

# Web/Internet-based telemonitoring of a randomised controlled trial evaluating the time-integrated effects of a 24-week multicomponent intervention on key health outcomes in patients with fibromyalgia

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## ABSTRACT

**Objective.** The aims of the study were to assess the efficacy of a multicomponent intervention and evaluate the feasibility and user acceptance of an internet-based home telemedical surveillance system for the evaluation of pain and other key health outcomes in patients with fibromyalgia (FM).

**Methods.** The study involved 76 FM patients who were randomised to usual care or the multicomponent exercise programme, which consisted of 24 twice-weekly sessions of combined aerobic, muscle strength training exercises and education. All the patients completed the revised version of the Fibromyalgia Impact Questionnaire (FIQR) and the self-administered Fibromyalgia Activity Score (FAS). A predefined website allowed authorised users to enter data via a personal computer (PC) and Internet browser. The differences between the groups were assessed using the Mann-Whitney U-test and Fisher's exact test, and the correlations were analysed using Spearman's rank correlation test.

**Results.** The multicomponent intervention led to a clinically relevant difference in improvement in comparison with the standard approach. It markedly improved the FIQR symptom subscale score, significantly increased the time-integrated area under the curve (AUC) of the FAS scores, and led to a greater benefit in terms of fatigue and the quality of sleep. The mean change in the AUC of the total FIQR score closely correlated with the changes in the AUC of the total FAS score.

**Conclusion.** The multicomponent approach to FM was effective in treating the key symptoms and maintaining the improvements in the short term, and telemonitoring proved to be an easy-

to-use solution for patient-centred data acquisition.

## Introduction

Fibromyalgia (FM) is a chronic multisymptom disease (1-3) that affects approximately 2-3% of the general population (90% of the patients are female). Its most characteristic symptom is pain (4, 5), but the disease has a profound impact on global health and well-being (6) and is often associated with high rates of the use of healthcare resources and an increased risk of working disability (7).

There is still considerable disagreement concerning the best way to manage FM. The clinical guidelines recommend a broad range of pharmacological and non-pharmacological therapies, but their impact on health-related quality of life (HRQoL) and function is still controversial (8). It is well known that antidepressants can reduce some of the symptoms of various chronic pain conditions, including FM (9), and other widely used medications are anxiolytics, hypnotics, analgesics and agents that relieve gastrointestinal symptoms (10, 11). However, no single treatment has been found to be consistently successful (12), and it is not surprising that the majority of FM patients tend to discontinue treatment after one year because of lack of efficacy (13).

A number of meta-analyses and many clinical trials have shown that physical exercise training benefits patients with FM and other chronic pain conditions, especially when combined with cognitive-behavioural therapy (CBT) (14-21), and it has been shown that a combination of pharmacological treatment, education, supervised physical exercise and CBT improves symptom severity, physical function, global well-

Competing interests: none declared.

being, anxiety and depression (22–26). Furthermore, the guidelines of both the American Pain Society (27) and the German Association of Scientific Medical Societies (28, 29) indicate that there is better-quality evidence in favour of multidisciplinary treatment for FM.

Growing interest in monitoring disease progression and/or therapeutic responses has led to the use of various patient-reported outcomes (PROs) as a means of improving care and screening for physical or psychosocial problems in routine clinical practice, clinical trials and long-term clinical registries. Some of these have been adapted from those used in rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis, and others have been (or are being) specifically developed for FM patients (30–32). However, one of their main limitations is the difficulty of using them in routine clinical practice because they can be difficult to administer, score and interpret, and the need for manual data computation is not only time consuming, but may also be a source of error.

Advances in interactive computer technology have already allowed patients to become more involved in the management and evaluation of their care and, in order to facilitate the use of PROs, researchers have developed and validated computerised alternatives to traditional paper-based instruments. The introduction of office-based touch-screen computers (32, 33), telephone-based interactive voice-response (IVR) systems (34), handheld computers (35), mobile phones (36) and, more recently, Internet-based approaches (37) have facilitated routine PRO data collection and support the transition from institution-centred to patient-centred applications (37).

Web/Internet-based home telemonitoring, which allows physiological and clinical data to be transferred from patients' homes to a telemonitoring centre for interpretation and clinical decision making (38), is beginning to be used for an increasing number of applications in both industrialised and developing countries (39). It is seen by many healthcare systems throughout the world as an integral part of the de-institutionalisation reflecting society's

orientation toward treating patients at home (40), and is the most promising telemonitoring application for delivering cost-effective quality care (41–44).

The aims of this study were:

1. to evaluate the feasibility and user acceptance of Internet-based home telemedical surveillance for the evaluation of pain and other key health outcomes; and
2. to assess the efficacy of a multidisciplinary intervention based on 24 twice-weekly sessions of combined aerobic, muscle strength training exercises and education in patients with FM.

## Material and methods

### Study design

#### • Population sample and setting

The participants were randomly selected from a large database of FM patients. A total of 96 women were screened, but 20 declined to participate because of the distance between their homes and the study centre.

All of the 76 enrolled patients were aged 18–65 years and fulfilled the American College of Rheumatology (ACR) classification criteria for FM (45); had an average numerical rating scale (NRS) pain score of  $\geq 4$ ; had been on stable doses of FM medications for  $\geq 4$  weeks; and were willing to limit the introduction of new FM medications. The exclusion criteria were cardiovascular disease; moderate-severe chronic lung disease; uncontrolled hypertension; uncontrolled thyroid disorders; orthopaedic or musculoskeletal conditions prohibiting moderate-intense exercise; active suicidal ideation; planned elective surgery during the study period; inflammatory rheumatic conditions (*i.e.* rheumatoid arthritis, systemic lupus erythematosus, and other connective tissue disease); schizophrenia or other psychoses; and participation in moderate or vigorous exercise for  $\geq 3$  days a week.

All the subjects were examined by a rheumatologist to confirm the diagnosis of FM (46) at study entry, and re-examined by the same rheumatologist (blinded to their randomisation status) three months post-treatment.

The patients were randomised 1:1 to a usual-care control group or the multicomponent exercise group using a

computer-generated randomisation list prepared by biostatisticians uninvolved in the clinical conduct of the trial, and kept at a purpose-designed control centre, which allocated the assigned treatment when telephoned by the clinical investigators, who were blinded to the allocation sequence. After group allocation, it was not possible to blind the investigators or study participants to the treatment actually received.

The study was approved by the Institutional Review Board of the Hospital's Ethics Committee, and all the patients gave their informed consent.

### Study intervention

The Rehabilitation Unit in Jesi, Ancona, Italy, provided an outpatient programme consisting of 24 twice-weekly sessions of combined aerobic, muscle strength training exercises and education. The sessions were organised as closed groups of six patients each (*i.e.* no new admissions were permitted after the start of the programme), and each treatment modality was delivered by a different health professional. The programmes were individually tailored depending on the severity of FM, accessibility to equipment, time constraints and the enjoyment of the various activities, and followed the American College of Sports Medicine (ACSM) guidelines for developing and maintaining cardiorespiratory fitness (47) and the American Pain Society's guidelines on FM (27).

The exercise programme included 60–120 min/week of aerobic exercise within the patient's target heart rate zone (60–85% of maximal heart rate); the duration depended on the intensity of the activity, which began at 60–70% of maximal heart rate and was gradually increased to 75–85%. Stretching and strength exercises were prescribed on the basis of individual needs, with one set of 10 repetitions being completed at individually specified loads. The initial loads were 1–3 kg for the upper limbs and 3–5 kg for the lower limbs, and the subjects were encouraged to increase the load by 1 kg per week during the course of the 24-week study. All the sessions were supervised by two physiotherapists uninvolved in the clinical assessments.

The intervention was further refined after discussions within the research group, and completed by one further 45-minute session of educational activities with a physician and physiotherapist covering topics related to the characteristics of FM, such as its nature and usual course, treatment options, the appropriate organisation of daily activities, and physician/patient relationships. The patients were also given a basis for understanding and applying self-control techniques, and an opportunity to discuss the difficulties of everyday life and share possible solutions.

The pharmacological treatment arranged during the recruitment phase was not modified and included tricyclic antidepressants (amitriptyline, maximum dose 75 mg/24 h), an anti-inflammatory drug (ibuprofen, maximum dose of 1800 mg/die), an analgesic (paracetamol, maximum dose 3 g/24 h), and a central opioid analgesic (tramadol, maximum dose 400 mg/24 h). The patients were asked not to change medications during the study period.

#### *Outcome measures*

##### • *Primary outcome measure*

Primary outcomes were evaluated using the FIQR, a version of the FIQ (48) developed by Bennett *et al.* (49) in an attempt to address the limitations of the original (50), which was done mainly by adding new questions relating to memory, tenderness, balance, and environmental sensitivity. The new version, which has been validated in Italy for use with FM patients (51) has 21 items scored 0–10 (with 10 being the “worst”), and covers the three domains of function, overall impact, and symptoms.

##### • *Secondary outcome measures*

Secondary outcomes were evaluated using the self-administered Fibromyalgia Activity Score (FAS), a valid, reliable and responsive disease-specific composite response measure for assessing treatment effects in patients with FM (52, 53). The FAS index combines a set of questions relating to non-articular pain (SAPS, range 0–10), fatigue (range 0–10) and the quality of sleep (range 0–10) and provides a single

composite measure of disease activity ranging from 0 to 10. All three measures are printed on one side of one page for rapid review, and scored by a health professional without the need for a ruler, calculator, computer or website.

#### *Web-Internet based self-reporting questionnaires*

A special website was constructed for this study in order to minimise the risk of keying errors and ensure cost-effectiveness. Research has shown that the Internet-administered self-reporting of the questionnaires is as valid as the paper and pencil versions (54). The Web portal allows authorised users to access the system via personal computer and Internet browser using the site address [www.fibromialgiaitalia.it/site/](http://www.fibromialgiaitalia.it/site/).

The components of the graphic interface offered users a quick overview and supported straightforward navigation. The data were entered by clicking on the appropriate box, and were then processed to generate statistics and trends. The recorded variables were demographic data, disease duration, and the patient's 11-number NRS format for the FIQR and FAS scores (51, 52). The study used the Italian versions of the FIQR and FAS (51, 52). The frequency of logging into the website was recorded by means of a questionnaire to be completed every week for 12 months by the patients in both groups. An automatic reminder was sent by e-mail to patients who transmitted less than two successful data measurements.

At the end of the study, the electronically collected HRQoL raw data (including the number, age and gender of participating patients, the duration of the assessments, and the test results produced by Web system) were extracted from practice computers and pseudonymised.

#### *Sample size calculation*

The study sample size was determined considering FIQR scores as the primary outcome and, given that minimally clinical relevant difference (MCID) value of the FIQ is unknown (55), using preliminary data obtained from a series of FM patients undergoing standard drug treatment (date not shown).

Assuming a 10% change in the total FIQR score between the two groups, with a standard deviation (SD) of 14%, it was calculated that 32 patients in each group would provide a power of 80% at a *p*-level of <0.05. This number was then adjusted to a total of 76 patients in order to allow for an attrition rate of approximately 20%.

#### *Statistical analysis*

The continuous data are expressed as mean values  $\pm$  SD or median values with their 95% coefficient intervals (95% CI), and the categorical data as absolute numbers and percentages. The cumulative burden in both groups was estimated on the basis of the total FIQR and FAS scores, expressed as time-integrated values (the area under the curve, AUC) calculated for each patient during the 3-month follow-up (56). The differences between the groups were computed by using the Mann-Whitney U-test for continuous variables and Fisher's exact test for categorical variables, and correlations were analysed using Spearman's rank correlation test. The data were statistically analysed using the Statistical Package for Social Sciences (SPSS Inc., Windows release 11.0; Chicago, Illinois, USA), and MedCalc version 12.7.0 (Mariakerke, Belgium) software. The level of statistical significance for all of the tests was 5%.

## **Results**

#### *Baseline clinical and demographic characteristics*

Seventy-two of the 76 randomised patients completed the three-month study. Among these patients, one patient stopped the physiotherapy, according to advices of therapists, two participants in the control group explicitly cited an increase in pain as the reason for dropping out, and one patient moved to another region. These four patients were not included in the subsequent analysis.

Of the 72 patients who completed the programme had a mean age of approximately 49 years, 62.5% were married and 72.2% had a secondary and/or high/university education. The mean time from pain onset was 9.3 years (range 1–20 years). There was no significant difference in the distribution of age,

**Table I.** Demographic details and medication use at baseline.

	Treatment group	
	Multicomponent treatment (n=36)	Controls (n=36)
Mean age, years ( $\pm$ SD)	48.3 (11.3)	49.6 (12.3)
Women, n. (%)	34 (94.4)	33 (91.7)
Mean disease duration, years ( $\pm$ SD)	10.1 (9.6)	8.5 (8.8)
Marital status, n. (%)		
Single	10 (27.8)	8 (22.2)
Married	21 (58.3)	24 (66.7)
Separated	5 (13.9)	4 (11.1)
Educational level, n. (%)		
Primary school	11 (30.5)	9 (25.0)
Middle school	18 (50.0)	21 (58.3)
High school/university	7 (19.5)	6 (16.7)
Medications, n. (%)		
None	4 (11.1)	3 (8.3)
Analgesics or NSAIDs	11 (30.6)	10 (27.8)
Tricyclic antidepressants	13 (36.1)	11 (30.6)
Combined analgesic + other agent	8 (22.2)	12 (33.3)

NSAID: non-steroidal anti-inflammatory drugs; SD: standard deviation.

gender, marital status, educational level or the use of medications between the two groups (Table I). Mean symptom duration was longer in the multicomponent treatment group ( $10.1 \pm 9.6$  years vs.  $8.5 \pm 8.8$  years), but this difference was not significant ( $p=0.072$ ). Table II shows the mean and median total and subtotal scores of the FIQR and FAS in the two groups: there were no statistically significant differences in the median values (Mann-Whitney U-test).

### Feasibility

The participants who completed the multicomponent programme attended 97.9% of the sessions. Nobody reported any problems in reading the display or entering data. The Web-service was

well accepted by the majority of patients (94.4%).

### Efficacy

Table III shows the total FIQR and FAS scores expressed as the time-integrated values (AUC, which can be considered more representative of the patients' global outcomes) calculated for each patient during the 3-month follow-up. A significant greater benefit was found in the aggregate evaluation using the AUC. The multicomponent intervention led to a significant improvement in the total FIQR and FAS scores and their subscores (FIQR: function, overall impact and symptoms; FAS: SAPS, fatigue and sleep) (Table III, Fig. 1–2) after three months of follow-up.

The AUC values of the total FIQR scores progressively improved and, although both groups experienced a decrease in values from baseline to 12 week, the patients undergoing multicomponent therapy showed a high clinically relevant improvement ( $p=0.0006$ ). The findings were similar in relation to each of the three subdimensions of the FIQR: in particular, the FIQR symptoms subscore showed the greatest improvement ( $p=0.0001$ ) in the multicomponent treatment group. In general, the greatest improvements in the multicomponent treatment group were achieved by week 9 (Fig. 1).

Similar behaviour was observed in relation to the FAS total score and subscores. The AUC values of the total FAS scores were significantly better in the multicomponent treatment group ( $p=0.0002$ ), with the greatest improvements being shown in relation to the quality of sleep ( $p=0.0015$ ) and fatigue subscores ( $p=0.0064$ ). As in the case of the FIQR, the greatest improvements in the multicomponent treatment group were achieved by week 9 (Fig. 2).

There was a close correlation between the mean change in the AUC of the FIQR total score and the change in the AUC of the FAS total score ( $r=0.942$ ,  $p<0.0001$ ) (53).

### Discussion

The hallmarks of FM are widespread pain, chronic fatigue, sleep disturbances, and a range of other still unexplained symptoms (57). Treatment options include both pharmacological

**Table II.** Baseline FIQR and FAS scores.

	Treatment groups*							
	Multicomponent treatment (n=36)				Controls (n=36)			
	Mean	95% CI	Median	95% CI	Mean	95% CI	Median	95% CI
FIQR Function	12.76	11.16-13.97	12.00	11.31-14.00	11.91	9.65-11.96	11.00	9.00-12.00
FIQR Overall impact	8.22	7.349-8.30	8.00	8.00-9.00	7.91	6.41-8.44	7.50	6.00-8.00
FIQR Symptoms	25.96	22.28-27.63	24.00	22.00-27.00	24.51	22.60-26.35	23.25	23.00-24.00
FIQR Total score	46.94	43.83-50.96	47.00	45.00-50.00	44.33	41.77-46.42	45.50	40.80-47.69
FAS SAPS	5.32	5.17-5.48	5.42	5.42-5.83	4.59	4.40-4.78	5.00	4.38-5.21
FAS Sleep	6.04	6.07-6.45	6.000	6.00-7.00	5.75	5.01-5.99	5.00	5.00-6.00
FAS Fatigue	6.54	6.18-7.04	7.00	6.50-7.50	6.08	5.87-6.29	6.50	6.00-7.00
FAS Total score	5.97	5.82-6.28	5.75	5.50-6.22	5.47	5.04-5.97	5.55	5.02-5.91

\*There were no statistically significant differences between the treatment groups. FIQR: Fibromyalgia Impact Questionnaire - revised version; FAS: Self-administered Fibromyalgia Activity Score; SAPS: Self-assessment Pain Scale.



**Table III.** Summary of FIQR and FAS scores expressed as the time-integrated values (AUC) calculated for each patient during the study period.

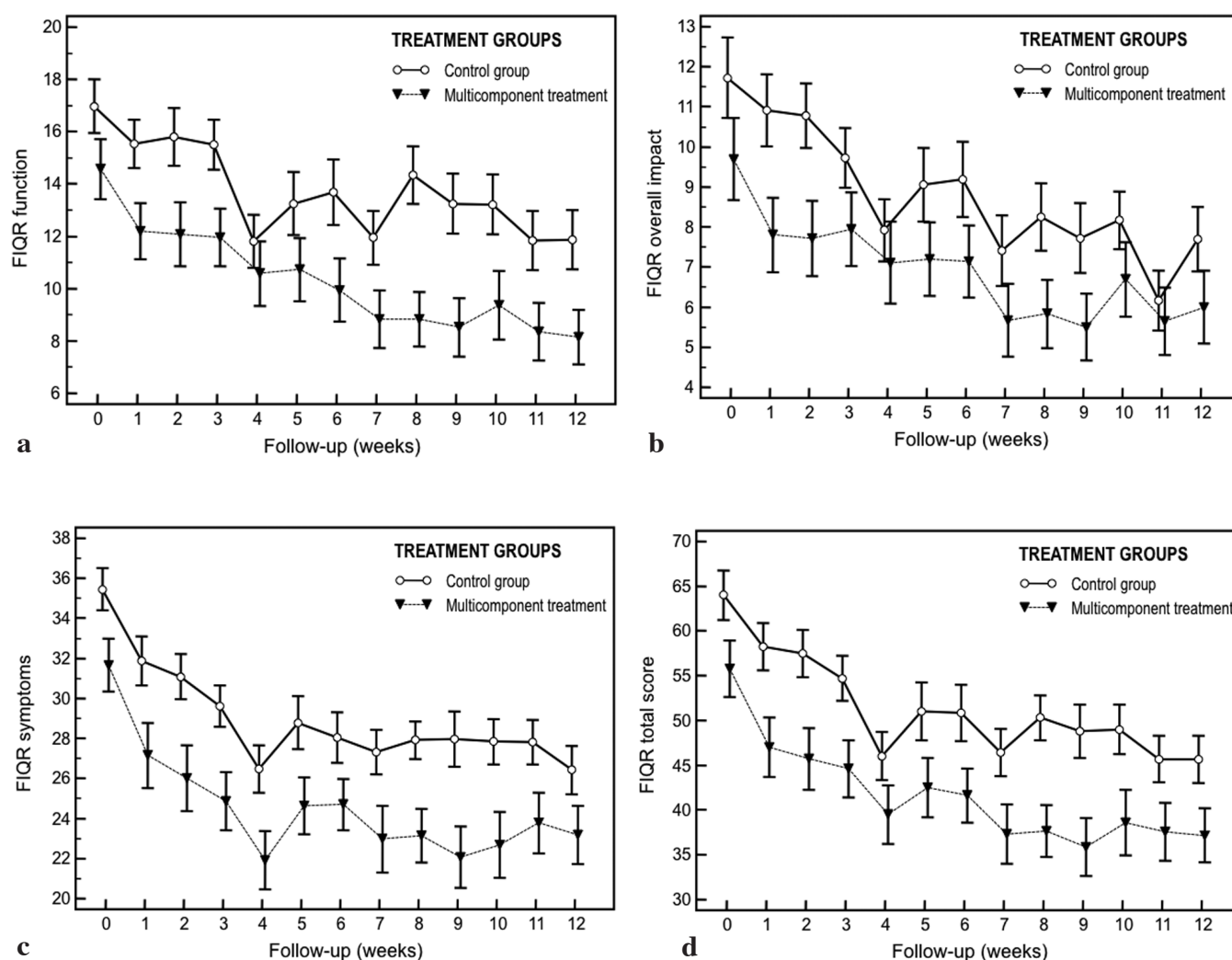
	Multicomponent Treatment (n=36)				Control Group (n=36)				Z	p-value
	Mean	95% CI	Median	95% CI	Mean	95% CI	Median	95% CI		
FIQR Function	122.74	103.50-141.97	121.18	99.65-153.98	164.58	148.38-180.78	167.50	151-185.58	3.05	0.0023
FIQR Overall impact	82.10	68.02-96.18	88.25	75.31-99.67	105.01	91.73-118.30	102.50	89-47-114.21	2.45	0.0189
FIQR Symptoms	291.31	268.32-314.30	291.50	278.19-313.18	345.63	328.57-362.69	347.75	324.65-373.35	3.91	0.0001
FIQR Total score	494.44	440.84-548.04	507.42	433.33-556.19	613.29	569.91-656.67	606.50	585.14-691.04	3.44	0.0006
FAS SASP	54.98	49.21-60.75	57.43	49.27-62.08	63.44	60.32-66.55	63.71	60.74-68.37	2.39	0.0167
FAS Sleep	62.32	56.84-67.80	62.75	57.66-67.34	74.57	69.76-79.38	71.25	67.83-79.38	3.18	0.0015
FAS Fatigue	72.40	67.13-77.68	72.25	68.16-79.17	81.51	77.78-85.25	84.25	79.33-86.50	2.73	0.0064
FAS Total score	63.23	58.71-67.74	64.71	61.35-68.22	73.18	70.17-76.18	71.34	68.86-79.27	3.75	0.0002

FIQR: Fibromyalgia Impact Questionnaire - revised version; FAS: Self-administered Fibromyalgia Activity Score; SASP: Self-assessment Pain Scale.

and non-pharmacological interventions (9, 11, 58), but no single option has yet been consistently successful, and it is not surprising that most FM patients discontinue treatment within one

year (12). Evidence-based therapeutic guidelines have been formulated by the European League Against Rheumatism (EULAR) (59), which recommend a set of pharmacological treatments,

whereas the American Pain Society (APS) (27) and the German Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) (29) recommend mainly non-

**Fig. 1.**

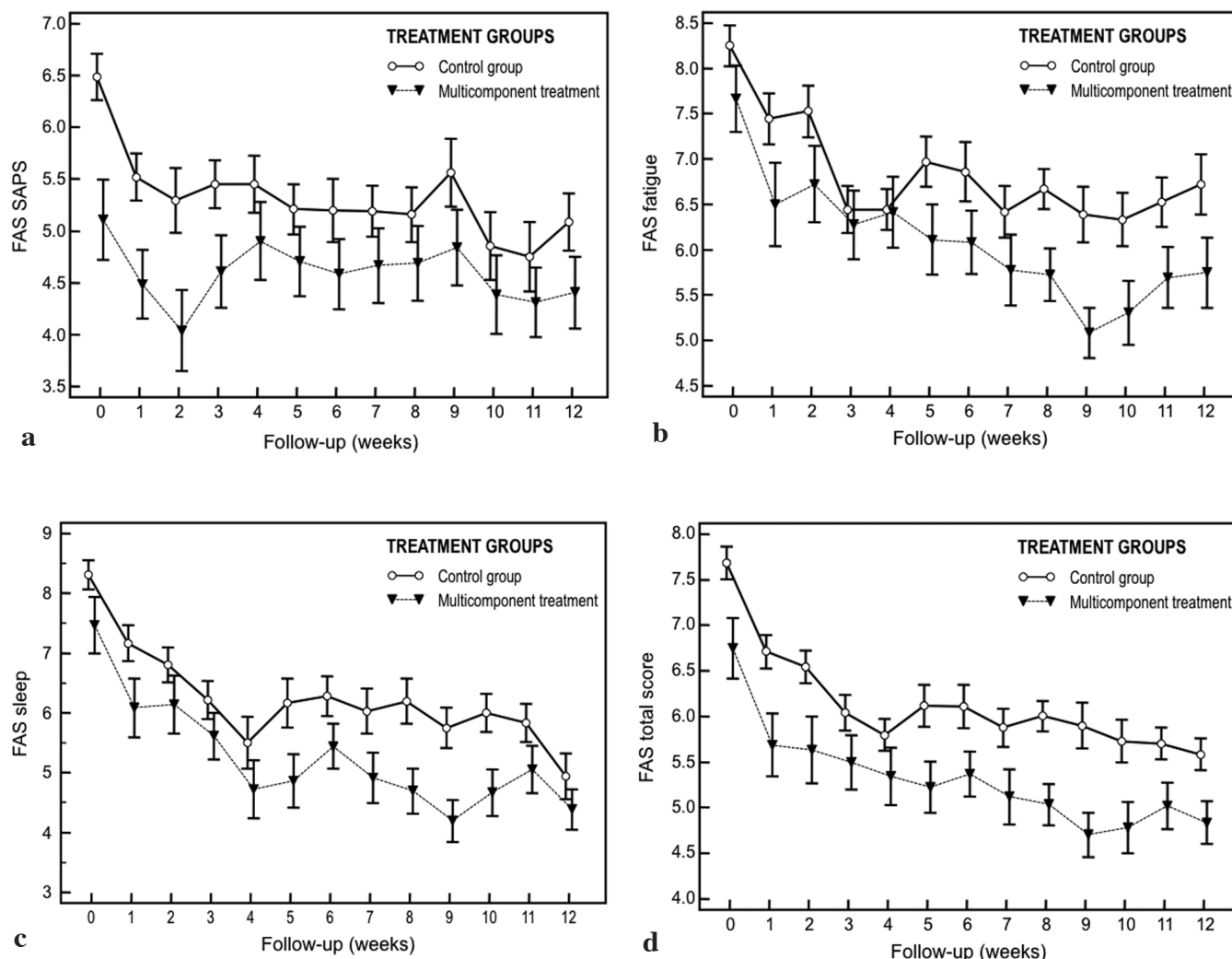


Fig. 2.

pharmacological treatments (including aerobic exercise, CBT and multicomponent treatment) and identify amitriptyline as the only strongly recommended pharmacological agent (29).

In line with the recommendations of the APS and AWMF [(27, 29), our analysis used the area-under-the-time-response curve (AUC) as a measure of cumulative response, showed that multicomponent therapy can provide some potentially important benefits. The use of the AUC simplifies statistical analyses by transforming multivariate data into univariate space and reduces the number of between-group statistical comparisons, which minimises the need to adjust significance level, and is particularly useful when there are a large number of repeated measurements and there is a need to summarise the information (60-62).

A number of studies of integrated treatments have led to promising results (25, 63). It has been demonstrated that the tailored multidisciplinary treatment of FM using medications, CBT is effective in women with a low educational level (63), and Martin *et al.* (24) found that six weeks of treatment combining coordinated psychological, medical, educational and physiotherapeutic components led to significantly greater improvements in the quality of life, physical function and pain six months later than standard pharmacological care. Cedraschi *et al.* (64) and Carbonell-Baeza *et al.* (25) have also demonstrated that a low-to-moderate intensity multidisciplinary intervention of 6-12 weeks improved symptoms and the HRQoL in women with FM. Finally, systematic reviews and network meta-analysis have concluded that the

multicomponent treatment of FM is effective in decreasing some key symptoms such as pain, fatigue, and depressed mood, and improving self-efficacy and physical fitness (23, 65, 66), although some of the studies did not include control groups, which may make it difficult to interpret the results correctly (67-70).

None of the randomised and controlled studies showing the immediate benefit of multicomponent FM treatment included close telemonitoring. The Internet has brought about many opportunities for self-care as it can be used as a powerful medium for promoting a healthy lifestyle and increasing a patient's understanding of his/her condition (71). Interactive e-Health technologies positively contribute to health care in patients with chronic diseases by improving patient/physician com-

munications, the HRQoL and treatment adherence, and reducing costs (72-75), and computerised self-assessments can usefully support shared decision-making (SDM) (76-78). The Internet also provides an effective means of collecting PROs: it is currently estimated that 28 million adults in Italy have access to the Internet [<http://www.gandalf.it/dati/dati3.htm>], and one survey has found that 90% of current Internet users would like to be able to interact with their physicians using an Internet website (79, 80).

The greater use of home tele-health applications (such as telemonitoring) may not only save costs, but can also help divert more resources to those most in need of face-to-face forms of treatment. It can improve data quality via automatic data-checking functions that can be used to remind patients to complete omitted questions, and another advantage is the ability to incorporate real-time question selection using branching logic and computer-adaptive testing (81-84).

Our previous studies have shown that the time required to complete an electronic questionnaire is similar to, and sometimes less than that time required to complete a paper-based instrument (32, 33), and that patients prefer electronic data collection methods (32, 33). Despite several studies, the reasons for the success of telemonitoring are still unclear although it has been suggested that it increases treatment compliance. Adherence has an ongoing significant effect on patients' well-being, as shown by Lemstra and Olszynski (85), who found that FM patients who maintained the exercise component of their multimodal intervention program during a 15-month follow-up period experienced better health-related outcomes in terms of pain, disability, mental health, and non-prescription medication use than those that did not (85). Unfortunately, adherence to an exercise regimen after a structured supervised programme is disappointingly low (84-87).

The limitations of this study include the relatively small sample size, which limits the generalisability of results. The users were self-selected as they were motivated to use the Web appli-

cation, and the patients who chose to participate in the project may differ from other patient groups. Although Internet-based assessments will not be used by all patients, we found assessment rates of 74%, thus indicating that a sizeable percentage of patients may be included when using an Internet-based system. Further research should be conducted (preferably using larger samples) in order to gain further insights into the technology preferences of the different patient groups.

Another important consideration is whether instruments intended for use on an Internet-based PRO system are valid for Internet-based administration. Much of the research related to the use of electronic PRO collection has focused on evaluating the validity and comparability of electronic versions (usually touchscreens) of a variety of paper-based instruments (32, 33). Further research is needed to understand differences in Internet and paper-based modes of administration, and establish the validity of Internet-based instruments.

In conclusion, our multicomponent FM treatment programme combining pharmacological treatment, education, physical therapy, and CBT proved to be effective in treating the key symptoms of FM (88-90). A further emerging issue concerns patient satisfaction with telemedicine, and indications that telemonitoring may alter the relationships between patients and health professionals (54). Interactive health communication applications for patients with FM appear to be beneficial in terms of improved support, better knowledge and improved health outcomes. Strategies to support the large-scale implementation of the telemonitoring of chronic musculoskeletal pain disorder in primary care should focus on healthcare professionals' perceptions of being supported by their organisation and reinforced in their changing practices. Moreover, cost-effectiveness analyses of Web-based communication are urgently needed to determine its added value in everyday clinical practice.

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