Review

Systematic Review of Discriminating Power of Outcome Measures Used in Clinical Trials of Fibromyalgia

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ABSTRACT. ***Objective.*** Fibromyalgia (FM) comprises many symptoms and features. Consequently, studies on the condition have used a wide variety of outcome measures and assessment instruments. We investigated those outcome measures and instruments in association with the OMERACT (Outcome measures in Rheumatoid Arthritis Clinical Trials) FM Workshop initiative to define core outcome measures that should be used to assess FM.

Methods. A systematic literature review up to December 2007 was carried out using the keywords "fibromyalgia," "treatment" or "management," and "trial." Data were extracted on outcome measures and assessment instruments used and the pre and post mean and standard deviation to calculate effect sizes (ES). Further sensitivity analysis was carried out according to treatment type, blinding status, and study outcome.

Results. The outcome domains identified fell largely within those defined by OMERACT. Morning stiffness was frequently assessed and therefore has been included here. The number of assessment instruments used was wide-ranging, so sensitivity analysis was only carried out on the top 5 within each domain. ES ranged from 0.54 to 3.77 for the key OMERACT domains. Health-related quality of life (HRQOL) was the only exception that had no instrument with moderate sensitivity. Of the secondary domains, dyscognition was lacking any sensitive instrument, as were fatigue and anxiety in pharmacological trials.

Conclusion. Each of the key OMERACT domains has an instrument that appears to be sensitive to change, with the exception of HRQOL, which requires further research. Dyscognition, fatigue, and anxiety would all benefit from more research into their assessment instruments. (First Release Sept 15 2008; J Rheumatol 2008;35:2094–105; doi:10.3899/jrheum.080077)

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FIBROMYALGIA OUTCOME MEASURES CLINICAL TRIAL SENSITIVITY

Fibromyalgia (FM) is a rheumatologic condition characterized by chronic widespread pain with hyperalgesia and allodynia. Current diagnostic criteria state that pain must have been present for at least 3 months in all 4 quadrants of the body, and pain on palpation at 11 out of 18 predefined tender points[1]. FM is associated with a wide range of symptoms including fatigue, sleep disturbance, psychological and cognitive alterations, headache, migraine, variable bowel habits, diffuse abdominal pain, and urinary frequency[2,3]. Reflecting this, numerous outcome measures have been used in clinical trials resulting in large variations and inconsistencies in reporting outcomes. Previous systematic reviews have highlighted these problems in FM clinical trials[4-8]. Almost all the outcome measures used were not developed for use in FM and few have published psychometric results in FM patient populations.

Through the work of the Outcome Measures for Rheumatoid Arthritis Clinical Trials group (OMERACT), important efficacy outcome domains have been identified independently according to expert opinion and review of major clinical trials as well as clinician and patient Delphi exercises. Starting with a list of 40 potential domains that could be assessed in FM syndrome, the expert Delphi processes involved 3 rounds of voting to prioritize the domains. This was followed by multi-site patient focus groups that again revealed 40 potential domains, which were short-listed and prioritized by 2 rounds of voting among the patient participants. The results from experts and patients were very similar. The short-listed domains included within the "key domains" were pain, patient global, fatigue, health-related quality of life (HRQOL), multidimensional function,

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sleep, and depression; and within the "secondary domains," physical function, tender points, dyscognition (representing "problems with concentration," "disorganised thoughts," etc.), and anxiety[9,10].

The objectives of OMERACT are to identify and come to a consensus on core sets of domains for rheumatologic conditions, and within these to evaluate the quality of outcome measures used to assess them. This fundamentally includes determining the sensitivity, feasibility, and reliability of instruments. This study aimed to supplement the OMERACT FM work by systematically reviewing outcome instruments that have been used in FM clinical trials. The aim was to map individual instruments to appropriate outcome domains previously identified at OMERACT. The discriminating power of these instruments, a critical aspect of an instrument's measurement properties, was assessed by their sensitivity to change as measured by effect sizes (ES).

MATERIALS AND METHODS

Search strategy. A systematic review using the key words "fibromyalgia," "treatment" or "management," and "trial" for all publications until the end of December 2007 was carried out across a range of databases designed to detect all published clinical trials in fibromyalgia — these were Medline, PubMed, EMBASE, PsycINFO, CINAHL, Web of Sciences, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. A manual search was also undertaken of the bibliographies of trials identified, to verify that all published trials had been detected. Every effort was made to obtain all studies, including those that were not published in English. Where possible, English translations were obtained, or alternatively, assessment and data extraction were performed by native speakers of the respective languages.

Inclusion criteria. Studies were only included if they used the American College of Rheumatology (ACR) 1990 classification criteria for FM[1] to select patients. Studies that included patients with chronic fatigue syndrome or myalgic encephalomyelitis were excluded unless they were divided into separate comparator groups for analysis. The focus of the search was on clinical trials. Reviews were assessed only to verify that all trials had been identified. There was no limitation on quality of study, to ensure that a full range of assessment instruments was included, and also as this would have biased against nonpharmacological studies.

Data extraction. Information for each of the identified reports was tabulated using a custom-made data-extraction form. This included intervention type, randomization (randomised/quasi-randomised or nonrandomised), and blinding status (double-blind/single-blind/open), as well as details of each outcome measure assessed. For each outcome measure, the method of assessment (instrument) was then recorded. Instruments were listed under the outcome measure that the trial reported they had been used for — for example, multi-item assessments may be listed under more than one outcome measure due to their subscales being used for different purposes. The between-group difference was calculated from the mean change between the pre- and post-treatment values for each. When data were available, ES for each instrument within each outcome measure were calculated using these values. Rosnow and Rosenthal's modified version of the Cohen's d method[11] for ES calculation was used:

$$d = M_1 - M_2/s_{pooled}$$
$$s_{pooled} = v[(s_1^2 + s_2^2)/2]$$

Where d = effect size, M = mean change, s = standard deviation, and 1 and 2 are the treated and controlled groups, respectively. The thresholds used for interpretation were as follows: values > 0.2 = small, > 0.5 = medium, and > 0.8 = large. If required data were recorded, but either were not presented or were not presented in a suitable format, the author was contacted whenever possible. When the data were provided only in graphic format, if possible these data were extracted and included.

Sensitivity analyses. ES can be influenced by treatment effect and trial design. Ineffective treatment reduces ES, while open-label studies may inflate them. Further, nonpharmacological studies often aim to improve function but may have a smaller effect on pain. Therefore sensitivity analyses were performed to assess whether ES were affected by treatment type (pharmacological and nonpharmacological studies) and blinding and/or randomization status of the study, and excluding studies that had negative overall effect (indication of ineffective treatment or intervention).

RESULTS

Out of 185 trials that were identified (Table 1), outcome measures could be subdivided into 15 domains. Seven of these came under the 8 most important domains that had been identified by OMERACT, a further 3 were considered important, and the remaining 5 did not fit into any of these specific headings. Dyscognition is the only domain identified by OMERACT for which data have not been reported in FM clinical trials, although some studies stated that this was assessed. A full list of outcome domains identified, and the number of different instruments used to assess them, is shown in Figure 1.

Some assessments did not fall clearly within any of the OMERACT domains. These included "Feeling on waking," assessed by visual analog scale (VAS); "psychological assessments" that did not fit within depression or anxiety (e.g., helplessness, coping strategies, and personality); "associated symptoms" recorded by a variety of means including severity assessed by VAS or Likert scales, symptom diaries, checklists, or by a record of GP visits. Two additional assessments that did not fit in to any subheading were work capacity and knowledge of FM. No further assessment of these miscellaneous domains or instruments was carried out due to the small numbers of each. For domains in which a large number of different instruments had been used, only the top 5 most frequently used assessment instruments were analyzed further (Table 2).

Results for the previously defined key OMERACT domains are given in Table 3. Table 4 shows results for instruments that were included in the secondary OMERACT domains, plus morning stiffness, with the omission of dyscognition. Dyscognition is rarely assessed in clinical trials. In the few trials that assessed dyscognition, none reported the results in a format allowing analysis. "Tender point analysis" was included within "pain"; "function" was grouped under one heading for multidimensional and physical components. "Morning stiffness" was added due to the large number of trials that had considered this outcome. Values shown represent average ES (95% confidence levels), unless stated otherwise.

Table 1. Studies identified for the review.

Class of Treatment			
Nonpharmacological	n	Pharmacological	n
Aerobic exercise[78–90]	11	Selective serotonin reuptake inhibitors[17–21]	4
Strength training[91–94]	4	Tricyclic antidepressants[18,21-28]	8
Mixed exercise[95–98]	4	Dual reuptake inhibitors[19,29-33]	5
Pool based[99–103]	2	5HT2/3 antagonists[34–43]	10
Dietary interventions[104–111]	7	Monoamine oxidase inhibitors[28–46]	4
Cognitive behavioral therapy[112–115] (CBT)	2	Systemic analgesics[47–52]	6
CBT and exercise[116–120]	5	Topical analgesics[53–55]	3
Education[121–124]	4	Triiodothyronine[56–58]	3
Education and exercise[95,125–131]	8	Others[59–77]	15
Balneotherapy[130, 132–34]	4		
Homeopathy[135–37]	3		
Physiotherapy-related[138–145]	5		
Meditation[145–147]	2		
Laser/light[148–151]	2		
Acupuncture[152–158]	4		
Magnets[159,160]	2		
Others[161–194]	11		

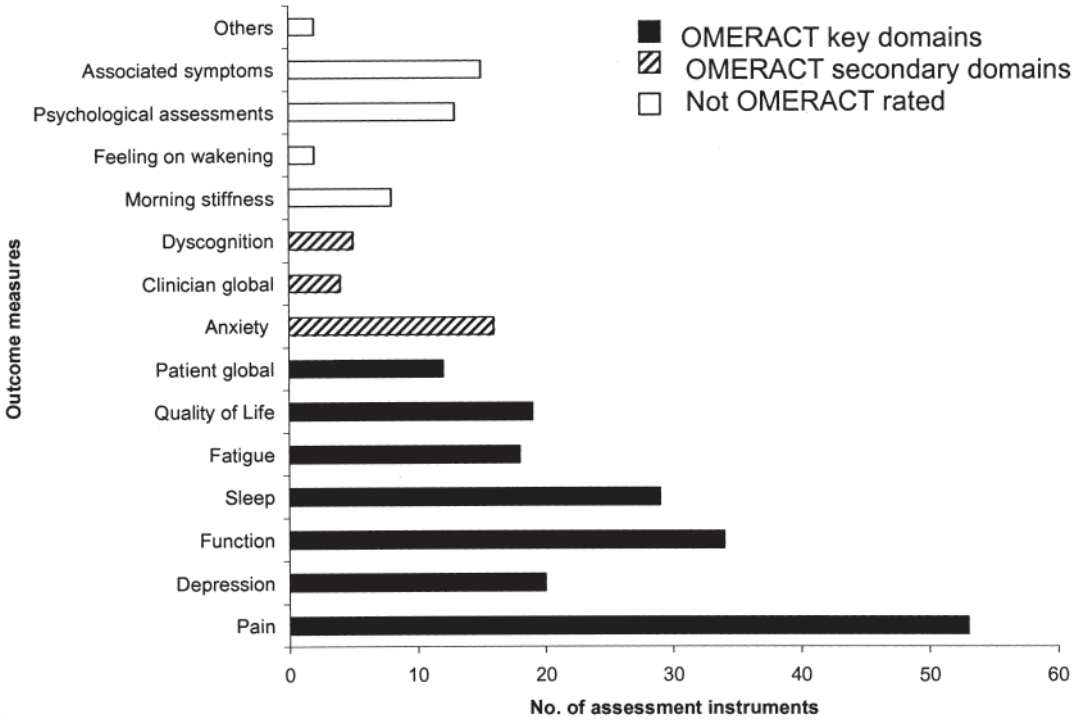

Figure 1. Outcome measures identified in FM clinical trials and the number of different instruments used to assess them.

Key domains

Pain. The VAS is commonly used and is a sensitive instrument in both pharmacological [0.77 (–0.97, 2.64)] and nonpharmacological trials [0.67 (–2.5, 3.84)]. However, trials differ in the exact question used, varying from "current" and "average over last week" to "average over last month." Despite controversy about the usefulness of the tender point count in clinical trials (and for diagnosis of FM)[12,13], and suggestions that dolorimetry is a more appropriate measure of tenderness, the results reported here found the tender point count to be sensitive in nonpharmacological trials, with moderate to large ES [0.7 (–1.04, 2.48)]. In pharmacological trials, average ES was small to moderate [0.41 (–1.05, 1.87)], but one single-blind trial reported a large ES [0.77 (–1.57, 3.11)]. However, pressure pain threshold (PPT), measured by dolorimetry, was sensitive only in phar-

Table 2. Top 5 instruments used in the core outcome domains (plus morning stiffness).

Outcome Domain	Instrument	No. of Trials
Key Domains		
Pain	VAS	112
	FIQ	42
	Tender point count	67
	Myalgic score	39
	PPT	29
Patient global	VAS global FM assessment	15
	VAS global well-being	6
	VAS global improvement	3
	Likert global improvement	2
	Impression of change	3
Depression	FIQ	36
	BDI	34
	Hamilton	12
	CESD	7
	VAS	7
Fatigue	FIQ	34
	VAS	31
	Likert 0–4	4
	CPRS	2
	Multidimensional	2
Quality of life	VAS	6
	SF-36	15
	ASES	8
	NHP	3
	FAI	3
Sleep	VAS	34
	FIQ	17
	No. awakenings	3
	EEG	4
	Hours of sleep	5
Secondary domains		
Function	FIQ	880
	HAQ	13
	Strength	11
	6-min walk	9
	SF-36	12
Dyscognition	VAS	5
	CPRS	2
	Ability to concentrate	1
	SF-MPQ	1
	Cognitive difficulties scale	1
Anxiety	FIQ	35
	VAS	9
	STAI	7
	Beck Anxiety Index	6
	Hamilton	5
Clinical global	VAS FM severity	3
	Severity	6
	Impression of change	4
	VAS general state	2
Morning stiffness	FIQ	38
	VAS	10
	Duration (min)	8
	Likert	3
	CPRS	2

VAS: visual analog scale, FIQ: Fibromyalgia Impact Questionnaire, PPT: pressure pain threshold, BDI: Beck Depression Inventory, CESD: Centre for Epidemiological Studies Depression scale, CPRS: Comprehensive Psychopathological Rating Scale, SF-36: Short Form-36, ASES: Arthritis Self Efficacy Scale, NHP: Nottingham Health Profile, FAI: Fibromyalgia Attitudes Index, EEG: electroencephalogram, HAQ: Health Assessment Questionnaire, SF-MPQ: short form McGill Pain Questionnaire, STAT: State-Trait Anxiety index.

macological trials [3.77 (2.73, 3.82)], based on 2 trials, and had low sensitivity in nonpharmacological trials [0.09 (–1.34, 2.34)].

Patient global assessment. Patient global assessment was commonly assessed by VAS. It was sensitive to change across all trials [pharmacological, 1.01 (–0.31, 2.34); nonpharmacological, 0.48 (–0.54, 1.51)]. Other instruments were studied less extensively.

Depression. Both the Hamilton scale and Centre for Epidemiologic Studies Depression scale (CESD) appeared to be sensitive in pharmacological studies [0.72 (–1.7, 3.14) and 1.4 (0.36, 2.43) respectively], although with further analysis it seemed that the sensitivity of the Hamilton was inflated by 2 single-blind studies, and the CESD results were based on only one trial. The Beck Depression Inventory (BDI) in nonpharmacological trials was sensitive to change [0.9 (–2.33, 4.13)]; however, this was based on data from only single-blind and open-label studies. The ES of the BDI appeared to be smaller in pharmacological trials [0.19 (–3.44, 3.82)]. Recently, many pharmacological studies have excluded patients with significant depression; this could have resulted in underestimation of the performance of these instruments as baseline depression scores in these studies would have been low.

Fatigue. The VAS and Likert scales for nonpharmacological trials had good sensitivity for fatigue [1.3 (–0.08, 2.68) and 1.09 (–0.53, 1.65), respectively]. VAS were predominantly used in pharmacological trials, with an ES of 0.34 (–0.94, 1.63).

Health-related quality of life. There was no instrument that was particularly sensitive to change for HRQOL. The physical and mental component summary scores from the Short Form-36 (SF-36) health survey were reported only in pharmacological trials, with the physical component gaining the most support (of all subscales) for pharmacological studies [0.43 (–1.59, 2.44)], although this was based on only 2 studies. Results from all of the 8 subscales are available in both pharmacological and nonpharmacological trials; however, all have low sensitivity (range 0.002–0.32, role limitation physical, nonpharmacological and pharmacological, respectively) and are based on only a very small number of studies (maximum of 3).

Sleep. The VAS scale may be moderately useful across trials for sleep assessment [pharmacological, 0.54 (–1.03, 2.12); nonpharmacological, 0.43 (–0.92, 1.7)]; and the Fibromyalgia Impact Questionnaire (FIQ) sleep item was sensitive in nonpharmacological trials [0.51 (–1.21, 2.23)], although based on mainly single-blind studies.

Function. When the overall FIQ score was used as a measure of function it was moderately sensitive across trials, with smaller effect seen in pharmacological trials versus nonpharmacological trials [pharmacological, 0.45 (–7.12, 8.02); nonpharmacological, 0.52 (–4.31, 5.36)]. In single-blind trials in pharmacological trials the sensitivity was good [phar-

Table 3. Effect sizes (ES) for selected instruments used within the key OMERACT domains: Pain, Patient global, Depression, Fatigue, Quality of life, Sleep, and Function. Results reported as mean ES (95% confidence levels); n = number of trials averaged.

OMERACT Domain	Instrument	Pharmacological ES			Nonpharmacological ES			
		Average	Double-blind	Single-blind/ open	Average	Double-blind	Single-blind	Open
Pain	VAS	0.77 (-0.97, 2.64) n = 23	0.77 (-0.97, 2.64) n = 23	—	0.67 (-2.5, 3.84) n = 36	1.1 (-0.16, 2.36) n = 6	0.51 (-2.42, 3.44) n = 8	0.7 (-2.88, 4.29) n = 20
	FIQ	0.33 (-0.14, 0.8) n = 1	0.33 (-0.14, 0.8) n = 1	—	0.57 (-0.56, 1.69) n = 10	—	1.04 (-0.17, 2.24) n = 4	0.31 (-0.72, 1.35) n = 4
	Tender point count	0.41 (-1.05, 1.87) n = 13	0.29 (-1.08, 1.67) n = 12	0.77 (-1.57, 3.11) n = 1	0.7 (-1.04, 2.48) n = 23	3.2 (1.71, 4.69) n = 3	0.6 (-1.29, 2.5) n = 8	0.14 (-1.6, 1.86) n = 12
	PPT	3.77 (3.73, 3.82) n = 2	3.77 (3.73, 3.82) n = 2	—	0.09 (-1.34, 2.34) n = 11	0.11 (-0.37, 0.6) n = 4	0.07 (-7.28, 7.41) n = 2	0.3 (-0.13, 0.73) n = 3
Patient global	VAS global FM assessment	1.01 (-0.31, 2.34) n = 6	1.01 (-0.31, 2.34) n = 6	—	0.48 (-0.54, 1.51) n = 1	—	0.48 (-0.54, 1.51) n = 1	—
Depression								
	FIQ depression subscale	0.4 (-0.79, 1.59) n = 3	0.4 (-0.79, 1.59) n = 3	—	0.01 (-1.55, 1.53) n = 10	-0.18 (-1.63, 1.27) n = 2	0.21 (-1.5, 1.93) n = 2	0.03 (-1.54, 1.49) n = 6
	BDI	0.19 (-3.44, 3.82) n = 5	0.19 (-3.44, 3.82) n = 5	—	0.9 (-2.33, 4.13) n = 14	—	0.54 (-3.82, 4.9) n = 7	1.26 (-0.84, 3.36) n = 7
	Hamilton	0.72 (-1.7, 3.14) n = 5	0.26 (-2.35, 2.87) n = 3	1.41 (-0.73, 3.56) n = 2	0.45 (-3.34, 4.24) n = 3	—	0.47 (-3.88, 4.82) n = 2	0.4 (-2.26, 3.07) n = 1
	CESD	1.4 (0.36, 2.43)	1.4 (0.36, 2.43)	—	0.12 (-2.76, 2.99)	—	—	0.12 (-2.76, 2.99)
Fatigue	FIQ fatigue subscale	0.12 (-0.43, 0.67) n = 2	0.12 (-0.43, 0.67) n = 2	—	0.3 (-0.9, 1.5) n = 11	0.23 (-0.88, 1.34) n = 2	0.75 (-0.91, 2.42) n = 2	0.19 (-0.9, 1.29) n = 7
	VAS	0.34 (-0.94, 1.63) n = 10	0.34 (-0.94, 1.63) n = 10	—	1.3 (-0.08, 2.68) n = 3	2.66 (2.18, 3.13) n = 1	0.51 (-1.01, 2.04) n = 1	0.72 (-1.43, 2.87) n = 1
	Likert 0–4	—	—	—	1.09 (0.53, 1.65) n = 3	—	1.09 (0.53, 1.65) n = 3	—
Quality of life	SF-36 physical component	0.43 (-1.59, 2.44) n = 2	0.43 (-1.59, 2.44) n = 2	—	—	—	—	—
	SF-36 mental component	0.18 (-2.88, 3.24) n = 2	0.18 (-2.88, 3.24) n = 2	—	—	—	—	—
	ASES	—	—	—	0.39 (-8.1, 8.87) n = 9	—	—	0.39 (-8.1, 8.87) n = 9
Sleep	VAS	0.54 (-1.03, 2.12) n = 9	0.54 (-1.03, 2.12) n = 9	—	0.43 (-0.92, 1.7) n = 3	1.01 (0.45, 1.56) n = 1	-0.05 (-1.62, 1.53) n = 1	0.32 (-1.6, 2.34) n = 1
	FIQ sleep subscale	0.26 (-0.91, 1.43) n = 3	0.26 (-0.91, 1.43) n = 3	—	0.51 (-1.2, 2.23) n = 5	0.15 (-1.29, 2.23) n = 1	0.75 (-0.73, 2.22) n = 3	0.16 (-2.59, 2.91) n = 1
Function	FIQ physical function subscale	0.45 (-7.12, 8.02) n = 17	0.53 (-7.5, 8.56) n = 16	0.96 (-3.87, 5.78) n = 1	0.52 (-4.31, 5.36) n = 39	0.58 (-6.64, 7.6) n = 6	0.67 (-6.4, 7.73) n = 10	0.65 (-2.64, 3.95) n = 23
	HAQ	-0.08 (-0.66, 0.49) n = 4	-0.08 (-0.66, 0.49) n = 4	—	0.6 (0.28, 0.92) n = 2	—	0.59 (0.37, 0.81) n = 1	0.6 (0.19, 1.02) n = 1

VAS: visual analog scale, FIQ: Fibromyalgia Impact Questionnaire, PPT: pressure pain threshold, BDI: Beck Depression Inventory, CESD: Centre for Epidemiologic Studies Depression scale, SF-36: Short form-36, ASES: Arthritis Self Efficacy Scale, HAQ: Health Assessment Questionnaire.

macological, 0.96 (–3.87, 5.78)], but these were not well controlled studies, so the ES may have been biased. The 6-minute walk may be of some use in nonpharmacological studies [0.6 (–40.98, 42.18)], although these data were collected from uncontrolled studies and the confidence levels were very wide.

Secondary domains

Anxiety. The VAS and the State-Trait Anxiety Inventory (STAI) were both sensitive in nonpharmacological trials [0.81 (–0.87, 2.5) and 1.32 (–5.35, 7.98), respectively]; however, these results were each from 2 uncontrolled trials. There did not appear to be a sensitive measure for pharmacological interventions, although again the small number of assessments of this measure require more attention before firm conclusions can be reached on the performance of the existing instruments.

Clinician global. The assessment of clinical global impres-

Table 4. Effect sizes (ES) for the top 5 instruments used within 2 of the secondary OMERACT domains: Anxiety and Clinician Global plus Morning Stiffness. Results reported as mean ES (95% confidence levels); n = number of trials averaged.

OMERACT Domain	Instrument	Pharmacological ES			Nonpharmacological ES			
		Average	Double-blind	Single-blind/ Open	Average	Double-blind	Single-blind	Open
Anxiety	FIQ anxiety subscale	0.2 (-1.05, 1.46) n = 3	0.2 (-1.05, 1.46) n = 3	—	0.09 (-1.48, 1.66) n = 11	-0.18 (-1.59, 1.22) n = 2	-0.4 (-2.41, 1.6) n = 1	0.22 (-1.34, 1.78) n = 8
	VAS	—	—	—	0.81 (-0.87, 2.5) n = 2	—	—	0.81 (-0.87, 2.5) n = 2
	STAI	0.03 (-5.83, 5.9) n = 1	0.03 (-5.83, 5.9) n = 1	—	1.32 (-5.35, 7.98) n = 2	—	—	1.32 (-5.35, 7.98) n = 2
	Beck anxiety index	0.22 (-3.06, 3.5) n = 2	0.22 (-3.06, 3.5) n = 2	—	0.08 (-7.25, 7.42) n = 1	—	0.08 (-7.25, 7.42) n = 1	—
Clinician global	VAS FM severity	0.19 (-0.2, 0.58) n = 2	0.19 (-0.2, 0.58) n = 2	—	0.12 (-0.58, 0.82) n = 2	—	—	0.12 (-0.58, 0.82) n = 2
	Severity, 1-7 scale	0.26 (-0.87, 1.4) n = 4	0.26 (-0.87, 1.4) n = 4	—	—	—	—	—
	Impression of change	0.37 (-0.18, 0.93) n = 2	0.37 (-0.18, 0.93) n = 2	—	—	—	—	—
	VAS general state	—	—	—	-3.84 (-4.02, -3.67) n = 1	-3.84 (-4.02, -3.67) n = 1	—	—
Morning stiffness	FIQ stiffness subscale	0.27 (-0.83, 1.37) n = 4	0.27 (-0.83, 1.37) n = 4	—	0.26 (-0.89, 1.41) n = 12	0.27 (-0.98, 1.52) n = 2	-0.69 (-2.42, 1.05) n = 1	0.36 (-0.7, 1.42) n = 9
	VAS	—	—	—	-0.53 (-2.62, 1.55) n = 1	—	—	-0.53 (-2.62, 1.55) n = 1
	Duration (min)	0.34 (-9.35, 10.02) n = 3	0.44 (-10.98, 11.87) n = 2	0.13 (-6.07, 6.33) n = 1	1.41 (-4.64, 7.46) n = 1	1.41 (-4.64, 7.46) n = 1	—	—
	Likert	0.67 (0.22, 1.12) n = 1	—	0.67 (0.22, 1.12) n = 1	0.63 (0.12, 1.45) n = 3	0.08 (-0.43, 0.59) n = 1	0.91 (0.39, 1.42) n = 2	—

FIQ: Fibromyalgia Impact Questionnaire, VAS: visual analog scale, STAI: State-Trait Anxiety Inventory.

sion was a common endpoint in FM studies; however, in recent years this outcome assessment has been dropped in favor of a reliance on the patient as the best reporter of his or her improvement or worsening, particularly as it relates to the inherently subjective measure of pain. Therefore only a few ES calculations are available for this endpoint (Table 3).

Morning stiffness. These results suggest that there are sensitive instruments available for both pharmacological and nonpharmacological studies. Duration had large ES in nonpharmacological studies [1.41 (–4.64, 7.46)], and the VAS and Likert scales may be moderately sensitive [0.53 (–2.62, 1.55) and 0.63 (0.12, 1.45), respectively], but the VAS data were from uncontrolled trials. Likert scales were also moderately sensitive in pharmacological interventions [0.67 (0.22, 1.12)], although this was from just one uncontrolled study.

Sensitivity analyses

The results from the analysis only of effective treatments did not alter the findings substantially. There were some notable exceptions that improved in sensitivity, although these were mainly in nonpharmacological trials based on uncontrolled studies. The only one within the pharmacological trials was the tender point count, which appeared to be slightly more sensitive, increasing from low to moderate sensitivity [0.53 (–0.98, 2.04)] and high sensitivity in nonpharmacological, including double-blind trials [1.68 (0.47, 3.3)]. Excluding negative studies can also inflate the ES and introduces a dissemination bias. For these reasons, we have reported results with all included studies.

ES can be inflated by including open-label studies. Indeed, sensitivity analysis excluding these trials showed that the average ES of the Hamilton scale for depression [double-blind, 0.26 (–2.35, 2.87); uncontrolled, 1.41 (–0.73, 3.56)], tender point count for pain [double-blind, 0.29 (–1.08, 1.67); uncontrolled, 0.77 (–1.57, 3.11)], and FIQ for function [double-blind, 0.53 (–7.5, 8.56); uncontrolled, 0.96 (–3.87, 5.78)] all seemed to be inflated by including uncontrolled open-label trials. However, it is important to note that it is not possible for all nonpharmacological trials to be double-blind, or even single-blind in some cases.

DISCUSSION

This systematic literature review highlighted the vast number of outcome measures that have been used in FM clinical trials. Compounded by inconsistencies in reporting results in publications, the argument for the need to develop a glob-

al consensus on core outcome domains to be used in all clinical trial is overwhelming.

The aim of our review was not to compare instruments to one another, but to identify whether or not there were assessment instruments currently being used that were sensitive to change across treatments in FM. Our results indicated that for each of the outcome domains identified by OMERACT 8 (with the exception of dyscognition and HRQOL), there is at least one instrument that is discriminatory. Pain, patient global, sleep, depression, and function all had instruments that were at least moderately sensitive in either pharmacological or nonpharmacological interventions. These results are promising for outcome assessment in FM. This review was not able to examine sensitivity analyses for all instruments, and consequently some were omitted due to our limit of assessing only the top 5 most widely used, and there may be more sensitive instruments that were not examined here. We also limited studies to those that used the ACR 1990 criteria[1]; using a wider range of diagnosis classification may have resulted in more information being gained.

Interpreting ES is not straightforward. It can be influenced by a number of factors, including study design, patient population, and treatment efficacy. Open-label studies can inflate the ES and ineffective treatments reduce it. Our sensitivity analyses showed that in current FM trials, the former is indeed the case. Therefore in cases where data are available only from uncontrolled studies the results should be interpreted with caution. However, in the nonpharmacological studies, despite uncontrolled studies being more common, many discriminatory instruments (VAS for pain, fatigue and sleep; FIQ for function; and duration of morning stiffness) are validated in double-blinded trials.

In many trials, especially pharmacological studies, patients with significant depression were excluded. With low baseline depression scores in these studies, the likelihood of change is reduced and may underestimate the discriminatory power of instruments that measure depression. The Hamilton scale for depression did prove to be relatively sensitive to change in both pharmacological and nonpharmacological trials, as was the BDI for the nonpharmacological trials. All the pharmacological trials that provided results for the Hamilton, except one, did not exclude depressed patients. This suggests that outcome measures may be more sensitive to change when appropriate populations are included such that they have impairment of the domains that the instrument was designed to measure.

For assessment of VAS, all time-ranges were included, e.g., current, worst, average over last week, etc. Further research will be necessary to determine which time period is the most appropriate to use for the corresponding outcome measures in clinical trials.

FM is characterized by manifold symptoms. Some treatments target specific features such as exercise to improve function, which has resulted in mixed reports on influence on pain. By pooling all the studies, it is likely that we have underestimated the discriminatory power of these instruments. It has also been suggested that there are different subgroups of patients with FM displaying different symptom profiles[14], and consequently responding to different treatments. This may also lead to an underestimation of ES.

According to this work, single-item assessments consistently appeared to have greater discriminative properties than multi-item assessments. This may be because single-item assessments have been used more commonly than multiple-items assessments. Also, reliability is directly related to the number of items within a scale, so single-item assessments can be of lower reliability and consequently limited validity. Thus it is important not to rule out multi-item assessments when choosing the right instrument for any particular study.

This work supports results from the previous OMERACT workshop on the main outcome domains recommended to be considered for inclusion in the core data set[15]. The notable exception was "morning stiffness," which was ranked highly for importance by patients but not experts[16]. Interestingly, morning stiffness was commonly measured and was assessed by relatively few instruments (8), so reporting was fairly consistent.

This work also revealed that further research is needed to develop validated and sensitive instruments to assess dyscognition. HRQOL, anxiety, and fatigue would also benefit from more research to develop more sensitive instruments, and morning stiffness as an outcome domain. Finally, while important, discrimination is only one of the key measurement properties to consider in instrument selection. Other properties, such as validity and reliability and how the instrument fits into the overall conceptual framework, must also be considered — further work to assess these additional properties is called for.

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