Predicting acupuncture efficacy in fibromyalgia: results of a pragmatic open-label study

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Abstract

Objective

To identify the predictive factors of treatment response to acupuncture in patients with fibromyalgia (FM).

Methods

Patients with FM refractory to standard drug therapy underwent eight weekly acupuncture sessions. Significant improvement, defined as a reduction of at least 30% of the revised Fibromyalgia Impact Questionnaire (FIQR), was assessed at the end of the eight weeks (T1) of treatment and three months after the end of treatment (T2). Univariate analysis was conducted to identify predictors of significant improvement at T1 and T2. Variables that resulted to be significantly associated with clinical improvement at univariate analysis were included in multivariate models.

Results

Analyses were conducted on 77 patients (9 males, 11.7%). At T1, significant improvement in FIQR was recorded in 44.2% of patients. At T2, persistent significant improvement was recorded in 20.8% of patients. In the multivariate analysis, predictive variables of treatment failure were tender point count (TPC) (odds ratio [OR] =0.49, 95% confidence interval [95% CI]: 0.28–0.86, p=0.01) and pain magnification (OR=0.68, 95% CI: 0.47–0.99, p=0.04) assessed with the Pain Catastrophising Scale, at T1. At T2, the only predictive variable of treatment failure was concomitant duloxetine use (OR=0.21, 95% CI: 0.05–0.95, p=0.04).

Conclusion

High TPC and a tendency for pain magnification predict immediate treatment failure, while duloxetine therapy predicts it three months after completion of the acupuncture course. The identification of clinical characteristics of unfavourable response to acupuncture could help to implement a cost-effective prevention of treatment failure in FM.

Key words

fibromyalgia, acupuncture, therapy, tender point count, pain magnification, duloxetine

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Introduction

Fibromyalgia (FM) is a condition mainly characterised by the presence of chronic widespread musculoskeletal pain that affects a large proportion of the general population. The diagnosis of FM is often delayed because of the variability and the variety of symptoms, with heavy consequences on the quality of life of patients (1, 2).

The pathophysiology of FM is still far from being fully elucidated. It is believed, however, that FM is the prototype of diseases characterised by the presence of central sensitisation (3). In addition, a number of evidence has documented a potential involvement of the peripheral nervous system, defined by the presence of a small sensory fibre neuropathy (4, 5). Moreover, a recent study has hypothesised that FM may have an autoimmune basis. In fact, administrating IgG from FM patients to mice transferred the typical FM symptoms through a mechanism involving satellite glial cells and neurons of the dorsal root ganglia (6).

Pathophysiological uncertainties are reflected in therapeutic inadequacy. There is no pharmacological therapy of recognised efficacy approved for FM, but international recommendations suggest non-pharmacological approaches as the first-line option. Acupuncture is among the non-pharmacological treatments which have demonstrated efficacy. Acupuncture is a holistic treatment strategy, potentially effective on both musculoskeletal pain and somatic symptoms. Acupuncture integrates well with pharmacologic treatments, is generally well tolerated, and the latest EUropean League Against Rheumatism (EULAR) recommendations on the management of FM made a weak recommendation for acupuncture in FM (7). Several studies have been conducted and a recent meta-analysis of randomised-controlled trials has demonstrated the superiority of true acupuncture over sham acupuncture on pain and quality of life in FM patients (8). Acupuncture is considered a rational choice in the treatment of conditions characterised by the presence of chronic pain such as knee osteoarthritis or low back pain, but with short-term benefit also for FM (9). A previous study has shown that a course of eight weekly sessions of acupuncture treatment, according to a pre-established treatment schedule, in FM patients with severe symptoms and substantial refractoriness/intolerance to pregabalin and duloxetine, is effective on multiple health domains, including difficult-to-treat symptoms such as neuropathic pain features and pain catastrophising (10).

Acupuncture, like other complementary and alternative medicines (CAMs), is a patient-centered treatment and is generally well tolerated and appreciated by patients (11, 12).

However, since acupuncture is a treatment option that is not reimbursed by all health care systems and involves a financial and time commitment for patients, identifying the "right" patients and the appropriate timing is of paramount importance.

To date, there is no study that indicates which variables predict response to acupuncture treatment in FM, either in terms of immediate response or persistence of response, and thus can enable the implementation of personalised treatment a prevention of therapeutic failure. To personalise therapeutic decisions in FM patients, those with the most suitable characteristics for acupuncture should be identified.

Based on these assumptions, the working hypothesis of this study is to identify the predictors of response to acupuncture treatment in patients with FM.

Materials and methods

Setting and study design

Patients with FM, diagnosed according to the 2010 American College of Rheumatology (ACR) criteria (13), were prospectively enrolled at a tertiary referral centre in the diagnosis and treatment of FM, from January 2018 to June 2019.

The study had an open-label, pragmatic, non-controlled design. Patients underwent a baseline assessment (T0) on the same date as the first acupuncture session. Then, they were treated with a weekly acupuncture session for eight weeks. Treatment response was investigated at the end of treatment

(T1), and three months after the end of treatment (T2).

Inclusion and exclusion criteria

Patients with severe symptoms, defined as such by the presence of a Revised Fibromyalgia Impact Questionnaire (FIQR ≥ 39) and a Patient Health Questionnaire 15 items (PHQ15) ≥5, were included. This definition of severity, although arbitrary, represents a proposal based on expert opinion in the absence of a validate definition of difficult-to-treat FM and biomarkers indicative of disease severity (14). Alongside the clinimetry-defined disease severity, patients included in the study had to be intolerant or non-responsive to standard drug therapy, defined as the combination of duloxetine 60 mg/day and pregabalin 300 mg/day. Patients treated with lower dosages of the respective molecules, or patients in the absence of drug treatment, were also included in cases of intolerance toward duloxetine or pregabalin at standard dosages. At the time of inclusion in the study, patients were required to have been on the reference drug therapy at a stable dosage for at least three months, and no changes in dosage were allowed during the study period. Paracetamol (up to 3 g/day) was allowed as needed during the study.

Patients who were receiving or had received acupuncture in the three months before inclusion, those with comorbidities that could be confused with FM or able to interfere with the clinimetric evaluation of disease severity (*e.g.* inflammatory arthritis, connective tissue diseases, vasculitis, uncontrolled endocrinopathies, Parkinson's disease, Alzheimer's disease or other dementias, severe depressive syndrome, opioid-induced hyperalgesia), potentially life-threatening diseases (*e.g.* uncontrolled heart failure, severe infections, active neoplasms), or diseases that contraindicate acupuncture (*e.g.* diffuse skin diseases) were excluded. Given the high prevalence of other conditions such as osteoarthritis or radiculopathies, these kinds of concomitant conditions were not considered an exclusion criterion if the dominant musculoskeletal symptomatology was attributable to chronic widespread pain.

The study procedures were conducted in accordance with the 1964 Declaration of Helsinki and subsequent amendments and were approved by the local ethics committee (Comitato Etico Unico Regione Marche, number 1970/AV2). All patients voluntarily participated in the study and signed the informed consent.

Clinimetric assessment

At T0, T1, and T2, the clinimetric assessment was essentially based on several patient-reported outcomes (PROs), in particular the FIQR and FAS (Fibromyalgia Assessment Status) as a disease-specific measures of disease severity, the PHQ15 as assessment of somatic symptoms, the PainDetect Questionnaire (PDQ) as a measure of neuropathic pain characteristics, the Pain Catastrophising Scale (PCS) to investigate characteristics the psychological attitudes of catastrophising related to pain. Tender point count (TPC) was also performed. Questionnaires were all administered by GB, a fellow in rheumatology experienced in clinimetric assessment of rheumatic diseases. During each clinical assessment, TPC was conducted in all patients by FS, a rheumatologist with over 30 years of experience in the diagnosis and treatment of FM.

FIQR. The FIQR is a disease severity index specific to FM with broad international acceptance. It consists of 21 items in the form of 0-10 numerical rating scales (NRS) including three health domains: physical function, symptoms, and overall health status. The final score ranges from 0 to 100 and can be interpreted as remission (score 0–23), mild severity (score 24–40), moderate severity (score 41–63), severe disease (score 64–82), and very severe disease (score > 82) (15).

FAS. The FAS is a fully patient-reported instrument dedicated to FM, composed of two parts. The first part consists of two 0–10 NRS investigating fatigue and sleep quality. The second part is the assessment of chronic widespread pain on a front-back dummy with 16 non-articular body areas, termed the Self-Assessment Pain Scale (SAPS). For each body area, the pain rating ranges from 0 (no pain) to 3 (severe pain). The final SAPS score ranges from 0 to 48 and is normalised on a scale of 0 to 10. The final FAS score ranges from 0 to 10 and is the average of the 3 scales (16).

PHQ15. The PHQ15 is a generic, fast and focused solely on somatic symptoms tool. It has demonstrated its validity in FM. The score ranges from 0–30, with proposed interpretative cut-offs for FM being 0–9 for mild, 10–14 moderate, and 15–30 severe symptoms (17).

PCS. The PCS is a 13-item self-report instrument designed to investigate catastrophic thinking related to chronic pain. Each item is rated on a 5-point scale (where 0 stands for "never" and 4 for "always"). Item scores are summated into a total score (range 0–52) and three subscale scores: the helplessness (range 0–24), the rumination (range 0–20), and the magnification (0-8) domains (18).

PDQ. The PDQ is designed to study the neuropathic components of pain in a fully patient-reported manner, investigating the presence of allodynia, hyperalgesia, dysesetesias, sudden pain, and pain irradiation. The final result, ranging from -1 to 38, should be interpreted as the probability of having neuropathic pain: for values ≤12 the probability of neuropathic pain is low, while for values ≥19 the probability is high (>90%), while intermediate values are defined as ambiguous (19).

TPC. The TPC, which evaluates the degree of tenderness, although no longer necessary for the diagnosis of FM, is still considered in the evaluation of patients as it is considered a measure of distress of which it would represent a "sedimentation rate" (20).

Acupuncture treatment

All acupuncture sessions were conducted by a single physician (MDC), a rheumatologist licensed to practice acupuncture (recognised upon completion of a four-year course), with many years of experience in acupuncture and

management of FM patients. Each patient underwent weekly sessions for a total number of eight sessions. Treatment was performed in each session and for each patient according to a predetermined acupuncture scheme that included the acupoints LV3, SP6, ST36, LI4, CV6, CV12, Ex-HN-3 (Yintang), and GV20. Symmetrical acupoints were treated bilaterally. According to Traditional Chinese Medicine (TCM), this acupuncture formula is intended to move, tonify, and raise Qi, tonify Blood, and calm Shen (21). Each acupoint was infixed with sterile, single-use needles, equipped with a guide tube, measuring 0.25x25 mm (Huanqiu®). After insertion, each needle was manipulated until it evoked the sensations of paresthesia characteristic of de Qi (22), and then was left for 30 minutes, the whole duration of a single session. Each patient therefore received a total of 240 minutes of acupuncture treatment.

Throughout the duration of the study, the acupuncturist was blinded to the clinimetric evaluation. During the sessions, only minimal interaction was allowed between the acupuncturist and the patients, and the acupuncturist was not allowed to ask the patients questions about their health status.

The procedures performed to conduct the study followed the STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist (23).

Statistical analysis

Qualitative variables were reported as absolute frequency and/or corresponding percentage. Quantitative variables were reported as median and interquartile range or mean±standard deviation, as appropriate. Only patients completing the three scheduled assessments (T0, T1, and T2) were included in the analyses. Predictors of clinically significant response were assessed both at T1, to identify features associated with immediate improvement at the end of treatment, and at T2, to identify features associated with the persistence of treatment effects.

A reduction in FIQR of at least 30% from baseline was considered a clinically significant response. A 30% improvement in symptoms was proposed as a reasonably achievable and easily applicable target in clinical practice (14). This dichotomisation based on percent reduction in FIQR was applied to both T1 and T2 assessments.

For T1 and T2 assessments, univariate analyses were first performed, using significant improvement in FIQR as dependent variable. The independent variables included in univariate analyses were demographic (age, sex), clinical (BMI, disease duration, duloxetine therapy and pregabalin therapy), and clinimetric (FIQR and subscales, FAS and subscales, PHQ15, PCS and subscales, PDQ and subscales, and TPC) variables. Next, two multivariate analyses were conducted, one for T1 and one for T2, including the independent variables with statistically significant association with clinical improvement at univariate analyses.

Statistical analyses were conducted with MedCalc version 19.0 and Stata 14. Values of $p<0.05$ were considered statistically significant.

Results

The study involved 102 patients, and the scheduled course of acupuncture treatment was completed by 96 patients. Detailed characteristics of this cohort has been published previously (10).

Analyses for this study were conducted in 77 patients, whose data were available at T0, T1, and T2. Nineteen out of 96 patients (19.8%) attended the final clinical assessment at T2. The main reason given for missing the follow-up visit consisted of logistic problems in reaching the centre.

Of the 77 patients, 9 were male (11.7%). Their mean age was 52.8 (±11.4) years and the mean duration of FM 6.2 (±6.6) years. The mean FIQR at baseline was 60.8 (±17.8). Eleven patients (14.3%) were on duloxetine treatment alone, 17 (22.1%) on pregabalin alone, 26 (33.8%) on combination therapy between the two molecules. Demographic, clinical and clinimetric variables at T0 are summarised in Table I.

Table I. Demographic, clinical and clinimetric variables at baseline.

Variable	Value
Age	52.8 (±11.4)
Sex (male)	9 (11.7%)
BMI (kg/m^2)	26.7 (±6.2)
Duloxetine use	37 (48.1%)
Pregabalin use	43 (55.8%)
Disease duration (years)	6.2 (±6.6)
FIQR	60.8 (±17.8)
FIQR physical function	17.5 (±6.0)
FIQR overall health status	11.4 (±5.0)
FIQR symptoms	31.8 (±8.9)
FAS	6.7 (±1.9)
FAS SAPS	5.7 (±1.9)
FAS sleep	6.8 (±2.9)
FAS fatigue	7.8 (±2.0)
PHQ15	14.4 (±5.3)
PCS	28.6 (±11.9)
PCS helplessness	12.5 (±5.8)
PCS rumination	12.5 (±4.8)
PCS magnification	3.5 (±2.1)
PDQ	19.9 (±7.3)
VAS acute pain	6.5 (±2.2)
VAS highest pain	8.2 (±1.8)
VAS mean pain	6.9 (±1.9)
TPC	17.1 (±1.1)

BMI: Body Mass Index; FIQR: Revised Fibromyalgia Impact Questionnaire; FAS: Fibromyalgia Assessment Status; SAPS: Self-Assessment Pain Scale; PHQ15: Patient Health Questionnaire 15 items; PCS: Pain Catastrophising Scale; PDQ: PainDetect Questionnaire; VAS: Visual Analogue Scale; TPC: Tender Point Count.

At the end of treatment (T1), significant improvement in FIQR was recorded in 34 out of 77 patients (44.2%). At three months after the end of treatment (T2), significant improvement in FIQR persisted in 16 out of 77 patients (20.8%).

Predictors of non-response at the end of treatment

At T1, predictors of treatment response were not observed. Conversely, predictors of treatment failure were TPC (OR=0.45, $p<0.01$), VAS highest pain (OR=0.69, $p=0.01$) and VAS mean pain (OR=0.76, $p=0.03$) included in the PDQ, the PHQ15 (OR=0.91, $p=0.04$), the overall PCS score (OR=0.93, $p<0.01$) and its subscales magnification (OR=0.62, $p<0.01$), rumination (OR=0.87, $p<0.01$) and helplessness (OR=0.88, p 0.01), the overall FIQR score (OR=0.97, $p=0.02$) and its subscales physical function (OR=0.89, $p=0.01$) and overall health status (OR=0.88, $p=0.01$) (Table II).

Multivariate analysis, showed that TPC

Table II. Univariate analysis considering the significant clinical improvement at the end of the treatment (T1) as dependent variable.

Independent variables	Odds ratio	95% CI	*p*
Age	0.99	0.95 - 1.03	0.74
Sex (male)	1.01	0.25 - 4.11	0.99
BMI	0.95	0.88 - 1.03	0.20
Duloxetine use	0.49	0.20 - 1.23	0.13
Pregabalin use	0.81	0.33 - 2.00	0.65
Disease duration (years)	0.97	0.91 - 1.04	0.44
FIQR	0.97	0.94 - 1.00	0.02
FIQR physical function	0.89	0.82 - 0.97	0.01
FIQR overall health status	0.88	0.80 - 0.98	0.01
FIQR symptoms	0.97	0.92 - 1.02	0.19
FAS	0.94	0.74 - 1.20	0.64
FAS SAPS	0.79	0.61 - 1.02	0.07
FAS sleep	1.03	0.88 - 1.20	0.73
FAS fatigue	0.96	0.76 - 1.21	0.72
PHQ15	0.91	0.83 - 0.99	0.04
PCS	0.93	0.89 - 0.97	<0.01
PCS helplessness	0.88	0.80 - 0.96	<0.01
PCS rumination	0.87	0.78 - 0.96	0.01
PCS magnification	0.62	0.48 - 0.81	<0.01
PDQ	0.96	0.91 - 1.03	0.26
PDQ VAS acute pain	0.83	0.67 - 1.03	0.09
PDQ VAS highest pain	0.69	0.52 - 0.92	0.01
PDQ VAS mean pain	0.76	0.59 - 0.98	0.03
TPC	0.45	0.27 - 0.73	< 0.01

CI: confidence interval; BMI: body mass index; FIQR: revised Fibromyalgia Impact Questionnaire; FAS: Fibromyalgia Assessment Status; SAPS: Self-Assessment Pain Scale; PHQ15: Patient Health Questionnaire 15 items; PCS: Pain Catastrophising Scale; PDQ: PainDetect Questionnaire; VAS: Visual Analogue Scale; TPC: tender point count.

Table III. Multivariate analysis considering the significant clinical improvement at the end of treatment (T1) as dependent variable, independent variables the parameters that achieved statistical significance at univariate analysis in Table II.

Independent variables	Odds ratio	95% CI	*p*
FIQR	1.00	0.96 - 1.05	0.88
PHQ15	0.95	0.83 - 1.09	0.47
PCS helplessness	0.92	0.76 - 1.13	0.43
PCS rumination	1.07	0.86 - 1.32	0.54
PCS magnification	0.68	0.47 - 0.99	0.04
PDQ VAS highest pain	0.91	0.53 - 1.55	0.72
PDQ VAS mean pain	1.06	0.64 - 1.77	0.81
TPC	0.49	0.28 - 0.86	0.01

CI: confidence interval; BMI: Body Mass Index; FIQR: Revised Fibromyalgia Impact Questionnaire; PCS: Pain Catastrophising Scale; PDQ: PainDetect Questionnaire; VAS: Visual Analogue Scale; TPC: tender point count.

(OR=0.49, *p*=0.01) and magnification (OR=0.68, *p*=0.04) were the only predictors of treatment failure at T1 (Table III).

Predictors of non-response three months after the end of treatment

Also at T2 predictors of treatment response were not identified, while the univariate analysis revealed that the independent variables associated with non-response at 3 months after the end of treatment were concomitant duloxetine therapy (OR=0.18, *p*=0.01), TPC (OR=0.57, *p*=0.03), FIQR physical function (OR=0.88, *p*=0.01), overall PCS score (OR=0.94, *p*=0.02) and its subscales magnification (OR=0.68, *p*=0.01) and helplessness (OR=0.89, *p*=0.04) (Table IV).

Multivariate analysis revealed that concomitant duloxetine therapy (OR=0.21, *p*=0.04) was the main variable associated with no significant response at T2 (Table V).

Discussion

To the best of our knowledge, this is the first study to analyse the predictors of poor improvement in symptom severity at the end, and three months after completion, of eight-session cycle of acupuncture treatment in FM patients. The results of this study can provide a reference for the integration of a non-drug treatment such as acupuncture into the complex FM scenario. The identification of predictors at two different time points, namely at the end of the treatment course (T1) and after three months (T2), may provide useful information to know what to expect in the immediate and near future.

Specifically, a high number of tender points and high levels of pain magnification and concomitant duloxetine therapy, respectively, were identified as the main predictors of significant non-response to acupuncture.

Nowadays, the widespread prevalence of chronic non-communicable diseases results in an important global socio-economic burden. Though FM to date is not a preventable disease, something can be done in tertiary prevention, seeking treatments that are effective, well tolerated, and not harmful to patients. Acupuncture meets these characteristics; however, there is some variability in efficacy in patients with FM and therefore it is highly desirable to be able to identify patients with low probability of response.

The need to identify predictive risk factors for a given disease is especially critical for those non-communicable conditions with high prevalence, for which the implementation of simple and inexpensive biomarkers would be welcome. For these conditions, which include those characterised by chronic pain, it is also very important to identify predictive variables of response (or non-response) to treatment.

Acupuncture, with its history dating back thousands of years, has a body of evidence for efficacy in the area of chronic pain and FM (8, 24), which, however, is predominantly derived from a reactive medical approach. For example, a 2008 study showed the efficacy of acupuncture in addition to usual care (exercise and tricyclic anti-

Table IV. Univariate analysis considering the significant clinical improvement 3 months after the end of the treatment (T2) as dependent variable.

Independent variables	Odds ratio	95% CI	*p*
Age	0.98	0.93 - 1.02	0.32
Sex (male)	0.44	0.05 - 3.82	0.46
BMI	0.95	0.86 -1.05	0.36
Duloxetine use	0.18	0.05 - 0.71	0.01
Pregabalin use	1.02	0.34 - 3.10	0.97
Disease duration (years)	0.86	0.73 - 1.02	0.08
FIQR	0.97	0.94 - 1.00	0.05
FIQR physical function	0.88	0.80 - 0.97	0.01
FIQR overall health status	0.89	0.80 - 1.00	0.05
FIQR symptoms	0.97	0.91 - 1.03	0.30
FAS	0.98	0.74 - 1.32	0.91
FAS SAPS	0.84	0.63 - 1.13	0.25
FAS sleep	1.08	0.88 - 1.32	0.45
FAS fatigue	0.96	0.73 - 1.26	0.75
PHQ15	0.95	0.85 - 1.05	0.32
PCS	0.94	0.89 - 0.99	0.02
PCS helplessness	0.89	0.80 - 0.99	0.04
PCS rumination	0.89	0.79 - 1.00	0.06
PCS magnification	0.68	0.50 - 0.92	0.01
PDQ	0.96	0.89 - 1.04	0.29
PDQ VAS acute pain	1.01	0.79 - 1.30	0.93
PDQ VAS highest pain	0.87	0.65 - 1.17	0.35
PDQ VAS mean pain	0.92	0.70 - 1.22	0.57
TPC	0.57	0.34 - 0.93	0.03

CI: confidence interval; BMI: Body Mass Index; FIQR: Revised Fibromyalgia Impact Questionnaire; FAS: Fibromyalgia Assessment Status; SAPS: Self-Assessment Pain Scale; PHQ15: Patient Health Questionnaire 15 items; PCS: Pain Catastrophising Scale; PDQ: PainDetect Questionnaire; VAS: Visual Analogue Scale; TPC: tender point count.

Table V. Multivariate analysis considering the significant clinical improvement 3 months after the end of the treatment (T2) as dependent variable, independent variables the parameters that achieved statistical significance at univariate analysis in Table IV.

Independent variables	Odds ratio	95% CI	p
Duloxetin use	0.21	0.05 - 0.95	0.04
FIQR physical function	0.94	0.82 - 1.06	0.31
PCS helplessness	0.98	0.83 - 1.15	0.76
PCS magnification	0.75	0.50 - 1.12	0.16
TPC	0.69	0.40 - 1.19	0.18

CI: confidence interval; FIQR: Revised Fibromyalgia Impact Questionnaire; PCS: Pain Catastrophising Scale; TPC: tender point count.

depressants), but without studying the predictor variables of efficacy itself (25). Subsequent studies, although well conducted and adhering to the rules of randomised controlled trials, were always characterised by the absence of analysis of predictive variables of efficacy so that individualised treatment could be carried out and therapeutic failure prevented (26, 27).

The role of acupuncture in personalised medicine is beginning to be studied in multiple disciplines, first of all in oncology (28, 29). Being able to predict treatment response is one of the cornerstones of precision medicine. On the other hand, response to a given treatment is a complex phenomenon, depending on genetically determined factors, biomarkers, and also on measurable clinical and psychosocial characteristics (30).

Stratification of patients with FM based on genetic characteristics or biomarkers is still far from being applicable to clinical practice (31, 32). Therefore, the present study focused on identifying clinical predictive variables that can be easily measured and applied to daily practice.

Interestingly, clinical features that represent the diagnostic/classifying definition of FM in the latest ACR and AAPT criteria sets (13, 33, 34), namely chronic widespread pain (in this study assessed through the SAPS), fatigue, and non-restorative sleep, were not identified as predictive variables. It is also interesting to note that while chronic widespread pain was not predictive of treatment response, TPC predicted immediate response to acupuncture. Though TPC has been basically abandoned for diagnostic/classification purposes by the most recent criterion sets, its assessment may represent a measure of distress and be more informative than dolorimetry (20).

Pain catastrophising has been shown to be related to tenderness and affective distress in patients with FM and rheumatic diseases (35). Pain catastrophising, particularly in terms of pain magnification, is associated with a decreased response to acupuncture based on the results of this study. A functional magnetic resonance imaging study demonstrated how the tendency to pain catastrophising interferes with neural mechanisms involved in pain processing. In patients with high pain catastrophising, increased brain activity has been detected in the bilateral dorsolateral prefrontal cortex. This kind of patients would appear to be less easily distracted by pain, and thus pain catastrophising would seem to be a feature strongly associated with the persistence of chronic pain (36). In a previous study, it was shown that among the various scales of the PCS, magnification is the one that does not experience significant improvement with acupuncture compared with helplessness and rumination (10). Therefore, magnification is a psychological trait that does not only yield to substantial improvement with acupuncture, but also predicts its lack of efficacy in the immediate future, and patients with high magnification should probably be directed to other therapeutic approaches.

The relationship between concomitant duloxetine treatment and lower chance of improvement three months after the end of acupuncture treatment is probably less intuitive. A possible explanation involves the pharmacodynamics of duloxetine and the mechanisms of

action of acupuncture. Duloxetine is a dual serotonin and norepinephrine reuptake inhibitor. Acupuncture in chronic pain exerts multiple effects peripherally and centrally involving multiple mediators. Numerous studies conducted in the animal models, show that serotonin and norepinephrine are two pivotal neurotransmitters in the effect of acupuncture with actions at both the encephalic (*e.g.* raphe magnus, locus coeruleus) and spinal levels (37). One hypothesis that can be advanced is that some of the effect of acupuncture overlaps with pathways that are already pharmacologically elicited. However, this remains a theoretical speculation that needs experimental verification.

The main potential limitation of the study is the absence of a control group with sham acupuncture. It was chosen to treat all patients with verum acupuncture due to symptom severity since the latter has been shown to be more effective than sham interventions in patients with FM (38). In addition, there is some direction in the literature suggesting the execution of pragmatic real-life studies since acupuncture is a complex therapy and sham procedures have been shown to be non-inert and potentially, rather than reducing bias, may introduce additional ones (39, 40).

Conclusions

This research article adds important novelties to the existing literature regarding acupuncture in FM. Specifically, the results of the work allow to distinguish between patients with clinical characteristics indicating unfavourable response to acupuncture, both in the immediate and 3 months after the end of treatment. Patients with severe symptomatic FM are less likely to have a significant response to acupuncture at the end of treatment if they had with a high number of tender points and with a tendency to pain magnification, and and persistence of therapeutic efficacy is reduced to three months if patients take duloxetine.

Second, by assessing simple clinical variables, a targeted tertiary prevention can be implemented, avoiding unnecessary burdens on patients both in terms of cost and in terms of potential complications of ineffective treatment. Third, this study emphasises the role of acupuncture as a personalised medical service, to be tailored to clinical features that fall outside the concept of FM severity but are of paramount importance for therapeutic success.

In conclusion, this study helps to identify the "right" FM patient to whom acupuncture should be proposed, helping to prevent treatment failures and proposing an advancement of management of this disease.

Take home messages

- Acupuncture significantly reduces the severity of fibromyalgia in 44.2% of patients at the end of treatment, with significant improvement persisting in 20.8% of patients three months after completion.
- Predictors of failure at the end of acupuncture treatment are a high number of tender points and high levels of pain magnification at baseline.
- Concomitant use of duloxetine is a predictor of failure to maintain response at three months after completion of acupuncture treatment.

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