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# Cognitive Behavior Therapy, Exercise, or Both for Treating Chronic Widespread Pain

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**Background:** The clinical impact of telephone-delivered cognitive behavioral therapy (TCBT), exercise, or a combined intervention in primary care patients with chronic widespread pain (CWP) is unclear.

**Methods:** A total of 442 patients with CWP (meeting the American College of Rheumatology criteria) were randomized to receive 6 months of TCBT, graded exercise, combined intervention, or treatment as usual (TAU). The primary outcome, using a 7-point patient global assessment scale of change in health since trial enrollment (range: very much worse to very much better), was assessed at baseline and 6 months (intervention end) and 9 months after randomization. A positive outcome was defined as “much better” or “very much better.” Data were analyzed using logistic regression according to the intention-to-treat principle.

**Results:** The percentages reporting a positive outcome at 6 and 9 months, respectively, were TAU group, 8% and 8%; TCBT group, 30% and 33%; exercise group, 35% and 24%; and combined intervention group, 37% and 37% ( $P < .001$ ). After adjustment for age, sex, center, and base-

line predictors of outcome, active interventions improved outcome compared with TAU: TCBT (6 months: odds ratio [OR], 5.0 [95% CI, 2.0-12.5]; 9 months: OR, 5.4 [95% CI, 2.3-12.8]), exercise (6 months: OR, 6.1 [95% CI, 2.5-15.1]; 9 months: OR, 3.6 [95% CI, 1.5-8.5]), and combined intervention (6 months: OR, 7.1 [95% CI, 2.9-17.2]; 9 months: OR, 6.2 [95% CI, 2.7-14.4]). At 6 and 9 months, combined intervention was associated with improvements in the 36-Item Short Form Health Questionnaire physical component score and a reduction in passive coping strategies. Conclusions on cost-effectiveness were sensitive to missing data.

**Conclusion:** TCBT was associated with substantial, statistically significant, and sustained improvements in patient global assessment.

**Trial Registration:** clinicaltrials.gov Identifier: ISRCTN67013851

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**C**HRONIC WIDESPREAD PAIN (CWP), the cardinal feature of fibromyalgia,<sup>1</sup> is associated with lost work productivity,<sup>2</sup> mental ill health,<sup>3</sup> and reduced quality of life.<sup>4</sup> In the United States, mean per-patient costs (including pain and non-pain-related medication, physician consultations, tests and procedures, and emergency department visits) in the 6 months following a new diagnosis of fibromyalgia were \$3481.<sup>5</sup> Health care costs were higher among patients with fibromyalgia compared with those of patients without,<sup>6</sup> and were comparable with those of patients with rheumatoid arthritis.<sup>7</sup> There is a need to develop clinically effective and cost-effective, acceptable interventions at a primary care level that could

potentially be available to a large number of patients. Current guidelines recommend pharmacological, physical, and psychological therapies,<sup>8-10</sup> although the importance attributed to individual therapies is inconsistent.<sup>11</sup> Systematic reviews show

*For editorial comment  
see page 10*

that while no individual treatment modality is effective in relieving symptoms, physical exercise<sup>11</sup> and cognitive behavioral therapy (CBT)<sup>12</sup> are promising. While the demand for CBT exceeds supply,<sup>13</sup> there is increasing evidence that telephone-delivered CBT (TCBT) is effective, acceptable, and accessible.<sup>14</sup> However, to our

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knowledge there have been no high-quality trials of multidisciplinary approaches.<sup>15</sup> This trial estimated the clinical effectiveness and cost-effectiveness of a TCBT, exercise, and combined intervention compared with treatment as usual (TAU) among primary care patients with CWP.

## METHODS

### TRIAL DESIGN AND PATIENTS

The Managing Unexplained Symptoms (CWP) In Primary Care: Involving Traditional and Accessible New Approaches (MUSICIAN) Trial was a 2 × 2 factorial randomized controlled trial.

Identifying primary care patients with CWP is challenging. They consult frequently<sup>16</sup> with a variety of different symptoms,<sup>17</sup> there are no standard recording codes, and use varies among individual physicians and practices. To identify patients, all individuals at least 25 years old registered to receive care from 1 of 8 general practices in Aberdeen, Scotland, and Macclesfield, Northwest England, were mailed a brief screening questionnaire asking about (1) pain (location, distribution, frequency); (2) the Chronic Pain Grade (CPG) questionnaire<sup>18</sup> (classifies no pain as 0 and the global severity of chronic pain from I [low disability, low intensity] to IV [high disability, severely limiting]); (3) the General Health Questionnaire (GHQ)<sup>19</sup> (measures psychological distress; score range, 0-12; higher scores indicate more distress); and (5) diagnosed osteoarthritis or rheumatoid arthritis. Eligible patients reported CWP (classified according to the definition used in the American College of Rheumatology criteria for fibromyalgia<sup>20</sup>) for which they had consulted their physician within the past year. Patient exclusions were a severe psychiatric disorder (currently suicidal or psychotic) impairing ability to engage with interventions, contraindications for exercise (eg, forbidden by family physician, chest pain on exercise, syncope, uncontrolled epilepsy, current fracture), or a condition for which the interventions were not indicated (eg, metastatic cancer). At a research nurse–led clinic visit, patient eligibility, and absence of exercise contraindications were confirmed and informed consent obtained.

### RANDOMIZATION AND MASKING

Electronic individual randomization to active interventions or TAU, stratified by 2 important predictors of outcome, CPG (grades I-II, III-IV) and GHQ (scores 0-1, 2-12), was conducted at the Centre for Healthcare Randomized Trials, Aberdeen. Patients were notified of treatment allocation, and, if applicable, initial TCBT and/or exercise appointments were made. Owing to the nature of the interventions, neither patients nor therapists were masked to treatment allocation. However, outcome data were collected, entered, coded, cleaned, and analyzed blind to treatment allocation.

### TREATMENTS PROVIDED

#### TCBT

In addition to TAU, patients received TCBT: an initial assessment (45-60 minutes), 7 weekly sessions (each 30-45 minutes long), and 1 session 3 months and 1 session 6 months after randomization. Therapists conducted a patient-centered assessment, developed a shared understanding and formulation of the current problem, and identified 2 to 3 patient-defined goals. Patients received a self-management CBT manual, “Managing Chronic Widespread Pain,” developed for the study (unpub-

lished). To enable patients to make an informed choice of the form of CBT they preferred, the manual included stories of fictitious patients (but ones based on clinical knowledge) using specific CBT techniques: *behavioral activation* (increasing, decreasing, pacing activities), *cognitive restructuring* (identifying and evaluating unhelpful thinking styles), and *lifestyle changes* (managing sleep, fatigue, irritability). Sessions 2 to 9 involved implementing CBT techniques, working toward goals, and problem solving barriers to improvement. Later sessions focused on relapse prevention. Therapists mailed brief details welcoming patients to the study, giving a brief introduction to what CBT is and providing contact details.

TCBT was delivered by 4 therapists (located in France, Canada, Ireland, and England) accredited by the British Association for Behavior and Cognitive Psychotherapies (mean years of experience, 11 years [range, 2-20 years]). Therapists received 3 days of trial-specific training, a therapist manual, and fortnightly clinical supervision. All sessions were digitally recorded for use in therapist supervision.

#### Exercise

In addition to TAU, patients received a leisure-facility– and gym-based exercise program consistent with American College of Sport Medicine (ACSM) guidelines for improving cardiorespiratory fitness.<sup>21</sup> Following an induction session, patients were offered 6 fitness instructor–led monthly appointments for program reassessment. Exercise intensity increased until exercise levels were sufficient to achieve 40% to 85% of heart rate reserve. The ACSM does not prescribe specific exercises; these are negotiated between fitness instructor and patient. The trial protocol reflected this, allowing exercises to be changed but maintaining the goal of improving cardiorespiratory fitness. Exercise intensity range was broad, allowing individuals with low fitness or those who were deconditioned to achieve goals with low-intensity exercise. To avoid musculoskeletal injuries and promote compliance, initial intensity was low to moderate. Patients were free to engage in additional exercises (eg, strength and flexibility training) done in addition to, not instead of, prescribed exercise. The recommended exercise session duration was 20 to 60 minutes. Patients completed a diary recording frequency of gym attendance, exercise duration, and type which was returned to the coordinating unit. The ACSM guidelines recommend an exercise frequency of 3 to 5 days per week. This was thought to be unrealistic, and patients were advised to attend at least twice a week and on non-gym days to engage in “everyday” activities (eg, brisk walking) to enhance cardiorespiratory fitness.

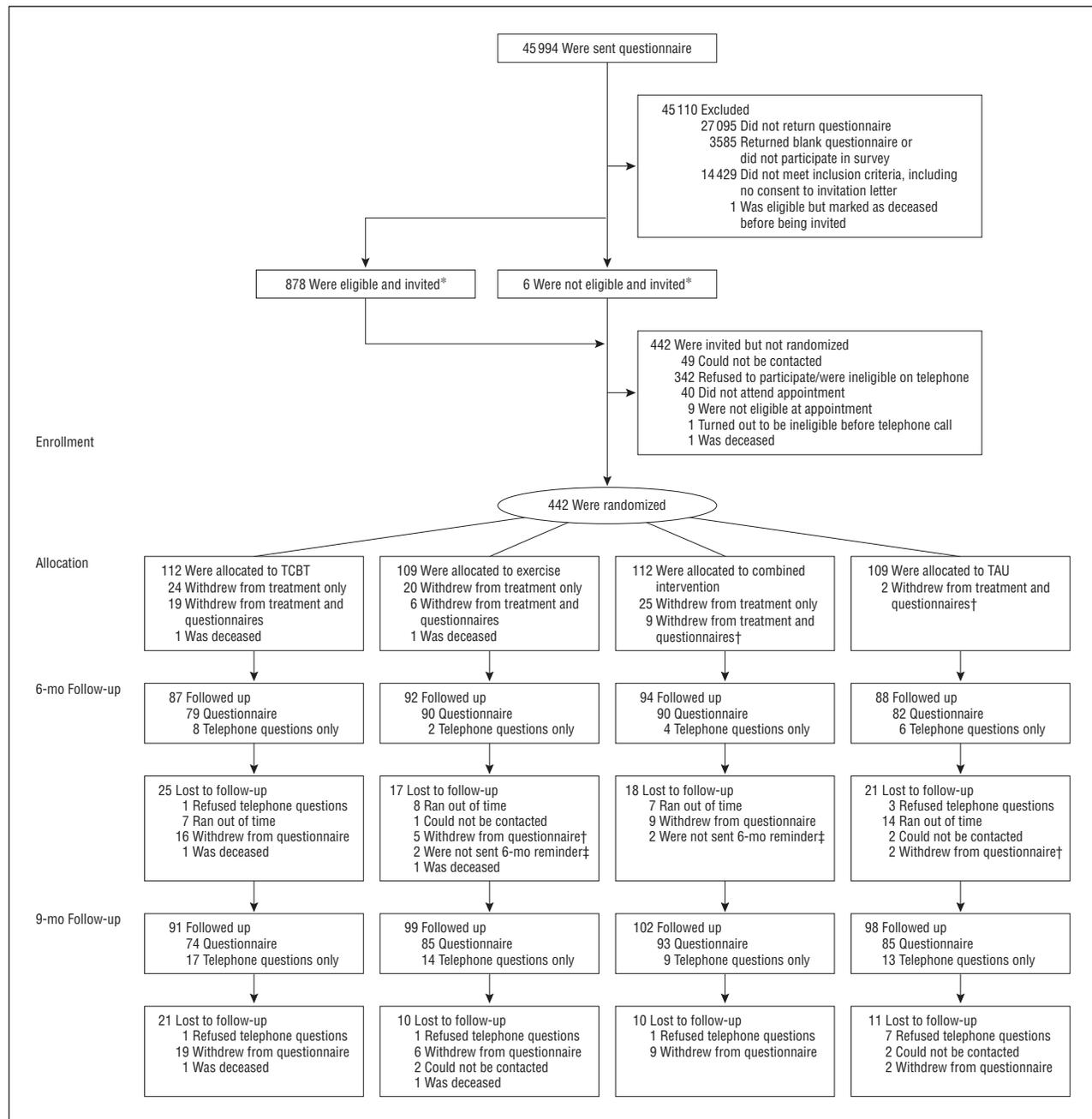
Experienced fitness instructors delivering the intervention received a 1-day training session on exercise prescription for patients with CWP and were observed during induction and follow-up meetings to monitor instructor protocol adherence.

#### Combined Intervention

Patients concurrently received TCBT and exercise with both protocols delivered as described in the previous subsection. Instructors exchanged information about patient treatment.

#### Treatment as Usual

In the United Kingdom, treatment of CWP is problematic and ad hoc. No drugs are approved for use in fibromyalgia, and access to CBT or exercise programs is limited, if available at all. The TAU group received the usual care from their family physician, although the precise care delivered, if any, was not recorded.



**Figure 1.** The Managing Unexplained Symptoms (Chronic Widespread Pain) In Primary Care: Involving Traditional and Accessible New Approaches (MUSICIAN) Trial CONSORT flow diagram. TAU indicates treatment as usual. \*One person who was not eligible but invited and randomized and so became eligible subsequently and is now counted in as “eligible and invited.” †Withdrawal status of participants changed at various times so some withdrew from questionnaires after they had already completed a 6-month follow-up. ‡Because of a mix-up in the way withdrawal forms were completed, some participants were not sent 6-month follow-up reminders.

## Outcome Measurements

Primary and secondary outcomes were measured by self-completed postal questionnaire (or telephone interview, administered by study personnel blind to treatment allocation, for questionnaire nonresponders) at 6 months (end of intervention) and 9 months after randomization. All randomized patients, excluding those actively withdrawing from the trial, were mailed a follow-up questionnaire at 6 months and, irrespective of participation at the 6-month follow-up, at 9 months. The primary outcome was a 7-point, self-rated, clinical global impression change score measuring how patients

felt their health had *changed* since the period prior to entering the trial ranging from 1 (“I feel very much worse”) to 6 (“I feel much better”) and 7 (“I feel very much better”). Scores of 6 or 7 are considered clinically relevant. The measure has been used frequently in trials of fibromyalgia<sup>22</sup> and related conditions.<sup>23</sup>

For safety outcomes, adverse events (serious and nonserious) were recorded. One of us (G.J.M., who was blind to treatment allocation) was notified of adverse events and determined whether the event was serious or nonserious. He was then unmasked to treatment allocation to determine whether adverse events were adverse reactions to treatment.

**Table 1. Baseline Characteristics of 442 Randomized Participants**

Characteristic <sup>a</sup>	No. (%)				P Value
	TAU (n=109)	TCBT (n=112)	Exercise (n=109)	Combined (n=112)	
Age, mean (SD), y	56.3 (12.5)	56.5 (13.7)	55.3 (12.5)	56.7 (13.4)	
Sex					
Female	76 (69.7)	80 (71.4)	72 (66.1)	79 (70.5)	
Employment status					
Working full time	35 (32.1)	38 (33.9)	37 (33.9)	38 (33.9)	.98
Working part time	18 (16.5)	17 (15.2)	17 (15.6)	16 (14.3)	
Retired	35 (32.1)	38 (32.1)	33 (30.3)	43 (38.4)	
Unable to work owing to ill health or disability	12 (11.0)	9 (8.0)	15 (13.8)	6 (5.4)	
Student	0	2 (1.8)	4 (3.7)	1 (0.9)	
Unemployed	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.9)	
At home	8 (7.3)	7 (6.3)	3 (2.8)	5 (4.5)	
CPG					
I, Low disability, low intensity	19 (17.4)	24 (21.4)	26 (23.9)	29 (25.9)	.74
II, Low disability, high intensity	56 (51.4)	53 (47.3)	50 (45.9)	49 (43.8)	
III, High disability, moderately limiting	18 (16.5)	23 (20.5)	20 (18.4)	25 (22.3)	
I, High disability, severely limiting	16 (14.7)	12 (10.7)	13 (11.9)	9 (8.0)	
GHQ, mean (SD)	3.4 (3.5)	3.3 (3.6)	3.2 (3.6)	3.1 (3.5)	.96
SF-36, mean (SD)					
Physical component score	37.4 (8.2)	38.9 (8.4)	37.8 (7.5)	38.1 (8.0)	.70
Mental component score	42.5 (10.6)	43.6 (10.9)	43.5 (10.1)	43.9 (10.0)	.72
Fatigue, mean (SD)	12.9 (5.6)	13.1 (5.3)	11.9 (3.3)	12.9 (4.9)	.65
VPMI, mean (SD)					
Passive coping	30.0 (7.8)	29.4 (7.1)	29.9 (7.2)	28.8 (7.2)	.80
Active coping	25.2 (4.5)	24.6 (4.2)	24.6 (4.0)	25.1 (4.3)	.44
Sleep scale, mean (SD)	13.8 (5.5)	13.3 (5.5)	13.7 (5.9)	12.1 (5.5)	.10
TSK, mean (SD)	36.2 (5.4)	36.0 (5.3)	35.7 (5.4)	35.5 (5.0)	.71

Abbreviations: CPG, Chronic Pain Grade questionnaire; GHQ, General Health Questionnaire; SF-36, 36-Item Short Form Health Questionnaire; TAU, treatment as usual; TCBT, telephone-delivered cognitive behavioral therapy; TSK, Tampa Scale for Kinesiophobia; VPMI, Vanderbilt Pain Management Inventory.

<sup>a</sup>Data are given as number (percentage) except where noted.

Secondary outcomes corresponded to the recommendations of the Outcome Measures in Rheumatology Clinical Trials initiative.<sup>24</sup> These were the CPG, Fatigue Scale<sup>25</sup> (14 items, with a score range of 0-42); the Vanderbilt Pain Management Inventory (VPMI)<sup>26</sup> (18 items assessing active and passive coping strategy use); the GHQ; the Sleep Scale<sup>27</sup> (measures sleep quality, onset, maintenance, early wakening, and non-restorative sleep; score range, 0-20; higher scores indicate more sleep disturbance); the Tampa Scale for Kinesiophobia (TSK)<sup>28</sup> (17 items that measure fear of movement; score range, 17-68); and the 36-Item Short Form Health Questionnaire (SF-36)<sup>29</sup> (score range, 0-100 for mental [SF-36 MCS] and physical [SF-36 PCS] quality of life [QoL]; lower scores indicate poorer QoL).

### Cost Data

Collection and analysis of cost data are described in detail in the eAppendix (<http://www.archinternmed.com>). All costs were expressed in 2009-2010 pounds sterling.

### Sample Size

The original sample size was 552. The trial steering and data-monitoring committees advised that the original power calculations were too stringent, having used a  $\chi^2$  test with a continuity correction. Without this correction, 398 participants (199 receiving exercise intervention and 199 receiving no exercise intervention across all trial arms) were required to complete follow-up to detect an improvement in at least 20% of individuals in the exercise arms compared with a difference of 10% in the

no-exercise arms (power, 80%;  $P < .05$ ). These differences were estimated assuming that of those randomized to exercise, half would receive the full intervention and the full benefit (30% having improvement), while half would receive little of the intervention and little benefit (10% having improvement). Based on a previous trial (Johnson et al<sup>30</sup>), 85% were expected to complete follow-up, requiring 468 patients to be randomized. Assuming that (1) 40% of eligible patients agreed to participate (1170 to be invited), (2) 40% of CWP participants were eligible for the trial (2925 to be identified), (3) the population prevalence of CWP was 13% (22 500 completed questionnaires required), and (4) a questionnaire return and completion rate of 45%, the required number of mailed questionnaires was 49 779.

### Statistical Analysis

An intention-to-treat analysis that included all participants who provided complete follow-up data was conducted. A positive primary outcome was defined a priori as feeling much better or very much better (score, 6-7). Logistic regression examined the impact of active interventions on the primary outcome, with feeling less than much better (score, 1-5 [the reference category]). Results are reported as an odds ratio (OR) with 95% CI, adjusted for age, sex, baseline CPG, GHQ scores, and study center. Secondary outcomes were analyzed using ordinal logistic regression or linear regression where appropriate with results expressed as unstandardized coefficients with 95% CIs adjusted as described with additional adjustment for baseline levels of the outcome of interest. Multiple imputation (MI) analysis<sup>31</sup> examined sensitivity to missing data. Because

**Table 2. Primary and Secondary Outcomes at the 6- and 9-Month Follow-up<sup>a</sup>**

Outcome	TAU		TCBT		Exercise		Combined	
	6 mo (n=88)	9 mo (n=98)	6 mo (n=87)	9 mo (n=91)	6 mo (n=92)	9 mo (n=99)	6 mo (n=94)	9 mo (n=102)
<b>Primary Outcome: Global Change in Health Since Entering Trial<sup>b</sup></b>								
Original data								
Very much better	1 (1.2)	3 (3.1)	7 (8.1)	11 (12.4)	4 (4.4)	6 (6.1)	8 (8.5)	12 (11.9)
Much better	6 (6.9)	5 (5.1)	19 (21.8)	18 (20.2)	28 (30.4)	18 (18.2)	27 (28.7)	24 (23.8)
A little better	17 (19.5)	17 (17.4)	26 (29.9)	16 (17.9)	36 (39.1)	31 (31.3)	30 (31.9)	24 (23.8)
No change	39 (44.8)	42 (42.9)	26 (29.9)	29 (32.6)	16 (17.4)	28 (28.3)	19 (20.2)	22 (21.8)
A little worse	18 (20.7)	25 (25.5)	7 (8.1)	11 (12.4)	5 (5.4)	13 (13.1)	7 (7.5)	13 (12.9)
Much worse	6 (6.9)	4 (4.1)	1 (1.2)	2 (2.3)	3 (3.3)	3 (3.0)	3 (3.2)	6 (5.9)
Very much worse	0	2 (2.0)	1 (1.2)	2 (2.3)	0	0	0	0
Dichotomized outcome								
Much better or very much better	7 (8.1)	8 (8.3)	26 (29.9)	29 (32.6)	32 (34.8)	24 (24.2)	35 (37.2)	36 (37.1)
Less than much better	80 (91.9)	90 (91.8)	61 (70.1)	60 (67.4)	60 (65.2)	75 (75.8)	59 (62.8)	65 (64.4)
<b>Secondary Outcome</b>								
CPG								
0, No pain	0	0	0	1 (1.7)	0	0	0	0
I, Low disability, low intensity	28 (41.2)	27 (35.5)	26 (44.8)	27 (46.6)	33 (43.4)	35 (47.3)	46 (60.5)	39 (54.9)
II, Low disability, high intensity	32 (47.1)	40 (52.6)	21 (36.2)	18 (31.0)	34 (44.7)	33 (44.6)	24 (31.6)	22 (31.0)
III, High disability, moderately limiting	5 (7.4)	3 (4.0)	10 (17.2)	10 (17.2)	8 (10.5)	6 (8.1)	4 (5.3)	8 (11.3)
IV, High disability, severely limiting	3 (4.4)	6 (7.9)	1 (1.7)	2 (3.5)	1 (1.3)	0	2 (2.6)	2.0 (2.8)
GHQ, score range, 1-12, mean (SD)	2.8 (3.5)	3.0 (3.8)	1.7 (2.9)	2.0 (3.6)	1.8 (2.8)	2.0 (3.0)	1.7 (2.8)	2.0 (3.4)
SF-36, score range, 1-100, mean (SD)								
General health	61.0 (21.0)	58.4 (20.9)	61.0 (22.0)	58.9 (20.4)	60.5 (20.1)	59.8 (19.9)	64.6 (18.9)	63.9 (20.1)
Physical function	61.1 (30.1)	60.2 (29.5)	66.6 (27.4)	67.7 (27.3)	68.6 (25.1)	72.6 (23.1)	71.2 (24.8)	71.3 (25.7)
Role physical	31.7 (35.5)	28.7 (37.2)	37.4 (40.1)	33.6 (38.6)	26.8 (36.3)	34.0 (39.2)	38.8 (38.9)	36.8 (40.0)
Bodily pain	53.5 (21.3)	56.2 (19.9)	61.3 (23.6)	62.1 (22.3)	57.6 (19.5)	59.8 (18.0)	60.4 (19.1)	59.8 (21.4)
Vitality	49.5 (16.8)	47.2 (17.7)	54.2 (16.3)	53.1 (16.5)	51.8 (16.0)	50.3 (15.9)	52.6 (17.5)	52.3 (17.6)
Social function	68.5 (25.7)	72.1 (27.5)	77.2 (25.1)	76.8 (24.5)	79.2 (21.4)	78.0 (21.0)	78.2 (24.4)	77.6 (25.1)
Role emotional	44.4 (44.5)	40.0 (45.1)	51.3 (42.5)	58.1 (45.6)	52.8 (43.8)	52.4 (48.4)	54.8 (43.7)	52.2 (43.5)
Mental health	59.9 (16.1)	62.0 (15.8)	66.5 (14.5)	66.1 (13.9)	65.9 (13.8)	65.7 (13.5)	65.2 (15.3)	65.1 (15.3)
Physical component score	39.9 (10.1)	39.6 (10.5)	41.5 (11.0)	40.8 (11.2)	40.2 (10.1)	41.9 (9.1)	43.0 (9.2)	42.8 (9.9)
Mental component score	43.4 (10.2)	43.4 (11.0)	46.3 (9.9)	47.0 (10.2)	46.7 (10.8)	45.8 (9.7)	46.0 (10.9)	45.5 (10.6)
Fatigue, score range, 0-42, mean (SD)	12.0 (6.1)	12.4 (5.8)	11.0 (5.9)	11.1 (5.3)	10.1 (3.0)	10.4 (2.8)	9.4 (5.5)	10.6 (6.6)
VPMI, mean (SD)								
Passive coping, score range, 11-44	28.0 (8.1)	27.9 (8.3)	27.6 (7.6)	26.8 (8.2)	26.6 (7.3)	26.0 (7.3)	24.4 (5.9)	24.5 (7.5)
Active coping, score range, 7-28	24.7 (4.5)	25.2 (4.0)	25.4 (4.2)	25.3 (4.3)	25.5 (3.7)	25.4 (3.6)	26.4 (3.9)	25.6 (4.7)
Sleep scale, score range, 0-20, mean (SD)	14.1 (6.0)	13.1 (5.4)	11.8 (5.6)	12.4 (5.7)	12.3 (5.2)	12.7 (4.9)	11.6 (5.7)	11.2 (5.4)
TSK, score range, 17-68, mean (SD)	36.0 (6.8)	36.1 (6.5)	34.2 (6.3)	34.1 (6.5)	33.6 (7.0)	33.8 (6.7)	32.8 (6.7)	32.0 (7.2)

Abbreviations: CPG, Chronic Pain Grade questionnaire; GHQ, General Health Questionnaire; SF-36, 36-Item Short-Form Health Questionnaire; TAU, treatment as usual; TCBT, telephone-delivered cognitive behavioral therapy; TSK, Tampa Scale for Kinesiophobia; VPMI, Vanderbilt Pain Management Inventory.

<sup>a</sup>Data are given as number (percentage) except where noted. Participants with missing data are excluded.

<sup>b</sup>Two participants in the TCBT and 1 participant in the combined intervention arm of the trial did not provide primary outcome data at the 9-month follow-up.

there were no differences in inference between the original and imputed analyses the former are reported (except for the economic analysis, where differences emerged). All analyses were conducted using STATA software (version 11; StataCorp, College Station, Texas).

## RESULTS

Of 45 994 questionnaires mailed, 15 313 (33.2%) were returned complete. Responders were more likely to be women (women, 37.2%, vs men, 29.2%), older (43.1% were > 50 years vs 24.2% ≤ 50 years), but there were no differences by practice or area of residence. A total of 442 patients were randomized (**Figure 1**). **Table 1** shows patient baseline characteristics: mean age was 56.2 years (range, 25-85 years), 69.5% were women, and 33.9% had full-time employment. Chronic widespread pain was graded as CPG III-IV for 30.0% of participants, and the

mean GHQ score was 3.1. Of 105 individuals who withdrew from treatment, 24.0% reported home, family, or work commitments, and this was consistent across active intervention arms (TCBT, 20.5%; exercise, 29.6%; combined intervention, 25.8%). After removing 6 persons who had died from the denominator (2 at treatment allocation, 2 at each follow-up), the follow-up rate was 82.4% at 6 months (TCBT, 79.1%; exercise, 86.0%; combined intervention, 83.9%; TAU, 80.7%) and 89.4% at 9 months (TCBT, 83.5%; exercise, 93.4%; combined intervention, 91.1%; TAU, 89.9%). Only SF-36 social functioning predicted follow-up attrition being significantly lower in nonparticipants at 9 months when compared with participants (median score [interquartile range], 62.5 [50-81] and 75 [50-100], respectively;  $P = .04$ ).

Of the 224 participants randomized to TCBT, 157 (70.1%) completed at least 6 therapy sessions. The mean (SD) duration of the first assessment was 39 (9) min-

**Table 3. Estimation of Intervention Effectiveness 6 and 9 Months After Randomization**

Outcome	Participants in Analysis, No.		Adjusted OR (95% CI)					
	6 mo	9 mo	TCBT		Exercise		Combined Intervention	
			6 mo	9 mo	6 mo	9 mo	6 mo	9 mo
<b>Primary Outcome: Global Change in Health Since Entering Trial<sup>a</sup></b>								
Less than much better	360	387	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Much better or very much better			5.0 <sup>b</sup>	5.4 <sup>c</sup>	6.2 <sup>c</sup>	3.6 <sup>c</sup>	7.1 <sup>c</sup>	6.2 <sup>c</sup>
			(2.0 to 12.5)	(2.3 to 12.8)	(2.5 to 15.1)	(1.5 to 8.5)	(2.9 to 17.2)	(2.7 to 14.4)
NNT <sup>b</sup>			4	4	4	6	3	3
<b>Secondary Outcome<sup>d</sup></b>								
CPG	277	278	-0.2	-0.6	-0.1	-0.6	-0.8	-0.6
			(0.01 to 1.3)	(-1.3 to 0.0)	(-0.7 to 0.6)	(-1.2 to 0.0)	(-0.5 to 0.7)	(-1.3 to 0.0)
GHQ	314	311	-1.2	-0.98	-0.9	-0.95	-1.1	-0.9
			(-2.1 to -0.4)	(-2.0 to 0.0)	(-1.8 to -0.1)	(-1.9 to 0.0)	(-1.9 to -0.2)	(-1.8 to 0.0)
SF-36								
Physical component score	325	320	0.8	1.4	0.8	2.6 <sup>b</sup>	3.5 <sup>b</sup>	3.6 <sup>e</sup>
			(-1.5 to 3.0)	(-0.9 to 3.7)	(-1.5 to 3.0)	(0.4 to 4.8)	(1.3 to 5.8)	(1.5 to 5.7)
Mental component score	325	320	3.4	3.7	2.7	1.5	2.1	1.2
			(0.9 to 5.6)	(0.9 to 6.4)	(0.2 to 5.1)	(-1.1 to 4.2)	(-0.3 to 4.5)	(-1.4 to 3.8)
Fatigue	295	299	-0.9	-1.4	-1.2	-1.7	-2.5 <sup>b</sup>	-1.8
			(-2.6 to 0.9)	(-3.1 to 0.3)	(-2.9 to 0.4)	(-3.3 to -0.8)	(-4.2 to -0.8)	(-3.4 to -0.1)
VPMI								
Passive	290	285	-1.5	-2.3	-1.5	-2.5	-3.2 <sup>c</sup>	-3.3 <sup>b</sup>
			(-3.3 to 0.3)	(-4.4 to -0.2)	(-3.2 to 0.2)	(-4.4 to -0.5)	(-4.9 to -1.5)	(-5.2 to -1.4)
Active	299	296	0.9	0.7	1.3	0.8	1.9 <sup>e</sup>	0.4
			(-0.1 to 1.9)	(-0.4 to 1.9)	(0.3 to 2.2)	(-0.3 to 1.8)	(1.0 to 2.9)	(-0.6 to 1.5)
Sleep	320	315	-2.4 <sup>b</sup>	-1.4	-1.8	-0.7	-1.7	-1.2
			(-3.9 to -1.0)	(-2.8 to -0.02)	(-3.2 to -0.4)	(-2.0 to 0.6)	(-3.1 to -0.3)	(-2.5 to 0.1)
TSK	298	310	-0.9	-1.8	-1.0	-1.9	-1.8	-3.6 <sup>c</sup>
			(-2.3 to 0.9)	(-3.6 to -0.1)	(-2.8 to 0.7)	(-3.5 to -0.2)	(-3.5 to -0.1)	(-5.2 to -1.9)

Abbreviations: CPG, Chronic Pain Grade questionnaire; GHQ, General Health Questionnaire; NNT, number needed to treat to achieve proportion of patients reporting a positive outcome on the primary outcome recorded in Table 2; OR, odds ratio; SF-36, 36-Item Short-Form Health Questionnaire; TCBT, telephone-delivered cognitive behavioral therapy; TSK, Tampa Scale for Kinesiophobia; VPMI, Vanderbilt Pain Management Inventory.

<sup>a</sup> Comparison group is treatment as usual. Values are given as ORs with 95% CIs derived from logistic regression models. Models are adjusted for age, sex, center, and baseline CPG and GHQ scores.

<sup>b</sup>  $P < .05$ .

<sup>c</sup>  $P < .001$ , adjusted for multiple testing by Bonferroni correction.

<sup>d</sup> Comparison group is treatment as usual. Values are b coefficients with 95% CIs derived from linear regression models except for CPG values, which were derived from ordinal regression models. All models were adjusted for age, sex, center, baseline CPG and GHQ scores, and baseline levels of the outcome of interest. For example, the model of fatigue was adjusted for age, sex, center, baseline CPG and GHQ scores, and baseline levels of fatigue.

<sup>e</sup>  $P < .01$ .

utes. The mean therapist time per patient over all sessions was 194 (128) minutes. Of the 130 participants randomized to exercise for whom records were available, 65 (50.0%) reached the compliance threshold of at least 2 sessions per week, whereas 21 (16.2%) did not attend any sessions on their own, although had attended their monthly sessions with the fitness instructor.

Adverse events were rare. Two deaths were recorded: 1 in the exercise group and 1 in the TCBT group (respectively, the deaths occurred 14 and 2 months after randomization, and the causes of death were metastatic cancer and pancreatic cancer). None of the adverse events were adverse reactions.

A positive outcome at 6 and 9 months was reported by 8.1% and 8.3%, respectively, of participants in the TAU group, 29.9% and 32.6% in the TCBT group, 34.8% and 24.2% in the exercise group, and 37.2% and 37.1% in the combined intervention group (Table 2). A 2-way factorial logistic regression analysis showed significant main effects for TCBT (OR, 5.4; 95% CI, 2.3-12.8) and exercise (OR, 3.6; 95% CI, 1.5, 8.5) and a significant antago-

nistic interaction (OR, 0.3; 95% CI, 0.1-0.9). When the combined effect is significantly less than the sum of the main treatment effects, inflated estimates are produced for the main treatment effects. Therefore, a 4-arm logistic regression comparison was adopted for ease of presentation and interpretation. This slightly reduced statistical power but did not affect inferences and showed significant main effects for TCBT, exercise, and combined intervention (Table 3). Main effects persisted after adjustment for self-reported OA, RA, and levels of disability (SF-36 PCS): for the TCBT group after 6 months, OR, 4.6 (95% CI, 1.8-11.5); after 9 months, OR, 5.3 (95% CI, 2.2-12.5); for the exercise group after 6 months, OR, 6.8 (95% CI, 2.7-17.0); after 9 months, OR, 3.9 (95% CI, 1.6-9.3); for the combined intervention group after 6 months, OR, 7.5 (95% CI, 3.0-18.4); after 9 months, OR, 6.6 (95% CI, 2.8-15.3). Improvements in GHQ, fatigue, VPMI, sleep, and TSK scores were observed, although few associations remained significant after adjusting for multiple comparisons: TCBT-improved sleep at 6 months (Table 3), exercise-improved SF-36 PCS

**Table 4. Adjusted Incremental Costs and QALYs for the Active Treatments vs TAU (Using Complete Case Data at 6 and 9 Months and Multiple Imputation)**

Intervention Arm	Mean (95% CI)		Additional Cost per QALY <sup>a</sup>
	Incremental Cost	Incremental QALYs	
Complete cases, 6 mo			
TAU (n=81)	1 [Reference]	1 [Reference]	1 [Reference]
TCBT (n=73)	385 (-0.26 to 793)	0.005 (-0.014 to 0.023)	£76 695
Exercise (n=87)	540 (285 to 780)	0.004 (-0.009 to 0.020)	£114 303
Combined intervention (n=84)	777 (497 to 1088)	0.012 (-0.002 to 0.028)	£63 858
Complete cases, 9 mo			
TAU (n=65)	1 [Reference]	1 [Reference]	1 [Reference]
TCBT (n=61)	345 (-177 to 887)	0.021 (-0.011 to 0.060)	£16 542
Exercise (n=71)	567 (174 to 943)	0.008 (-0.022 to 0.042)	£72,270
Combined intervention (n=76)	842 (422 to 1279)	0.024 (-0.004 to 0.061)	£34,731
Imputed data set, 9 mo			
TAU	1 [Reference]	1 [Reference]	1 [Reference]
TCBT	356 (-3 to 711)	0.009 (-0.017 to 0.032)	£39 868
Exercise	488 (209 to 789)	0.008 (-0.015 to 0.029)	£61 165
Combined intervention	744 (428 to 1069)	0.016 (-0.005 to 0.037)	£49 220

Abbreviations: QALY, quality-adjusted life-year; TAU, treatment as usual; TCBT, telephone-delivered cognitive behavioral therapy.

<sup>a</sup>£1.00=\$1.56 using 2008-2009 purchasing power parities.

scores at 9 months, combined intervention—improved SF-36 PCS scores, VPMI passive coping, and the TSK.

At 6 and 9 months after intervention, active interventions were associated with nonsignificant increases in QALYs (Table 4). Applying a cost-effectiveness ceiling ratio of £30 000 (\$46 770)/extra QALY, none of the active treatments were cost-effective at 6 months (Figure 2A). At 9 months, TCBT had the highest probability of being the preferred option (Figure 2B) with about a 70% chance of being cost-effective compared with TAU (Figure 2D). However, this finding was sensitive to imputation for missing data (Table 4; Figure 2C and D).

## COMMENT

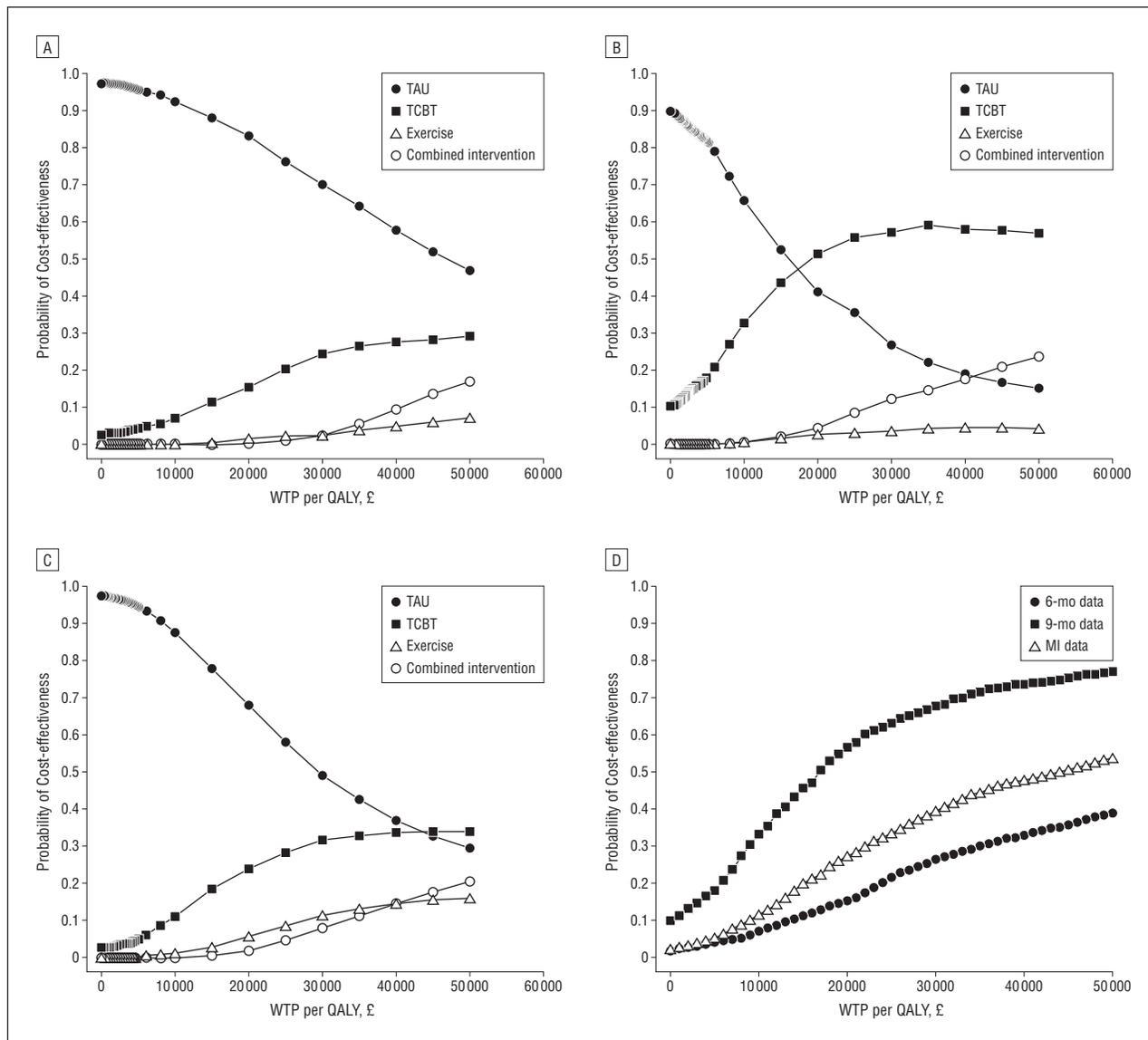
Effective treatment of fibromyalgia, a disorder characterized by CWP, is challenging. Three drugs (duloxetine hydrochloride, milnacipram hydrochloride, and pregabalin) are approved by the US Food and Drug Administration, although none adequately controls the multiple symptoms concomitant with the disorder.<sup>32</sup> Multidisciplinary physical and psychological approaches are recommended.<sup>8</sup> In this trial, a brief TCBT or exercise program was associated with substantial, significant, clinically meaningful improvements in self-rated global health. There was no effect on CPG. There was a high rate of missing CPG data, although MI analysis indicated that

this result was not sensitive to missing data. The 95% CIs around the estimates of association for the outcomes were wide, but even at the lower limit, active interventions significantly improved outcomes. After adjustment for multiple testing, a number of associations with secondary outcomes were no longer significant, although Bonferroni correction results in conservative *P* values and may introduce type II errors. Receiving both interventions was associated with a slight improvement in outcome but were not substantially better than single treatments. Possible explanations are that part of the TCBT model was behavioral activation and that participants receiving both interventions may have received a similar exercise message, or that the observed improvement associated with individual interventions was large and additional intervention added no significant benefit to that obtained from single interventions.

While CBT and physical exercise are recommended in this patient group, evidence from meta-analyses is equivocal. Patients receiving “psychological treatments” had small but significant improvements in pain, functional status, sleep, depression, and pain catastrophizing, with CBT having the largest effect sizes.<sup>33</sup> However, patients with fibromyalgia receiving CBT had no significant improvements in pain, fatigue, sleep, or QoL.<sup>12</sup> Aerobic exercise reduced pain, depression, fatigue, and QoL among patients with fibromyalgia,<sup>11</sup> although detailed exercise protocols were often unavailable, and specific exercise modalities unclear. Improvements were often not maintained, probably because patients stopped exercising after intervention end<sup>11</sup>; increased physical activity was associated with improved function and less pain at the end of a 12-week intervention,<sup>34</sup> although benefits were not maintained 6 and 12 months following intervention cessation.<sup>35</sup>

This trial has a number of strengths. It was pragmatic, patients were recruited from primary care, and few were excluded owing to exercise contraindications. Trial patients were representative of primary care patients with CWP in terms of age and sex.<sup>36</sup> A major strength was the brevity of the TCBT intervention. Coupled with the novel delivery mode, these findings suggest that a brief psychological intervention delivered remotely had positive impacts on outcome. The trial had a high follow-up rate, and follow-up attrition was not associated with important predictors of outcome. However, attrition had important implications for the health economic analysis.

The following trial limitations should be considered. Patients were recruited via questionnaire and not during general practice consultation. While patients with CWP seek health care, the reason for consultation is not accurately recorded.<sup>17</sup> Assessing accuracy of self-report consultation is complex, being influenced by physician-specific factors (perceived importance of the problem, whether the consultation leads to a prescription), and patient-specific factors (reporting consultations occurring outside of the recall period).<sup>37</sup> While medical records are unlikely to record multiple consultations for chronic pain disorders, moderate agreement has been reported for self-report and general practitioner-recorded knee pain consultations over 12 months.<sup>37</sup> Fewer than 468 patients were randomized, reducing study power with the potential for



**Figure 2.** Cost-effectiveness acceptability curves. A, All treatment groups using complete case data at 6 months. B, All treatment groups using complete case data at 9 months. C, All treatment groups using the imputed data. D, Cognitive behavioral therapy vs treatment as usual at 6 and 9 months and the multiple imputation dataset. MI indicates multiple imputation; QALY, quality-adjusted life-year; TAU, treatment as usual; TCBT, telephone-delivered cognitive behavioral therapy; and WTP, willingness to pay. £1.00=\$1.56 using 2008-2009 purchasing power parities.

real differences to be missed. However, statistically significant effects on the primary outcome were greater than anticipated across all treatment groups. In the TAU group, the precise care delivered, if any, was not recorded. However, the TAU group receiving either or both active interventions would have decreased the likelihood of observing a significant effect of treatment. It is also likely that any *additional* treatment received would be independent of intervention arm. Patient-practitioner (eg, nurse, physician, therapist) effects may influence outcome.<sup>38</sup> However, effects in chronic pain studies are conservative; are smaller in studies with fewer practitioners, perhaps reflecting increased conformity of treatment delivered; and any bias in estimating the true treatment effect by ignoring practitioner variability small owing to the randomized design of the trials.<sup>39</sup> Finally, in non-blind trials, social desirability bias may influence pa-

tients to report higher levels of disability and lower levels of psychological symptoms.<sup>40,41</sup> However, adults with fibromyalgia displayed high levels of social desirability and high levels of anxiety<sup>42</sup> and social desirability did not predict outcome in a trial of relaxation and education.<sup>43</sup>

This trial demonstrates short- to medium-term improvements in patients with CWP. Whether improvements continue in the longer term should be established. These results provide encouragement that short-term improvement is possible in a substantial proportion of patients with CWP.

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