedule of graded activity, establishment of a consistent sleep pattern and the introduction of cognitive strategies to modify unhelpful thoughts (a detailed description of the treatment protocol can be found in the original paper (Deale et al., 1997)). Patients were seen at 3 and 6 months post-treatment for a review of their progress. One clinical nurse therapist (AD) was involved in treatment delivery. She was trained in cognitive-behavioural psychotherapy and had been practising for 3 years but not specifically in the treatment of CFS. She met with the research team on a fortnightly basis for supervision and to ensure adherence to the treatment protocol.

Routine clinical practice: Seven clinical nurse therapists trained in cognitive-behavioural psychotherapy and in the treatment of CFS worked at the unit. Some had been working in the area of CFS for several years. However, all had been qualified for a minimum of 1 year and received individual supervision by a supervisor familiar with CFS. In addition, one trainee cognitive-behaviour therapist and three psychiatrists, all familiar with CBT for CFS, were involved in the provision of treatment. Patients received an average of 11 sessions of therapy on a fortnightly basis and their progress was reviewed at 3 and at 6 months post-treatment. The maximum number of sessions patients were offered was 12. The treatment received was not manualised but supervisors and therapists were familiar with the treatment offered in the RCT and ensured that the therapy they offered proceeded through the same stages.

Outcome measures

Routine clinical therapy patients all received three self-rated outcome measures examining social adjustment, level of fatigue and global improvement. These measures also formed part of a battery of tests given to the RCT participants. The questionnaires were administered at pre-therapy and post-therapy stages and at 6-month follow-up. They are outlined below.

Chalder Fatigue Scale (Chalder et al., 1993)

This is an 11-item scale measuring physical and mental fatigue. Four response options are available, ranging from "less than usual" to "much more than usual". Bimodal scoring gives a range of 0–11 and a cut-off score of 4 or more is considered indicative of excessive fatigue. It is both reliable (Cronbach's $\alpha = 0.88-0.90$) and valid (sensitivity 75.5 and specificity 74.5) (Chalder et al., 1993).

Work and Social Adjustment Scale (Mundt, Marks, Shear, & Greist, 2002)

This is a five-item scale which measures the extent to which work, home management, relationships and social and private activities are impaired by the patient's condition. Work and social adjustment is rated on a Likert scale from 8 indicating "very severely impaired" to 0 indicating "Not at all impaired". Items are averaged to give a final score ranging from 0 to 8. The scale has been shown to be reliable (Cronbach's $\alpha = 0.7-0.9$), to have good face validity, to correlate with symptom severity in depression and obsessive compulsive disorder and to be sensitive to change (Mundt et al., 2002).

Self-rated global outcomes

Overall improvement is measured on a 7-point scale ranging from very much better (1) to very much worse (7). Patient satisfaction with treatment outcome is examined with a response range from (1) very satisfied to (7)

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very dissatisfied. Patient perception of usefulness of treatment is measured using the response options (1) very useful through to (5) no use at all. Following the original RCT, the data were grouped into categories, where 1 and 2 represented "better" "satisfied" or "useful" and 3 or more represented a range which included "a little better or worse", "slightly satisfied or dissatisfied" and "not useful". This dichotomisation produces a more conservative estimate of global outcomes.

Statistical analysis

The demographic characteristics of patients in the RCT and the clinic were compared using a χ^2 analysis (except age and duration of fatigue which were examined through the Mann–Whitney U test).

The pre- and 6-month follow-up outcomes in social adjustment and in fatigue level for patients receiving usual clinical care were compared using the Wilcoxon signed-ranks test.

A substantially reduced number of patients in routine clinical practice completed the post-therapy and 6-month follow-up questionnaires compared to the number completing the pre-therapy tests. The demographic characteristics and the pre-therapy responses of questionnaire completers and questionnaire non-completers were therefore compared using the χ^2 and Mann–Whitney U tests, respectively.

Comparisons of outcomes in the RCT and the clinic were evaluated using the Mann–Whitney U test in terms of change over time. The percentage of RCT and clinic participants meeting fatigue caseness according to the Chalder Fatigue Scale was also examined using the McNemar statistic. Finally, the self-rated global improvement scores for patients in the RCT and routine clinical practice were compared using a χ^2 analysis.

Results

Participation and attrition

Of those patients who were assessed for the RCT and found to meet the diagnostic criteria for CFS, 25 were excluded. Reasons included a primary diagnosis of somatisation disorder (eight people), major depression (four people), inability to attend sessions regularly (12 people) and having recently started anti-depressants (one person). In addition, seven patients refused entry to the trial: three did not want to be randomised, two gave no reason and two did not want CBT (Deale et al., 1997). Of the 60 patients involved in the entire RCT, 23 had a co-morbid diagnosis, which included dysthymia, depression and/or anxiety.

A total of 30 patients were randomised to CBT. Three of those patients dropped out of treatment and did not return any more measures resulting in 27 who completed follow-up measures. One found therapy ineffective, one felt too ill to attend and one improved and did not want to continue treatment (Deale et al., 1997).

In contrast, 384 patients received routine clinical practice over the 5 years examined in this study. An additional 135 patients were not offered CBT at assessment. The main reasons included a primary diagnosis of major depression (70 people), chronic pain (six people), somatoform disorder (four people), conversion disorder (four people) and not meeting CFS criteria or refusing CBT (42 people). Nine more people were not offered therapy because of other primary diagnoses. Patients were not excluded if they were taking anti-depressants at any time. Of those receiving CBT, 361 completed pre-treatment measures and 227 completed at least some of the 6-month follow-up measures.

Since a reduced number of patients in routine clinical practice completed follow-up measures, potential biases in their follow-up data were examined. No significant differences between follow-up completers ($N = 227$) and non-completers ($N = 157$) were found for the demographic variables: age, $U = 16711.50$, $p = 0.33$; gender, $\chi^2 = 0.54$, $p = 0.46$, social group $\chi^2 = 3.87$, $p = 0.28$ and marital status $\chi^2 = 0.97$, $p = 0.62$. However, those who completed follow-up measures had experienced fatigue for a significantly longer period of time than non-completers ($U = 4259.50$, $p = 0.03$). In addition, there were no significant differences in the pre-treatment fatigue ($U = 15028.50$, $p = 0.49$) or work and social adjustment scores ($U = 15228.00$, $p = 0.53$), of those who responded to requests for post-treatment measures and those who did not.

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Demographic characteristics

Table 1 outlines the demographic characteristics of the 30 patients undertaking CBT in the RCT with those of the 384 patients receiving CBT as part of routine clinical practice.

The demographic characteristics of patients in the RCT were largely representative of the service setting. In both the trial and clinical practice, the majority of patients were female, following the usual pattern of referrals to CFS specialist clinics. In addition, the patients in both groups were of similar marital status with a relatively even divide between the number married or living as such, and the number single. However, patients receiving routine clinical practice were significantly older than those participating in the RCT. Furthermore, patients receiving routine clinical practice had experienced fatigue for a significantly longer period of time and received significantly fewer therapeutic contact hours compared to those in the RCT.

Fatigue and social adjustment outcomes

Prior to a comparison of patient outcomes for the clinic and the RCT, a Wilcoxon test was carried out to establish whether patients attending the clinic benefited from treatment, both in terms of fatigue and in terms of social adjustment. In the first instance, the focus was on long-term gains and hence pre-treatment and 6-month follow-up scores were compared. Evidence for improvement was identified: Fatigue scores for patients receiving usual clinical care were found to differ significantly between pre-treatment and 6-month follow-up ($Z = -9.42$, $p < 0.0001$, two-tailed), with fatigue being lower at the follow-up stage. In addition, patients' social adjustment scores were significantly better at the 6-month follow-up stage compared to before treatment ($Z = -9.90$, $p < 0.0001$, two-tailed).

In Table 2, the percentages of patients in the RCT and in the clinic who met the Chalder et al. (1993) criteria for fatigue caseness at pre-therapy, post-therapy and 6-month follow-up are reported.

Fewer patients in the RCT met fatigue caseness at 6-month follow-up (McNemar test: $p < 0.001$). A logistic regression ascertained that this difference between the RCT and routine care remained significant when controlling for baseline fatigue ($p = 0.003$, odds ratio = 0.28, 95% confidence interval 0.12–0.66).

Fig. 1 gives the mean fatigue ratings and Fig. 2 the mean social adjustment scores for patients treated as part of the RCT and those receiving CBT as part of clinical practice, where a lower score indicates improvement in fatigue or social adjustment.

The mean scores for all groups improved over the three measurement periods. Estimates of differences in longitudinal change in fatigue and in work and social adjustment scores for RCT and patients in routine clinical practice were obtained by running a Mann–Whitney analysis on the change scores from pre- to post-treatment, from post-treatment to follow-up and from pre-treatment to follow-up.

Table 1
Demographics of patients receiving CBT as part of the RCT (Deale et al., 1997) and routine clinical care

Characteristic	RCT ($N = 30$)	Clinic ($N = 384$)	U/χ^2 (p)
	M (SD)	*M* (SD)	
Age (years)	31.47 (8.78)	39.12 (10.91)	$U = 3390.50$ (<0.001)
Fatigue duration (years)	3.37 (2.14)	5.35 (4.63)	$U = 2168.50$ (<0.009)
Treatment duration (h)	14.83 (3.14)	11.39 (4.84)	$U = 697.00$ (<0.001)
	N (%)	*N* (%)	
Gender			
Female	21 (70)	244 (63.5)	
Male	9 (30)	140 (36.5)	$\chi^2 = 0.50$ (0.48)
Marital status			
Married/cohabiting	15 (50)	142 (43)	
Single	13 (43.3)	152 (46.1)	
Divorced/separated/widowed	2 (6.7)	36 (10.9)	$\chi^2 = 0.82$ (0.66)

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Table 2
Percentages of participants meeting fatigue caseness over time (i.e., a score of 4 or more on the Chalder Fatigue Scale)

	RCT *N* (%)	Clinic *N* (%)
Pre-treatment	30/30 (100.0)	338/361 (93.6)
Post-treatment	21/27 (77.8)	159/226 (70.4)
Six-month follow-up	10/27 (37.0)	145/227 (63.9)

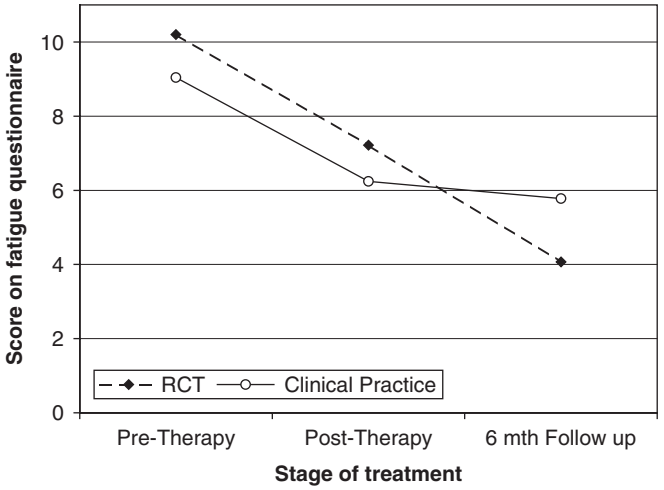

Fig. 1. Mean scores for RCT and clinic-based patients on the Fatigue Questionnaire (Chalder et al., 1993).

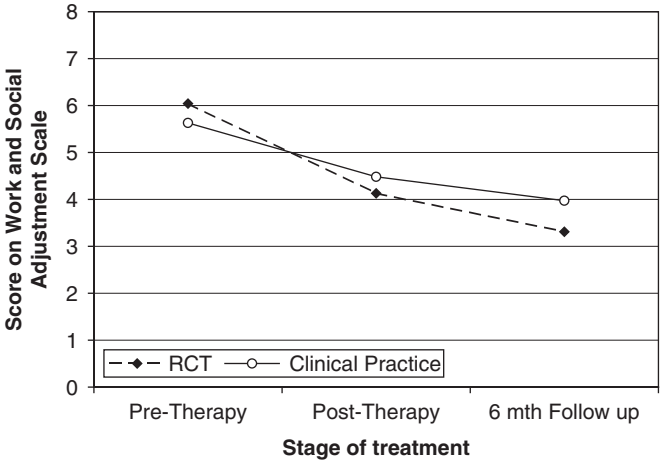

Fig. 2. Mean scores for RCT and clinic-based patients on the Work and Social Adjustment Scale (Mundt et al., 2002).

In relation to fatigue outcomes, a significantly larger overall reduction in fatigue took place from pre-therapy to 6-month follow-up for RCT patients compared to patients in routine clinical practice, ($U = 1876.00$, $p = 0.002$). Within this overall change, the RCT made similar average reductions in fatigue during the follow-up stage as during treatment, while reductions in levels of fatigue for patients in routine clinical practice were greater during therapy and less evident during the follow-up stage. The change in scores did not significantly differ between the two groups when comparing pre- and post-treatment ($U = 2744.50$,

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Table 3
Self-rated global improvement at 6-month follow-up in the randomised controlled trial and in routine clinical practice

Follow-up treatment self-rating	RCT	Clinic	Chi-squared analysis
	N (%)	*N* (%)	χ^2 (*p*)
Global improvement			
Better or much better	19 (70)	114 (57)	0.78 (0.38)
A little better, unchanged or worse	8 (30)	86 (43)	
Satisfaction with outcome of treatment			
Very satisfied or moderately satisfied	21 (78)	145 (73)	1.19 (0.28)
Slightly satisfied, neither, or dissatisfied	6 (22)	53 (27)	
Usefulness of treatment			
Useful or very useful	26 (96)	180 (91)	0.25 (0.61)
Not useful	1 (4)	17 (9)	

$p = 0.62$). However a greater change took place in the RCT compared to the clinical group between post-treatment and follow-up ($U = 1492.50$, $p = 0.003$).

Overall, from the pre-treatment to the follow-up stage, the work and social adjustment scores of RCT patients improved significantly more than those of patients receiving routine clinical practice; ($U = 2012.00$, $p = 0.007$). The greatest improvement in social adjustment scores for both the clinic and RCT took place between pre- and post-therapy. At this stage, there was a significantly larger change in the social adjustment scores of RCT patients compared to patients in routine clinical practice ($U = 2083.5$, $p < 0.01$). For both groups, scores continued to improve after treatment was complete, but the gains at this follow-up stage were only slight. Here, there was no significant difference in the change that took place in the RCT compared to in the clinic ($U = 1948$, $p = 0.21$).

Global improvement and satisfaction ratings

Table 3 indicates that patient ratings for global improvement, satisfaction with treatment outcome and perception of the usefulness of treatment at the follow-up stage are similar in the RCT and routine clinical practice.

The majority of patients in both conditions described themselves as better or much better than before treatment, as satisfied or very satisfied with the treatment outcome and as believing the treatment to be useful or very useful.

Predictors of outcome

A logistic regression revealed that older age was significantly associated with whether a patient still met the Chalder et al. (1993) criteria for fatigue caseness at follow-up. However, the odds ratio was very small ($p = 0.019$, odds ratio = 1.03, 95% confidence interval 1.01–1.05). When the variable 'group: RCT or clinic' was added into the logistic regression analysis, the effect of age was reduced and no longer significant ($p = 0.063$, odds ratio = 1.02, 95% confidence interval 1.00–1.05). The variables employment status, fatigue duration and number of treatment hours were not significantly associated with outcome: $p = 0.767$, odds ratio = 1.09; $p = 0.43$, odds ratio = 1.03, $p = 0.323$ odds ratio = 0.96, respectively.

Discussion

Patients with chronic fatigue syndrome (CFS) who were allocated CBT as part of a RCT showed significantly greater reductions in fatigue and improvements in social adjustment at 6-month follow-up than people who received CBT as part of routine clinical practice.

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A comparison of fatigue levels across the RCT and routine clinical practice revealed that, during treatment, levels of fatigue reduced for both groups with neither group experiencing a significantly greater improvement than the other. However, between end of treatment and 6-month follow-up, the RCT participants showed significantly greater reductions in fatigue than the routine clinical practice patients.

With regard to social adjustment, improvements were noted in both the RCT and routine clinical practice. However during treatment, these improvements were significantly greater for the RCT participants. In contrast, there was no significant difference between the two conditions at end of treatment to 6-month follow-up.

It is encouraging to note the general overall improvement in fatigue and social adjustment, supported by the generally high patient-rated satisfaction in treatment outcome and usefulness across both conditions. It is however vital to reflect upon why treatment gains were greater among RCT participants and the implications that this finding may have for routine clinical practice.

Participants in the RCT may have made significantly greater improvements because they differed in some way from patients receiving usual clinical care. For example, patients in routine clinical practice were significantly older than RCT patients and had experienced fatigue for a longer period of time. Previous studies have found that these factors are associated with symptom persistence (Joyce, Hotopf, & Wessely, 1997). In the current study, a small association was found between older age and poorer outcome, while fatigue duration was not identified as a significant factor.

The process of patient selection in the RCT may have led to differences between the groups. Thirty-two patients who met the criteria for CFS were excluded or declined to participate in the trial. Of these, 12 patients were screened-out because of co-morbid problems that were primary to CFS. Their exclusion does not appear to affect the generalisability of the current RCT since 93 patients were also excluded from routine clinical practice due to having other primary diagnoses.

The exclusion of participants with co-morbid disorders from RCTs does reduce a trial's external validity, where the co-morbid disorder is commonly found in practice and affects response to treatment (Westen & Morrisson, 2001). Thirty-eight percent of those in the trial experienced co-morbid anxiety or depression, conditions which frequently co-occur with CFS. The RCTs inclusion of people with these common problems serves to increase the trial's generalisability. Consideration of the selection process nevertheless underlines the need for the researcher to be explicit about the criteria applied, and for the practising clinician, not only to provide therapy that has been shown to be effective within a RCT, but also to remain aware of how the results of a trial translate to the individual with whom they are working (Rothwell, 1995).

It is possible that systematic differences between therapists may have influenced outcome. Treatment delivery for the RCT involved one therapist who received regular supervision through the research team. She was also the main researcher and hence would have been highly motivated to produce a good result. In contrast, the therapists involved in routine care would have had varying degrees of motivation, and while their supervisors were all experienced in CFS, it is possible that the supervision they received differed in both regularity and quality.

The difference in fatigue between the RCT patients and those in routine clinical practice was most evident at the 6-month follow-up stage, where 63% of RCT patients no longer met Chalder et al. (1993) criteria for fatigue caseness compared to 36% of those receiving routine care. This difference may be due to a detection bias in that 90% (27/30) of RCT participants completed follow-up measures compared to only 59% (226/384) of those receiving usual clinical care. This is not surprising given that more attention and resources are put into data collection in the context of RCTs than in routine clinical practice. It is possible that the questionnaire non-completers in routine care had improved to the extent that they no longer desired therapist input. Indeed, they had fatigue of significantly less duration than the questionnaire completers, a factor sometimes associated with better prognosis (Joyce et al., 1997). The absence of their responses would inevitably present the routine clinical gains in a more conservative light. This does, however, remain a postulation and only through encouraging an increased follow-up return rate in routine clinical practice will more clear insights be gained.

In the RCT, the therapist adhered to a manual, while recognising the value of some degree of flexibility and tailoring the approach to the individual. In contrast, therapists delivering routine clinical practice may have been less strict and focused. The continued improvements made by patients in the follow-up stage, particularly in the RCT, may have stemmed from their being "taught to treat themselves and to practice relapse

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prevention'' (Deale et al., 1997). It is possible that this was not given due emphasis in the clinic. Another potential explanation for the group difference is that RCT patients received more hours of treatment than those in routine care. However it is not possible to draw firm conclusions about this issue since the therapists and patients in routine care could be more flexible regarding treatment duration and could have stopped treatment early for a range of reasons, including significant improvement.

This study is the first to compare outcomes of CBT for CFS within and outside an RCT. The two interventions were carried out within the same clinical setting which adds import to the findings. However, the study has a number of limitations including the lower follow-up rate in routine clinical practice than in the RCT and the fact data for the routine clinical participants were collected at a later time point (i.e., between 1995 and 2000), than for the RCT. This may have influenced results since referral patterns may have changed between data collection points, indeed the patients in routine clinical practice had a higher mean age and longer illness durations.

In conclusion, the outcomes of CBT for CFS in the RCT were superior to those in routine clinical practice at the 6-month follow-up stage. Clinicians need to discuss with patients how they can continue with cognitive-behavioural strategies beyond the end of treatment, address relapse prevention issues, and ensure adequate follow-up. Future research should examine possible reasons for the poorer outcomes in routine clinical practice treatment of CFS compared to the outcomes seen in RCTs. Potential reasons to be investigated include patient selection, therapist factors and treatment differences such as the use of a manualised treatment protocol and length of treatment.

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