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Effectiveness of an Online Multicomponent Program (FATIGUEWALK) for Chronic Fatigue Syndrome: A Randomized Controlled Trial

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Objective: This study aimed to evaluate the effectiveness of an online multicomponent intervention called FATIGUEWALK (FaW) compared to treatment as usual (TAU) in patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). ***Method:*** FaW included pain neuroscience education, therapeutic exercise, cognitive restructuring, and mindfulness training. A total of 428 patients with CFS/ME were randomized into two study arms: online FaW plus TAU versus TAU alone. A single-blinded randomized controlled trial was conducted. Validated patient-reported outcome measures of fatigue, pain, anxiety, depression, and physical function were collected at baseline and posttreatment, following the FaW intervention, which lasted 12 weeks. ***Results:*** Statistically significant improvements (with small-to-moderate effect sizes) were observed in online FaW versus TAU alone with respect to multidimensional aspects of fatigue (Cohen's *d* ranging from 0.25 to 0.73) and most secondary outcomes (pain and fatigue intensity, depressive and anxious symptomatology, functional impairment, kinesiophobia, physical functioning). The absolute risk reduction in FaW versus TAU was 19%, 95% confidence interval (CI) [12.19, 25.80] with number needed to treat = 6, 95% CI [3.9, 8.2]. Overall, similar clinical improvements were observed in sensitivity analyses including a subgroup of patients without comorbidity with fibromyalgia ($n = 70$). ***Conclusions:*** This is the first study to assess the short-term effectiveness of an online multicomponent intervention added to TAU, compared to TAU alone, for the management of CFS/ME. Further trials, including active control groups with an equivalent treatment dose, and assessing the long-term effectiveness of the online FaW, are warranted.

Public Significance Statement
The FATIGUEWALK (FaW) program is a video-based multicomponent treatment for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). This trial strongly suggests that FaW is an effective treatment for improving fatigue and psychological and physical comorbid impairment in CFS/ME patients, both with and without fibromyalgia. This study highlights the importance of online and multicomponent interventions for CFS/ME treatment.

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Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a complex syndrome characterized by unexplained and persistent fatigue that lasts at least 6 months, accompanied by a constellation of symptoms related to cognitive, immune system, and autonomic nervous system dysfunction (Brurberg et al., 2014; Cortes-Rivera et al., 2019). CFS/ME can cause a wide range of symptom severity and functional impairment, leaving some people able to work while others are confined to home or bed. In fact, the most severely ill individuals may require total care (Montoya et al., 2021). Overall, it is estimated to affect up to 1% of the population (Lim & Son, 2020; Sotzny et al., 2018).

Treatment options are limited, which represents a significant unmet medical need (Toogood et al., 2021). Current therapeutic approaches in CFS/ME are generally pharmacological (e.g., antidepressants), nonpharmacological (e.g., cognitive behavioral therapy—CBT), or a combination of both approaches (Noor et al., 2021). Due to the lack of a curative drug, many patients are frequently referred to nonpharmacological therapies, which, in various ways, aim to help patients manage their symptoms (Mengshoel et al., 2020). In fact, randomized controlled trials (RCTs) studying the effectiveness of nonpharmacological interventions for CFS/ME patients have become a trend in the last decade (Kim et al., 2020). Nonpharmacological interventions such as pain neuroscience education (PNE; Amer-Cuenca et al., 2020; Louw et al., 2016), therapeutic exercise (Larun et al., 2021), CBT (White et al., 2011), and mindfulness training (Greeson & Chin, 2019; Lakhan & Schofield, 2013; Pauzano-Slamm, 2004; Surawy et al., 1999), have shown promising evidence in reducing CFS/ME severity. However, no single therapeutic approach supported by a RCT has shown to be definitely effective, with coherence and reproducibility, for CFS/ME management (Kim et al., 2020). Indeed, methodological reviews have criticized the scientific rigor of previous RCTs regarding the effectiveness of CBT and therapeutic exercise for CFS/ME (e.g., Ahmed et al., 2020, Kim et al., 2020).

More recent treatment recommendations include a holistic, patient-centered approach that integrates a variety of techniques to address physical, mental, and social well-being (Noor et al., 2021). Multicomponent nonpharmacological treatments are increasingly being studied and implemented for patients with chronic conditions (e.g., Geraghty et al., 2021). For instance, the intervention FIBROWALK is a multicomponent treatment that was originally designed for treatment of fibromyalgia (FM; Serrat et al., 2020). It includes PNE, therapeutic exercise, self-management patient education, CBT techniques, and mindfulness training. FIBROWALK has been shown to be effective in reducing symptoms of impairment, depression, and anxiety and improving physical functioning in FM patients compared to treatment as usual (TAU; Serrat et al., 2020, 2022; Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021). Recently, a video-based version of the FIBROWALK program was adapted into a home-based format during the Spanish COVID-19 lockdown and tested in two RCTs (Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021). Results showed that it was effective (with small-to-large effect sizes) for improving patient-reported functional impairment and other relevant FM-related symptoms (Serrat et al., 2022; Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021).

Overall, efficacious online interventions have several advantages over face-to-face interventions, such as lower cost, convenience, and potentially higher availability for patients with limited mobility (Andersson, 2018; Andersson & Titov, 2014). In addition, current evidence suggests that the use of telerehabilitation in CFS/ME patients is as effective as conventional in-person therapy for motor, cortical, and mood disorders (Janse et al., 2019; Worm-Smeitink et al., 2019). Given the high comorbidity (>80%) between FM and CFS/ME diagnoses (Serrat et al., 2020; Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021; Sotzny et al., 2018) and the fact that all therapeutic components of FIBROWALK have separately shown some evidence of efficacy in CFS/ME treatment, it would seem reasonable to expect that the FIBROWALK program could also be an effective therapeutic approach for the management of core CFS/ME symptoms.

The present RCT aimed to evaluate the short-term effectiveness of the online video-based FIBROWALK program, renamed FATIGUEWALK (FaW) for the present study, in people with CFS/ME and to compare it to TAU only. It was expected that the FaW arm would obtain greater improvements in multidimensional fatigue (primary outcome), pain, anxiety and depressive symptoms, overall functional impairment, kinesiophobia, and physical functioning when compared to TAU alone (Hypothesis 1 [H1]). Moreover, given the high comorbidity between CFS/ME and FM diagnoses that has been previously found (Serrat et al., 2020, 2022; Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021) and the fact that this virtual multicomponent intervention was determined to be effective in mixed samples of individuals with FM and CFS/ME (Serrat et al., 2022), a sensitivity analysis assessing the effects of the intervention in those participants having only CFS/ME, and not FM, was conducted to verify that the beneficial clinical effects of the intervention were not solely related to improvements in FM symptoms. It was expected that FaW would be effective in significantly improving the aforementioned symptoms in this subsample (Hypothesis 2 [H2]). Finally, an exploratory analysis was performed to determine for whom FaW worked better, by classifying participants into responders and nonresponders and assessing between-group differences at baseline in sociodemographic and clinical variables between these subgroups. On the latter point, no hypothesis was envisaged because it was the first time that the FaW was tested in this population.

Method

Study Design

We conducted a single-blinded RCT. Data were collected at baseline (pretest) and at the end of the 12-week intervention (posttest). All procedures were conducted in accordance with the ethical standards set out in the 1964 Declaration of Helsinki and subsequent updates. The FaW

study protocol was approved by the Clinical Research Ethics Committee of Vall d'Hebron Hospital (code: PR(AG)249/2020) and registered at ClinicalTrials.gov (identifier: NCT04593225). This study was performed in accordance with the guidelines issued by the consolidated standards of reporting trials (Schulz et al., 2010).

Sample Size

The required sample size was estimated to be $n = 105$ participants per study arm, considering a moderate effect size ($f = 0.25$) according to a previous meta-analysis (Marques et al., 2015) for the between-group differences at posttreatment for the primary outcome (i.e., Multidimensional Fatigue Inventory [MFI] total score) with an $\alpha = .05$ and power $1 - b = 0.95$. Expecting an attrition of at least 20% and a low presence of patients with only CFS/ME diagnosis (less than 20%; Serrat et al., 2020; Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021; Sotzny et al., 2018), this number was nearly doubled.

Participants

Of the 460 potentially eligible patients from the Central Sensitivity Syndromes Specialized Unit (CSSSU; Vall d'Hebron Hospital, Barcelona, Spain), 32 were not available to participate due to various personal reasons. The initial study sample consisted of 428 patients with a diagnosis of CFS/ME. They were randomized into the two study arms, with 212 (FaW group; 66.51% women; mean age of 51.79 ± 9.28) and 216 (TAU group; 62.44% women; mean age of 52.26 ± 8.69) individuals per arm (see Figure 1). All participants were Spaniards and their race was classified as white in all cases. Baseline sociodemographic characteristics are shown in Table 1.

Inclusion criteria were: (a) diagnosis of CFS/ME according to Carruthers et al. (2011) criteria, verified by an internal medicine doctor of the CSSSU; (b) being 18 years old or older, (c) being able to understand Spanish, and (d) having completed the written informed consent. The exclusion criteria were: (a) suffering from severe mental illnesses (e.g., psychotic disorders) or terminal illnesses (e.g., advanced cancer) or (b) being unavailable to follow the program, such as having scheduled surgical interventions.

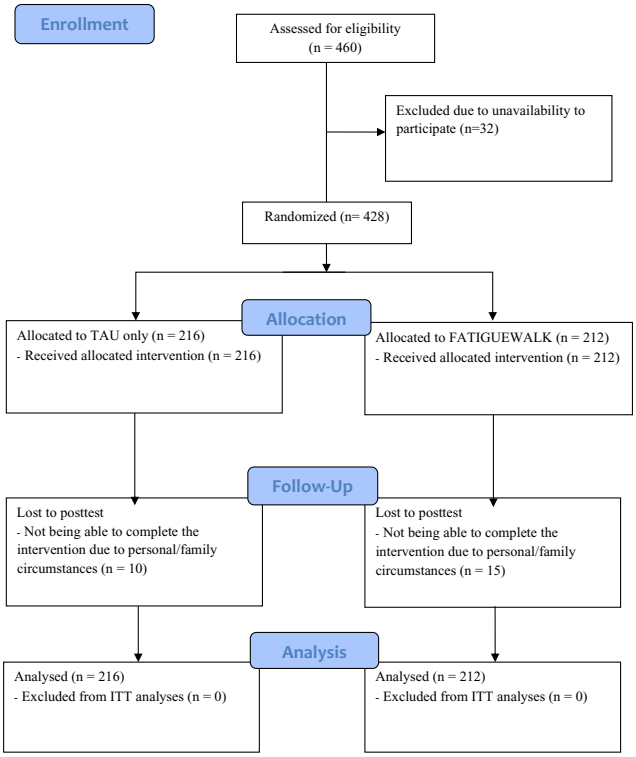
Procedure

Participant recruitment took place at the CSSSU located at Vall d'Hebron Hospital in Barcelona, Spain. The CSSSU is a clinic unit actively engaged in applied health research, focusing on both clinical and translational aspects. The unit specializes in the management of patients with FM and CFS/ME, receiving referrals from Primary Care services in the surrounding areas of Vall d'Hebron Hospital. Recruitment was performed in three waves, from September 2020 to July 2021.

The clinical professional in charge of the intervention was author Mayte Serrat, who has formation as a physiotherapist and health psychologist, with extensive experience (>20 years) treating patients with this type of conditions. MS verified the selection criteria for the whole pool of patients in the Unit, conducted an initial screening interview, and provided an overview of the study. Patients had previously been diagnosed of CFS/ME by a medical doctor (specialist in internal medicine). Written informed consent was obtained from all participants prior to the initial screening. Participants were informed of their right to withdraw from the study at any time, with the guarantee that they could continue to receive their usual treatment if they wished to do so. Those subjects who agreed to participate in the study completed a demographic questionnaire and a baseline test battery of standardized patient-reported outcome measures. Following testing, they were assigned to a list of alphanumeric codes, and randomized using the SPSS Version 26 statistical package (Kaysville, Utah, United States) to the FaW group or the control group. This process was carried out by means of numbered envelopes containing paper sheets with information on participant allocation. The envelopes were prepared by a CSSSU nurse. Neither the participants nor the clinician conducting the program (author Mayte Serrat) could be blinded within the study format. However, author Mayte Serrat was not involved in any stage of the patient assessment process and the researcher responsible for the outcome measures was unaware of the treatment allocation. All patients were assessed again with the same test battery of validated patient-reported outcome measures through an online survey after those subjects in the FaW treatment arm completed all 12-weeks of the FaW program.

Figure 1

CONSORT Flow Chart of Participants in the FaW Trial



Note. CONSORT = consolidated standards of reporting trials; FaW = FATIGUEWALK. See the online article for the color version of this figure.

Treatment Arms

Participants assigned to the FaW group underwent the online video-based FIBROWALK program—renamed here as FaW—following the usual curriculum (Serrat et al., 2022). It includes PNE (Sessions 1–10), therapeutic exercise (Sessions 2–9), self-management patient education (Sessions 2–9; 11–12), CBT techniques (Sessions 8–9; 11–12), and mindfulness training (Sessions 2–9; 11–12). The

Table 1
Baseline Demographic and Clinical Characteristics by Treatment Group

Variables	FaW ($n = 212$)	TAU ($n = 216$)	t/χ^2	p
Sociodemographic and clinical characteristics				
Age (years) $M \pm SD$	51.79 ± 9.28	52.26 ± 8.69	−0.53	.595
Women, n (%)	141 (66.51)	133 (62.44)	0.77	.381
BMI (kg/m^2) $M \pm SD$	27.05 ± 5.98	27.25 ± 5.99	−0.35	.726
ISPS (years) $M \pm SD$	16.59 ± 10.65	14.31 ± 9.63	2.33	**.020**
Civil status, n (%)			2.38	.497
Single	40 (18.87)	35 (16.20)		
Stable partner	120 (56.60)	116 (53.70)		
Divorced	43 (20.28)	57 (26.39)		
Widow	9 (4.25)	8 (3.71)		
Living alone, n (%)	16 (7.55)	12 (5.56)	2.90	.234
Education level, n (%)			6.14	.408
No schooling	2 (0.94)	6 (2.78)		
Primary studies not completed	10 (4.72)	15 (6.94)		
Primary studies	59 (27.83)	66 (30.56)		
Secondary studies	89 (41.98)	88 (40.74)		
University studies	49 (23.11)	36 (16.67)		
Other	3 (1.42)	5 (2.32)		
Disability certificate, n (%)			6.88	.230
No	63 (29.72)	74 (34.26)		
0%–33%	14 (6.60)	8 (3.70)		
33%–66%	111 (52.36)	108 (50.00)		
+66%	24 (11.32)	26 (12.26)		
FM comorbid, n (%)	174 (82.08)	181 (83.80)	0.22	.636
Outcome measures, M (SD)				
Primary measure				
MFI-total score	81.15 (11.87)	83.08 (11.38)	−1.72	.086
Secondary measures				
MFI-general	18.33 (2.15)	18.43 (2.37)	−0.46	.646
MFI-physical	17.14 (2.63)	17.51 (2.24)	−1.58	.115
MFI-reduced activity	15.21 (4.29)	15.96 (3.91)	−1.89	.059
MFI-reduced motivation	14.38 (3.66)	14.87 (3.66)	−1.39	.164
MFI-mental	16.09 (3.50)	16.31 (3.43)	−0.64	.520
Fatigue VAS	7.47 (2.43)	7.82 (2.26)	−1.53	.126
Pain VAS	7.56 (1.85)	7.70 (2.00)	−0.74	.459
HADS-A	12.50 (4.48)	13.50 (4.34)	−2.36	**.019**
HADS-D	11.92 (4.57)	12.28 (4.64)	−0.80	.422
HADS-total	24.42 (8.10)	25.79 (8.17)	−1.73	.084
FIQR	71.57 (17.01)	73.28 (16.67)	−1.05	.293
TKS	29.55 (7.75)	30.32 (7.29)	−1.06	.289
SF-PF	37.45 (20.22)	33.63 (20.30)	1.95	.052

Note. Statistically significant effects appear in bold ($p \leq .05$). FaW = FATIGUEWALK; TAU = treatment as usual; BMI = body mass index; FM = fibromyalgia; FIQR = Revised Fibromyalgia Impact Questionnaire; HADS = Hospital Anxiety and Depression Scale; ISPS = illness self-perceived start; MFI = multidimensional fatigue inventory; SF-PF = physical functioning component of the 36-Item short form health survey; TSK = Tampa Scale for Kinesiophobia; VAS = Visual Analogue Scale.

therapeutic exercise prescribed in this program is characterized by low intensity, and the intensity is gradually increased very gently from session to session. This approach was taken to specifically address and prevent postexercise discomfort/malaise. A link to a 60-min video (hosted on a private YouTube channel) was emailed once a week for the next 11 weeks (total time of the FaW: 12 weeks). Each video provided detailed guidelines about (a) the neuroscience of pain (explanations based on Butler & Moseley, 2013); (b) how to perform different aerobic exercises at home (such as walking down the hallway at home); (c) mindfulness practice (based on Mindfulness-Based Stress Reduction program; Kabat-Zinn, 2013); and (d) CBT basics (psychoeducation about psychological processes and cognitive restructuring). For more details on the contents of the intervention, see the study by Serrat et al. (2022). Renaming the FIBROWALK program to FaW occurred at the beginning of the research. With this, we wanted to quickly identify the name of the intervention with the main diagnosis (and symptoms) of participants in the present study.

As aforementioned, it was an online video-based intervention, allowing participants to engage with the program remotely from their homes. Participants were instructed to watch the videos, and were asked to self-report their adherence to the prescribed exercises/practices for each session. Concretely, each week a short questionnaire (5–10 items) with yes/no questions was sent by email to check whether participants had watched the videos and performed the homework exercises (i.e., mindfulness practice, breathing exercises, relaxation training, therapeutic physical training). This information was not

systematically registered, but the CSSSU staff monitored the visualization of the content to identify participants who lagged behind. In the questionnaires, subjects were asked to review very basic concepts explained in each video (e.g., "Please provide a brief example of a catastrophic thought"). These weekly checks were used for early detection of possible adherence problems (e.g., not watching the videos, not doing the exercises) as well as possible dropouts. The therapist (Mayte Serrat) contacted patients via short message service and/or phone calls who did not respond to the questionnaire or reported problems related to the program or the study (e.g., not being able to do the homework, watch the videos, answer the questionnaires, etc.) and provided solutions to improve adherence. If necessary, patients who could not watch or answer the questionnaire within a specific week could request an extension date (e.g., watch/answer within 3–5 days). Participants could also contact the therapist (by email) at any time if any other problems related to the treatment or the study arose.

TAU included administration of medications tailored to each patient's symptom profile, complementary advice on aerobic exercise adapted to the patients' physical abilities, and basic health education about their pathology provided at baseline. Those patients assigned to the TAU arm had the opportunity to receive the FaW intervention once the study was completed.

No drug prescriptions were changed for any participant during the 12 weeks of the study. Rescue tablets of paracetamol (acetaminophen) 1 g (maximum 1 tablet/8 hr) were allowed only in case of acute worsening of symptoms.

Study Measures

Sociodemographic and Clinical Characteristics

An ad hoc questionnaire of sociodemographic and clinical information was used to collect the following patient data: age, gender, body mass index, illness self-perceived start (ISPS; in years), marital status, educational level, living arrangements (alone/accompanied), and certificate of disability obtained (indicating degree of disability).

Primary Measure

The MFI-20 (Smets et al., 1995) was used to measure the treatment effectiveness of the FaW. The MFI-20 is a 20-item self-report questionnaire designed to measure fatigue in five subscales (four items each): general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. All items are rated on a 5-point Likert scale and subscale scores can be calculated as the sum of their specific items (score range from 4 to 20). According to a recent study of its psychometric properties (Hinz et al., 2020), a total fatigue score can be also calculated as the sum of subscale scores (ranging scores from 20 to 100). Higher scores indicate a higher level of fatigue. The total score of the MFI-20 was used as the main clinical endpoint of this trial. The Spanish validated version (Munguía-Izquierdo et al., 2012) of the scale was used in the present study, which showed adequate internal consistency of the MFI subscales ($\alpha = .52$—MFI-Physical fatigue- and $\alpha = .82$—MFI-Reduced activity) and the total scale ($\alpha = .90$).

Secondary Measures

The Visual Analog Scales for pain (i.e., "intensity of perceived pain during last week, from 0 = "no pain" to 10 = "unbearable pain") and fatigue (i.e., "level of perceived energy during last week, from 0 = "lots of energy" to 10 = "no energy") from the Spanish validated version of the Revised Fibromyalgia Impact Questionnaire (FIQR; Luciano et al., 2013) were used to assess pain and fatigue intensity, respectively.

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) was used to measure depressive and anxious symptomatology. It is divided into two dimensions (HADS-Anxiety [HADS-A] and HADS-Depression [HADS-D]). Each dimension is divided into seven items in a 4-point Likert scale response format. HADS-A and HADS-D subscale scores range from 0 to 21, with higher scores indicating greater symptom severity. The Spanish validated version was used (Terol et al., 2007), which showed adequate internal consistency in our sample: HADS-A ($\alpha = .86$), HADS-D ($\alpha = .87$), and total scale ($\alpha = .91$).

The FIQR (Bennett et al., 2009) is a 21-item questionnaire that measures perceived level of functional impairment related to FM during the last 7 days. Items are on a 0–10 numerical scale. The FIQR is divided into three dimensions: physical dysfunction (ranging from 0 to 30), overall impact (score ranges from 0 to 20), and intensity of symptoms (ranging from 0 to 50). A total score (from 0 to 100) can be calculated to provide a general endpoint for functional status in FM, with higher scores indicating greater functional impairment. The Spanish validated version was used in the present study (Luciano et al., 2013), which showed excellent internal consistency ($\alpha = .93$).

The Tampa Scale for Kinesiophobia (TSK; Miller et al., 1991) includes 11 items on a 4-point Likert-type scale (range 0–11). Total scores of the TSK can range from 11 to 44 points, where higher scores indicate greater fear of pain, movement, and reinjury. The Spanish validated version was used in the present study (Gómez-Pérez et al., 2011), which showed an adequate internal consistency in our sample ($\alpha = .87$).

The Short Form Health Survey—Physical Functioning subscale (SF-PF; Ware & Sherbourne, 1992) was used to measure physical functioning. This subscale consists of 10 items, with a 3-point Likert-type response format. Total scores range from 0 to 100, where higher scores indicate better physical functioning. The Spanish version (Alonso et al., 1995) was used, which showed an adequate internal consistency ($\alpha = .86$).

Data Analyses

Data analyses were computed with SPSS Version 26. Descriptive statistics were calculated for all variables and presented as means and standard deviations for continuous data or absolute numbers and percentages (%) for categorical data. Levene's test was used to assess equality of variances of continuous variables and Kolmogorov–Smirnov to test for normality and sampling distribution with no major violations noted. Student's t tests and χ^2 tests were used to examine any possible baseline differences between FaW and the TAU group and between participants who provided pre/post data and participants who did not provide pre/post data.

We used analysis of covariance (ANCOVA), including baseline values as covariates, to examine differences between FaW versus TAU alone after treatment on MFI scores and on each of the secondary outcomes. ANCOVA has been shown to have greater power to detect change than analysis of variance in randomized study designs (Van Breukelen, 2006). This analysis was conducted to examine between-group differences using both the full sample and the subsample of participants with CFS/ME but not FM. Analyses were

performed with all randomized participants and imputing missing values (i.e., an intention-to-treat approach) and additionally, including only those participants with complete data (i.e., a complete-case approach). The last observation carried forward method was used to impute missing data values despite its apparent drawbacks (Lachin, 2016) because the attrition rate was low ($n < 15$). In order to reduce the Type I error, we applied the Benjamini–Hochberg method, which controls the false discovery rate using sequential modified Bonferroni correction for multiple comparisons (Glickman et al., 2014).

As measures of effect sizes, partial eta squared, Cohen's *d*, the absolute risk reduction, and the number needed to treat (NNT) were calculated. The usual rule of thumb of $\eta_p^2 = .01$, small; 0.06, moderate; and 0.14, large was used to interpret the observed effect sizes associated to the group variable in the ANCOVAs (Cohen, 1988). In addition, we also calculated the effect size (Cohen's *d*) using the pooled initial *SD* to measure differences in the initial and subsequent mean values and to correct for the estimated population (Morris, 2008; $d = 0.20$, small effect size; 0.50, moderate; and 0.80, large). When determining the absolute risk reduction and NNT, the Jacobson and Truax method (1991) was used to calculate the clinically significant change (CSC; method C) criterium for the MFI-20, which established a cut-off point to classify participants into responders versus nonresponders. Participants were considered responders if their posttreatment MFI-20 total scores were below 65, meaning that they moved to a nonclinical level of fatigue. This value was the result of the Jacobson and Truax formula (1991): *SD* (normative data) × Pretest mean (FaW participants) + pretest *SD* (FaW participants) × Pretest mean (normative data))/(*SD* (normative data) + pretest *SD* (FaW participants). Normative data from the general population ($M = 44.3$; $SD = 14.1$; Hinz et al., 2013, 2020) were used for this calculus. An online calculator was used to compute the absolute risk reduction and NNT (https://www.graphpad.com/quickcalcs/NNT1.cfm). Finally, *t* tests and χ^2 tests were performed to assess baseline differences between responders and nonresponders to know for whom the FaW worked better.

Results

Treatment Adherence and Baseline Clinical Characteristics

All participants in the FaW group self-reported watching all the videos corresponding each of the 12 sessions and adhering to at-home practice. Baseline clinical characteristics are shown in Table 1. No differences were found between groups in posttreatment retention rate (FaW: 92.90%; TAU: 95.40%; $\chi^2 = 1.16$, $p = .309$). No differences were found between patients with data completed at posttreatment (FaW, $n = 197$; TAU, $n = 206$) and participants lost at posttreatment assessment (FaW, $n = 15$; TAU, $n = 10$) for any baseline variable (all $p > .05$).

As shown in Table 1, there were no statistically significant differences in patient-reported outcome measures between the two treatment groups (with imputed values), except for ISPS scores ($p = .020$) and HADS-A scores ($p = .019$). These between-group differences were controlled in further analyses, introducing ISPS and HADS-A baseline scores as covariables in the ANCOVAs. In parallel, three differences in questionnaire scores were found between the two treatment groups at baseline when assessing only the complete-case data set: illness self-perceive start ($p = .024$), HADS-A ($p = .039$), and SF-PF ($p = .026$). Therefore, the same covariable methodology as above was applied to further ANCOVA analyses in the complete-case data set.

Between-Group Differences in Primary and Secondary Outcomes

Table 2 shows means and *SD*s of the patient-reported outcome measures at baseline and at posttreatment (with imputed values) in the TAU and FaW groups (full sample). Statistically significant improvements ($p < .001$) were found for the primary outcome (with a moderate effect size; $\eta_p^2 = .11$) and all the secondary outcomes, with effect sizes ranging from small-to-very large (i.e., $\eta_p^2 = .02$–$.30$). Similar results were found in the complete-case data set (see Table S1 in the online supplemental materials for more details).

Table 3 shows means and *SD*s of the patient-reported outcome measures at baseline and at posttreatment (with imputed values) in the TAU only and FaW intervention groups when only CFS/ME patients without FM comorbidity were included. A post hoc power analysis was conducted to determine whether the present study was adequately powered with this subsample. Results indicated that the current study had 70.02% power for ANCOVA. Statistically significant effects with a medium effect size ($\eta_p^2 = .08$) for the primary outcome of multidimensional fatigue and most of the secondary outcomes (with moderate-to-very large effect sizes; from $\eta_p^2 = .06$ to .30) were found. Regarding the ANCOVAs with the complete-case data set of participants without FM comorbidity, similar results were found (see Table S2 in the online supplemental materials for more details).

Absolute Risk Reduction and Number Needed to Treat

From the FaW group, 55 (26%) were considered responders (MFI-20 total score < 65) and 157 (74%) nonresponders. Regarding baseline sociodemographics, as shown in Table S3 in the online supplemental materials, there were no statistically significant differences between responders and nonresponders. However, there were statistically significant differences between these groups in all clinical characteristics at baseline, showing that nonresponders reported more severe pretreatment symptomatology than responders. The absolute risk reduction in FaW versus TAU alone was 19% (95% confidence interval [CI: 12.19, 25.80]) with NNT = 6 (95% CI [3.9, 8.2]), meaning that six patients would need to be treated with FaW for one of them to become a responder, who would not have done so in the TAU alone group.

Discussion

This RCT aimed to assess the effectiveness of the FIBROWALK program (termed FaW for the present study) for CFS/ME patients, to target symptoms of fatigue, pain, anxiety, depression, kinesiophobia, and overall functional impairment. In brief, CFS/ME participants with and without comorbid FM, reported a significant decrease in all clinical symptoms measured at baseline compared to those who only received TAU. Thus, H1 was supported. Similarly, when examining the outcomes of CFS/ME participants without comorbid FM, the results showed that this subsample experienced a significant decrease in all clinical symptoms too, except for some specific aspects related to fatigue (intensity of

Table 2
Descriptive Statistics and Between-Group Differences for Primary and Secondary Outcomes From an ITT Approach (Imputation of Missing Values With LOCF Method)

Variable	FaW ($n = 212$)	TAU ($n = 216$)	FaW versus TAU			
	M (*SD*)	*M* (*SD*)	*F*	*p*	η_p^2	*d*
MFI-total			51.47	**<.001**	.11	0.56
Baseline	81.15 (11.87)	83.08 (11.38)				
Posttreatment	74.01 (15.16)	82.92 (11.10)				
MFI-general fatigue			40.78	**<.001**	.09	0.66
Baseline	18.33 (2.14)	18.43 (2.37)				
Posttreatment	16.91 (3.13)	18.50 (1.91)				
MFI-physical fatigue			56.26	**<.001**	.12	0.73
Baseline	17.14 (2.63)	17.51 (2.24)				
Posttreatment	15.30 (3.40)	17.46 (2.40)				
MFI-reduced activity			14.96	**<.001**	.03	0.27
Baseline	15.21 (4.29)	15.96 (3.91)				
Posttreatment	13.91 (4.47)	15.76 (4.11)				
MFI-reduced motivation			37.65	**<.001**	.08	0.47
Baseline	14.38 (3.66)	14.87 (3.66)				
Posttreatment	12.70 (4.10)	14.94 (3.64)				
MFI-mental fatigue			9.04	**.003**	.02	0.25
Baseline	16.09 (3.50)	16.31 (3.43)				
Posttreatment	15.18 (3.82)	16.26 (3.28)				
VAS-fatigue			23.71	**<.001**	.05	0.34
Baseline	7.47 (2.43)	7.82 (2.26)				
Posttreatment	6.65 (2.31)	7.80 (2.15)				
VAS-pain			44.63	**<.001**	.10	0.56
Baseline	7.56 (1.85)	7.70 (1.99)				
Posttreatment	6.59 (2.28)	7.80 (1.93)				
HADS-A			30.33	**<.001**	.07	0.31
Baseline	12.50 (4.48)	13.50 (4.34)				
Posttreatment	11.09 (4.56)	13.45 (4.20)				
HADS-D			47.37	**<.001**	.10	0.47
Baseline	11.92 (4.58)	12.28 (4.64)				
Posttreatment	10.19 (4.75)	12.74 (4.61)				
HADS-total			50.32	**<.001**	.11	0.43
Baseline	24.42 (8.10)	25.79 (8.17)				
Posttreatment	21.28 (8.48)	26.19 (7.96)				
FIQR			88.14	**<.001**	.17	0.72
Baseline	71.57 (17.01)	73.28 (16.67)				
Posttreatment	61.54 (20.13)	75.35 (15.17)				
TSK			177.78	**<.001**	.30	0.97
Baseline	29.55 (7.75)	30.32 (7.29)				
Posttreatment	22.56 (6.96)	30.63 (7.34)				
SF-PF			20.47	**<.001**	.05	0.28
Baseline	37.45 (20.22)	33.63 (20.30)				
Posttreatment	42.92 (21.35)	33.50 (19.87)				

Note. Statistically significant effects are shown in bold ($p \leq .05$). Unadjusted means are shown. All analyses were controlled by years since illness emerged ($p = .020$) and baseline HADS-A ($p = .019$). When the Benjamini–Hochberg correction was applied to correct for multiple comparisons, all significant effects remained significant. ITT = intention-to-treat; LOCF = last observation carried forward; FaW = FATIGUEWALK; TAU = treatment as usual; FIQR = Revised Fibromyalgia Impact Questionnaire; HADS = Hospital Anxiety and Depression Scale; ISPS = illness self-perceived start; MFI = multidimensional fatigue inventory; SF-PF = physical functioning component of the 36-item short form health survey; TSK = Tampa Scale for Kinesiophobia; VAS = Visual Analogue Scale.

fatigue, difficulties in concentrating, reduced motivation, reduced activity). Therefore, H2 was partially supported. Finally, it was also found that clinical responders to the FaW intervention reported milder clinical symptom severity than nonresponders at baseline.

Though multiple previous studies have demonstrated the effectiveness of FIBROWALK for management of FM symptoms (Serrat et al., 2020, 2022; Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021), measures of fatigue had not been previously assessed. In the present study, a significant reduction in the level of fatigue (i.e., MFI total scores), our main outcome, was measured in the total sample of participants in the FaW arm, with a moderate effect size. In addition, a significant reduction in fatigue was measured in the subsample of CFS/ME participants without comorbid FM, also with a moderate effect size. This core symptom of CFS/ME is often a distressing phenomenon that can impair patients' lives, personally, socially, and professionally (Norheim et al., 2011). As reported in previous studies, other nonpharmacological interventions (mainly CBT, therapeutic exercise, and self-care), either online or in-person, have shown promising results in reducing reported levels of fatigue with small-to-moderate effect sizes

Table 3

Descriptive Statistics and Between-Group Analyses for Primary and Secondary Outcomes From an ITT Approach (With Imputation of Missing Data) for Those Participants Who Did Not Have a Comorbid FM Diagnosis

Variable	FaW ($n = 38$)	TAU ($n = 35$)	FaW versus TAU			
	M (*SD*)	*M* (*SD*)	*F*	*p*	η_p^2	*d*
MFI-total			6.25	**.015**	.08	0.45
Baseline	79.82 (13.06)	77.97 (12.42)				
Posttreatment	75.37 (14.21)	79.31 (11.61)				
MFI-general fatigue			9.01	**.004**	.11	0.77
Baseline	18.55 (2.32)	17.74 (3.02)				
Posttreatment	17.39 (2.71)	18.66 (2.11)				
MFI-physical fatigue			7.82	**.007**	.10	0.58
Baseline	17.34 (2.70)	17.20 (2.37)				
Posttreatment	15.87 (3.35)	17.23 (2.41)				
MFI-reduced activity			1.38	.244	.02	0.26
Baseline	15.42 (4.33)	14.46 (4.14)				
Posttreatment	14.74 (4.41)	14.91 (3.90)				
MFI-reduced motivation			3.84	.054	.05	0.31
Baseline	13.66 (4.56)	13.23 (3.74)				
Posttreatment	12.42 (4.46)	13.31 (3.86)				
MFI-mental fatigue			0.00	.948	.00	0.06
Baseline	14.84 (3.90)	15.34 (3.77)				
Posttreatment	14.94 (3.77)	15.20 (3.17)				
VAS-fatigue			3.45	.067	.05	0.25
Baseline	6.82 (2.90)	7.14 (2.44)				
Posttreatment	6.74 (2.45)	7.74 (2.13)				
VAS-pain			4.72	**.033**	.06	0.38
Baseline	6.08 (2.57)	6.06 (2.89)				
Posttreatment	5.50 (2.67)	6.54 (2.93)				
HADS-A			10.64	**.002**	.13	0.41
Baseline	10.24 (4.97)	11.69 (4.92)				
Posttreatment	9.26 (4.99)	12.77 (4.44)				
HADS-D			6.60	**.012**	.09	0.37
Baseline	10.16 (5.23)	9.80 (4.78)				
Posttreatment	9.13 (5.46)	10.63 (4.17)				
HADS-Total			10.71	**.002**	.13	0.42
Baseline	20.39 (9.33)	21.49 (9.25)				
Posttreatment	18.39 (9.43)	23.40 (8.13)				
FIQR			20.53	**<.001**	.23	0.72
Baseline	57.81 (20.57)	59.44 (17.29)				
Posttreatment	52.65 (20.58)	68.22 (19.25)				
TSK			29.74	**<.001**	.30	1.10
Baseline	27.79 (8.13)	27.03 (6.82)				
Posttreatment	22.05 (7.69)	29.63 (8.00)				
SF-PF			5.19	**.030**	.07	0.41
Baseline	44.21 (22.53)	46.86 (21.46)				
Posttreatment	46.97 (21.13)	40.57 (21.72)				

Note. Statistically significant effects are shown in bold ($p \leq .05$). Unadjusted means are shown. Since no between-group differences for any variable were found at baseline, no covariates were added. When the Benjamini–Hochberg correction was applied to correct for multiple comparisons, all significant effects remained significant. ITT = intention-to-treat; FM = fibromyalgia; FaW = FATIGUEWALK; TAU = treatment as usual; FIQR = Revised Fibromyalgia Impact Questionnaire; HADS = Hospital Anxiety and Depression Scale; ISPS = illness self-perceived start; MFI = multidimensional fatigue inventory; sf-pf = physical functioning component of the 36-item short form health survey; TSK = Tampa Scale for Kinesiophobia; VAS = Visual Analogue Scale.

(Kim et al., 2020). Thus, the between-group differences in fatigue levels found in the present study are comparable to those reported in RCTs of the most studied nonpharmacological interventions for CFS/ME. This finding reinforces the recommendation to implement multicomponent nonpharmacological treatments for these patients, as indicated in recent clinical guidelines (Noor et al., 2021), and to consider remote delivery of these treatments.

In addition to the primary outcome of fatigue, the FaW intervention in the total sample (including subjects with comorbid FM) resulted in a reduction of all the secondary outcome domains of fatigue, perceived intensity of fatigue and pain, depressive and anxious symptomatology, kinesiophobia, and perceived functional impairment (related to FM symptoms), as well as an improvement in perceived physical functioning, with small-to-large effect sizes. These are promising results, since a 2008 Cochrane review of CBT in CFS/ME adults expressed doubts about its ability to manage CFS/ME symptoms beyond fatigue, such as depression/anxiety and physical functioning, either at posttreatment or at follow-up periods (Price et al., 2021). Hence, the integration of a

diverse range of techniques is likely to have a significant impact in improving both the physical and mental quality of life of these patients. That is to say, these symptom improvements reported in the present study might be due to the effect of FaW components other than CBT (therapeutic exercise, mindfulness training, and/or PNE). For example, another Cochrane review and meta-analysis on effectiveness of therapeutic exercise in treating CFS/ME concluded that it was effective for improving self-reported fatigue severity and physical functioning at posttreatment, with a slightly greater benefit for patients with comorbid depression (Edmonds et al., 2004). Moreover, although scarce, studies about mindfulness training for CFS/ME adults have shown promising effectiveness on fatigue severity, mental functioning, and anxiety/depression (Rimes & Wingrove, 2013; Surawy et al., 1999).

When analyzing data of CFS/ME participants without comorbid FM (i.e., 17% of the total sample), the results were overall similar to the total sample, with some exceptions. There were small differences in the effect sizes of pain intensity (in favor of the mixed sample) and physical functioning (in favor of the CFS/ME subsample). In addition, there was a lack of statistical significance in the reduction of fatigue intensity (according to the single-item measure) and concentration difficulties and improvements in motivation to start and perform activities (specific domains of the MFI-20). It could be argued that the participants with comorbid FM had a more severe clinical manifestation than those without it, as shown in previous studies (Ickmans et al., 2015; Meeus et al., 2016), which in turn, reduced the scope for improving. Another possible explanation is that the subsample of participants without comorbid FM was significantly smaller than the full sample, thus increasing the risk of a Type II error. Further RCTs on the effectiveness of FaW on this population should shed light on these aspects in the future. However, the present findings provide support for the implementation of our multicomponent program in individuals with CFS/ME, both with and without comorbid FM, with the anticipation of significant improvement in the key symptoms associated with the syndrome. Initially, it was deemed appropriate that our multicomponent program was tailored to address the symptoms experienced by CFS/ME patients, both with and without comorbid FM, due to the considerable comorbidity observed between these syndromes. Notably, a substantial proportion of CFS/ME patients experience pain, including recurrent headaches (Castro-Marrero et al., 2017). Furthermore, the content of the PNE module already encompasses strategies for managing fatigue (Serrat et al., 2022). This overlap might have ensured that the FIBROWALK intervention remained customized to effectively address the specific symptoms encountered by CFS/ME patients, regardless of the presence of comorbid FM.

Although pain is a prevalent symptom in individuals with CFS/ME, previous studies have not often focused on assessment of pain symptoms and specific management treatment approaches in this patient population (Ascough et al., 2020). In this vein, the present results are remarkably important, as they support the effectiveness of our online multicomponent approach to help reduce pain intensity. Similarly, studies investigating the prevalence of mental disorders in individuals with CFS/ME have consistently reported clinically significant rates of anxiety and depression within this population. Research findings indicate a significantly higher incidence of mood and anxiety disorders among individuals with CFS/ME compared to those without functional somatic syndromes. Furthermore, the prevalence of these mental problems tends to be higher in CFS/ME compared to FM and irritable bowel syndrome (Daniels et al., 2017; Janssens et al., 2015; Leong et al., 2022). In this line, the present sample showed in average a moderate level of anxiety and depression. As previously mentioned, CFS/ME symptomatology can cause substantial functional impairment in different areas of life (e.g., social and working life). A variable directly related to functional impairment is kinesiophobia, or fear of movement. Pain-neurophysiology education has been identified as a mechanism of positive change in kinesiophobia severity for individuals with CFS/ME (Malfliet et al., 2017). The results of the present study support that assertion, as demonstrated by a significant decrease in patient-reported kinesiophobia in the FaW treatment group.

Overall, similar results were found in the last RCT with FM patients on the effectiveness of FIBROWALK, which assessed all the same patient-reported variables as the present study, except for fatigue (Serrat et al., 2022). However, Cohen's *d* effect sizes were considerably larger in the FIBROWALK study compared to the present study, including pain intensity (0.76 vs. 0.56), anxiety levels (0.51 vs. 0.31), depression level (0.63 vs. 0.47), overall functional impairment (0.80 vs. 0.72), kinesiophobia (1.48 vs. 0.97), and physical functioning (0.83 vs. 0.28). Both studies included a relatively large percentage of comorbid subjects with both FM and CFS/ME diagnoses (between 80% and 90% of participants). They were about equal in sociodemographic and outcome variables at baseline, and sample sizes were large enough to discard problems related to statistical power. It is possible that the different recruitment waves used to gather the subject cohorts in the FIBROWALK and FaW studies may have created some confounding variables (i.e., chronobiological influences). Subject recruitment in the FIBROWALK study was performed in two waves, from September 2020 to January 2021 (Serrat et al., 2022). Subject recruitment in the present FaW study was performed in three waves, from September 2020 to July 2021.

As mentioned above, overall fatigue levels in the FaW cohort in the present study improved significantly, and a subgroup reported posttreatment fatigue levels within healthy proportions (responders, 26% of the total sample). This result is in line with a previous RCT study, in which internet-based CBT was found to be effective in recovering around 40% of participants in an RCT involving adults with CFS/ME (Janse et al., 2018). Moreover, compared to the responders in the present study, the nonresponders reported significantly higher baseline severity levels in all the clinical characteristics measured. It seems that some of the nonresponders may have improved in treatment, but since they had a higher level of symptomology to overcome, fewer were able to achieve fatigue levels within normal parameters. Similarly, the previous FIBROWALK study showed that FM individuals classified as nonresponders reported more anxiety and depressive symptoms and worse physical functioning prior to treatment compared to responders (Serrat et al., 2022). Perhaps a higher dosage of treatment (e.g., longer treatment program) may have resulted in a more improved treatment response for some of the nonresponders in both of these studies. It should be noted that differences in sociodemographic variables were not found in either the FIBROWALK RCT or the present one. Another explanation from machine learning studies is that the spectrum of chronic fatigue could actually comprise different diagnostic categories, depending on the severity of the disease, and each category might benefit from different types of intervention (Maes et al., 2012).

Furthermore, the NNT was adequate, being within the standard range (from 4 to 6) for interventions for chronic conditions

(Citrome & Ketter, 2013). This result suggests that FaW can be preferred to the usual treatment that CFS/ME patients receive here in Spain because of the greater likelihood of benefit. Concretely, a therapeutic advantage can be expected for every six patients, which can be considered a significant benefit, especially taking into account the usual overloading of medical facilities.

Finally, FaW showed a relatively low attrition rate (around 7%), even lower than FIBROWALK in the last trial (around 10%; Serrat et al., 2022), thus supporting the feasibility of this online intervention. Other online interventions in patients with chronic pain have shown an attrition rate ranging between 4% and 54% (Buhrman et al., 2016). The low attrition rate of participants in the present study could have been due to the superior ability of the online format for engaging participants who were not able to attend in-person sessions, in part due to the impairment of their fatigue. Other possible reasons are the emphasis at the beginning of the study about the importance of actively participating in the intervention, the weekly questionnaires, regular check-ups with a therapist to verify patient follow-through, the high flexibility of the online format, and the convenience sampling procedure applied, since recruitment was performed in the hospital where the research team was integrated. Besides that, the research team is strongly of the view that the following key aspects played a vital role in the effective implementation of the FaW program. First, the program benefitted from the involvement of a multidisciplinary team comprising rheumatologists, psychologists, and physiotherapists. In this regard, it is important to note that the FIBROWALK program was designed to be implemented by a psychologist and by a physiotherapist. Second, a strong emphasis was placed on fostering active engagement with the program's content and encouraging regular practice. This emphasis was established early in the intervention and reinforced through timely reminders when needed. Lastly, continuous monitoring of participant progress enabled prompt communication and support for individuals who failed to report adherence and at-home practices. All these factors, putatively contributed to the program's success in delivering positive outcomes.

Several limitations of this study need to be acknowledged, including the absence of an active control group and the lack of long-term assessment, which further RCTs should overcome. It is also important to highlight that this clinical trial was conducted in a specialized unit of a tertiary referral hospital in the context of clinical practice. In relation to the latter, strict selection criteria could not be established due to pressures in daily clinical practice (i.e., most patients were admitted), and, in particular, patients who applied for a certificate of incapacity were also included in this RCT. Furthermore, for ethical reasons, and because a pretest–posttest control-group design was implemented, the inclusion of follow-up assessments would have delayed the opportunity for the TAU group to undergo the FaW program. In response to the challenges posed by the COVID-19 pandemic to this population, the research team prioritized the prompt delivery of the intervention. However, it is important to note that follow-ups are crucial for evaluating the long-term effectiveness of treatments in real-world clinical practices. Therefore, these should be considered and assessed in additional RCTs. Besides, the patients included in the study had a long duration of illness and were recruited from the hospital to which the research team belonged, so the sample cannot be representative of the entire CFS/ME population. Moreover, the subsample without FM was not enough (power < 0.80) to ensure a low risk of Type II error, so reducing our ability to detect existing differences between groups. Additionally, the study did not examine the potential impact of adherence on treatment outcomes. It is recommended that future studies systematically record this information through reports of time spent per screen and number of therapist contacts for example. It would be valuable to understand the relationships between therapist contact frequency, adherence, and outcomes. Thus, further RCTs evaluating the effects of online FaW should include larger samples from multiple centers and also include complementary objective outcomes, such as aerobic fitness and other clinician-assessed measures.

Resumen

Objetivo: Este estudio tuvo como objetivo evaluar la efectividad de una intervención multicomponente en línea llamada FATIGUEWALK (FaW) en comparación con el tratamiento habitual (TAU, por sus siglas en inglés) en pacientes con síndrome de fatiga crónica/encefalomielitis miálgica (CFS/ME, por sus siglas en inglés). ***Método:*** FaW incluyó educación en neurociencia del dolor, ejercicio terapéutico, reestructuración cognitiva y entrenamiento de atención plena. Un total de 428 pacientes con CFS/ME fueron asignados aleatoriamente a dos grupos de estudio: FaW en línea más TAU versus TAU solo. Se llevó a cabo un estudio controlado aleatorio (ECA) simple ciego. Se recopilaron medidas de resultado validadas informadas por los pacientes de fatiga, dolor, ansiedad, depresión y función física al inicio y después del tratamiento, después de la intervención FaW, que duró 12 semanas. ***Resultados:*** Se observaron mejoras estadísticamente significativas (con tamaños de efecto pequeños a moderados) en FaW en línea versus TAU solo con respecto a los aspectos multidimensionales de la fatiga (la d de Cohen oscila entre 0.25 y 0.73) y la mayoría de los resultados secundarios (intensidad de dolor y la fatiga, depresión y ansiedad sintomatológica, deterioro funcional, kinesiofobia, funcionamiento físico). La reducción del riesgo absoluto en FaW versus TAU fue del 19% (IC del 95% = [12.19, 25.80]) con número necesario a tratar (NNT) = 6 (IC del 95% = 3.9–8.2). En general, se observaron mejoras clínicas similares en los análisis de sensibilidad que incluyeron un subgrupo de pacientes sin comorbilidad con fibromialgia ($n = 70$). ***Conclusiones:*** Este es el primer estudio que evalúa la efectividad a corto plazo de una intervención multicomponente en línea agregada a TAU, en comparación con TAU sola, para el tratamiento del CFS/ME. Se justifican ensayos adicionales, que incluyan grupos de control activo con una dosis de tratamiento equivalente y que evalúen la eficacia a largo plazo del FaW en línea.

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