Sustained Benefits of Exercise-based Motivational Interviewing, but Only among Nonusers of Opioids in Patients with Fibromyalgia

Sunghye Kim, James E. Slaven, and Dennis C. Ang

ABSTRACT. ***Objective.*** Given the known side effects of opioids and their potential effects on cognition, we sought to evaluate the benefits of motivational interviewing (MI) to promote physical activity on 2 subsets of participants with fibromyalgia (FM): nonusers and users of opioids.

Methods. This was a secondary data analysis of a 36-week randomized controlled trial to assess the efficacy of MI to promote physical activity among participants with FM. Participants were randomized to 1 of 2 treatment arms: 6 phone-based MI sessions (n = 107) or 6 sessions of FM self-management instructions [attention control (AC), n = 109]. The primary outcomes were changes in physical function (Medical Outcomes Study Short Form-36), pain severity (Brief Pain Inventory), global FM symptom severity (Fibromyalgia Impact Questionnaire), and the amount of light to moderate physical activity (LMPA) from baseline to each followup visit. At study entry, subjects were categorized as opioid nonusers versus users. Repeated measures ANOVA was used to assess treatment effects adjusting for potential confounders.

Results. Of the 216 participants, 145 (67%) were nonusers and 71 (33%) were opioid users. Among nonusers, MI was associated with improved physical function, reduced pain severity, and global FM severity, and increased LMPA at 6-month followup. Among opioid users, there were no significant differences in any outcome measures between the MI and AC groups.

Conclusion. Exercise-based MI was associated with sustained clinical benefits 6 months after completion of therapy, but only for those who were not taking opioids. (First Release December 1 2016; J Rheumatol 2017;44:505–11; doi:10.3899/jrheum.161003)

Key Indexing Terms:
OPIOID RISK
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Five million patients in the United States[1] have fibromyalgia (FM), with estimated annual costs of $18,671 per patient[2]. Exercise, both aerobic and resistance training, improves global well-being, physical function, and pain in patients with FM[3], and is considered a cornerstone of FM management. However, despite the well-known benefits of exercise, patients with FM are less active than healthy controls, and only 31% of patients with FM reported walking regularly[4]. For example, in a report of a 12-week supervised exercise program, adherence to aerobic exercise (participation in at least 120 min of aerobic exercise per week) was only about 40%[5].

Motivational interviewing (MI) is a collaborative conversational approach for strengthening a person's motivation and commitment to change. MI is associated with better adherence to medications[6], higher rates of successful smoking cessation[7], and increased physical activity[8]. Given this evidence, we previously hypothesized that MI would promote and help maintain adherence to an exercise prescription. In our study, MI was associated with increased physical activity and improved global FM symptom severity, but only during the acute treatment phase. Six months after completion of therapy (i.e., primary endpoint), benefits involving self-reported physical activity and clinical outcomes were not sustained[9]. The absence of longterm benefits of MI is likely multifactorial, one of which is the presence of treatment moderators (e.g., use of opioids) that may diminish the effects of MI.

With a more liberal prescribing pattern in the 1990s and a wider availability of opioids, chronic opioid usage has increased significantly in the past 2 decades with associated increases in deaths from overdoses and misuse, and in hospi-

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talization for substance abuse treatment[10]. Despite a consensus against the longterm use of opioids for FM from the American College of Neurology[11] and the European League Against Rheumatism[12], 11%–69% of patients with FM are reported to take them[13]. In patients with FM, the use of opioids is associated with worse clinical outcomes, such as pain severity, functional status, insomnia, depression, and disability[14]. Moreover, opioids are associated with deficits in cognitive function, especially in domains of attention, inhibitory control, strategic planning, decision making, and learning and memory — domains that are essential to behavioral changes[15]. Given the potential complications of opioids in cognitive function[15] and FM-relevant clinical outcomes[14], we hypothesized that MI would be beneficial among nonusers of opioids, but ineffective among opioid users. The objective of this report was to evaluate the benefits of MI over attention control (AC) on 2 subsets of participants with FM: nonusers and users of opioid.

MATERIALS AND METHODS

Study design. Ours was a secondary analysis of a 36-week randomized controlled trial (RCT) to assess the efficacy of MI to promote physical activity among patients with FM[9]. Participants were randomized to 1 of 2 groups: an MI group or an AC group. The MI group received 6 telephone-delivered, exercise-based MI sessions over 12 weeks. The AC group received 6 telephone contacts over 12 weeks to control for time and therapist attention. Outcome assessments were conducted at baseline, immediately post-treatment (Week 12), and at the 3-month (Week 24) and 6-month (Week 36) followups. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Study procedures, including written informed consent, were approved by the Indiana University–Purdue University Indianapolis Institutional Review Board (Study Number: 0708-62). The study enrollment started in December 2007 and the followup was completed in March 2010.

Study population. All participants met the following entry criteria: (1) the 1990 American College of Rheumatology classification criteria for FM[16], (2) the average Brief Pain Inventory (BPI) pain severity score ≥ 4[17], (3) the FM Impact Questionnaire-Physical Impact score ≥ 2[18], (4) receiving stable doses of medication for FM ≥ 4 weeks, and (5) being between the ages of 18 and 65 years old. To avoid the floor effect, we included only FM patients with moderate to severe symptoms. We excluded individuals with (1) known cardiovascular (CV) disease, (2) moderate to severe chronic lung disease, (3) uncontrolled hypertension, (4) orthopedic or musculoskeletal conditions that would prohibit moderate-intensity exercise, (5) active suicidal ideation, (6) planned elective surgery during the study period, (7) ongoing unresolved disability claims, (8) inflammatory rheumatic conditions (e.g., rheumatoid arthritis), (9) current use of heart rate–lowering medications (e.g., β-blocker), (10) pregnancy, (11) psychosis, or (12) currently participating in a structured exercise program 3 times or more per week. The diagnosis was corroborated by the corresponding author of our study (DCA).

Opioid usage. Opioid users were defined as patients who were taking any opioids (e.g., oxycodone, hydrocodone, propoxyphene, morphine, fentanyl, and codeine) for at least 2 weeks at the time of enrollment. The information on dose was not collected. All participants were taking opioid regularly (e.g., hydrocodone twice daily); none were taking it as needed. We did not consider medication changes that occurred after enrollment.

Randomization. Participants were randomized to 1 of the 2 treatment arms stratified by depression status, sex, and referral source (specialty vs primary care). Allocation to treatment arm was carried out by a computer-generated randomization list with a permuted block size of 2.

Supervised exercise training. All participants received an aerobic exercise prescription and 2 individualized supervised exercise sessions from a qualified fitness instructor who was blinded to treatment assignment. The written exercise prescription included the initial exercise intensity [(40–50% of the heart rate reserve (HRR)], duration (10–12 min/session), and frequency (2 days/week). Participants were instructed to gradually increase their total volume of exercise to a maximum of 55%–65% of HRR, 28–30 min/session, and 3–4 day/week over the ensuing 36 weeks. Details of the exercise prescription have been previously described[19].

After the 2 supervised exercise sessions, MI participants received the phone-delivered, exercise-based MI and the AC group received the phone-delivered education on FM-relevant topics. Each participant interacted with the same interventionist (MI-trained health practitioner or health educator) throughout our study.

Exercise-based MI. MI participants received 6 telephone calls over 12 weeks delivered by trained interventionists who used a standard MI handbook[20]. The first 2 MI sessions focused on enhancing patient motivation to exercise by eliciting (1) self-motivational statements related to problem recognition and concern about the status quo, (2) intent to participate in graded aerobic exercise, and (3) optimism that exercise-related change is possible. Calls 3 and 4 were devoted to strategies that strengthen commitment to exercise by helping the participant develop a plan for change and reviewing the positive consequences of graded aerobic exercise. The last 2 calls focused on follow-through strategies to prevent relapse of inactivity. As previously reported[9], adherence to the principles and spirit of MI was generally well maintained in the MI group, as assessed by the Motivational Interviewing Treatment Integrity scale[21].

AC group. Participants in the AC group received didactic health information delivered over the telephone on the following topics: (1) an overview of FM, (2) pain, (3) fatigue, (4) sleep, (5) stress, and (6) living well with FM.

Measures. All assessments were conducted in 1 day.

Body mass index (BMI). The BMI was calculated by dividing the weight in kilograms by height squared in meters.

Community Health Activities Model Program for Seniors (CHAMPS). CHAMPS is a 15-min survey that asks about the frequency and duration of physical activity in a typical week of the past month. The CHAMPS questionnaire provides a list of various activities ranging from light to vigorous intensity. Research supports the validity, reliability, and sensitivity to changes of CHAMPS among older adults[22]. The questionnaire provides measures of estimated hours per week spent performing light, moderate, and vigorous physical activity[22]. We concentrated on light to moderate physical activity (LMPA) because our exercise prescription was focused on LMPA, and vigorous exercise is poorly tolerated by patients with FM[23].

Fibromyalgia Impact Questionnaire (FIQ). The FIQ is a disease-specific, well-validated measure assessing a number of functioning domains related to FM[18]. The FIQ includes the FIQ-physical impairment, 6 visual analog scales for measuring FM-related symptoms (e.g., pain and fatigue), and 2 single-item questions assessing work status and overall well-being. A higher FIQ total score (range 0 to 100) indicates greater severity of global FM symptoms.

Medical Outcomes Study Short Form-36 (SF-36). The SF-36 is a multipurpose, short-form health survey with 36 questions on various aspects of health. For our current study, we calculated the physical functioning (PF) scale to assess physical function. The 10-item PF scale measures patient's perception of their limitations in the performance of various types of physical activities. Scale scores range from 0 to 100, with higher scores indicating better functioning. The psychometric properties of the PF scale are well established in patients with chronic pain[24], with demonstrated responsiveness to both medical and nonmedical interventions in individuals with FM[25,26].

Patient Health Questionnaire 8 (PHQ-8). The PHQ-8 Depression Scale is a self-administered scale that assesses core symptoms of major depressive disorder. Scores can range from 0 to 24; higher scores indicate more severe depressive symptoms[27].

BPI. The BPI is a measure of pain with proven reliability and validity across different pain conditions[28], including FM[29]. In our report, BPI pain severity is the average of 4 items asking about current, worse, least, and average pain in the past week.

Statistical analyses. Repeated ANOVA measures were used to assess treatment effects within each category. Mixed linear models were used for our analysis to control for covariates and to use the appropriate covariance structure. All analyses were adjusted for the baseline value of the outcome and BMI. BMI was the only baseline characteristic that was significantly different between MI and AC. All analytic assumptions for the statistical models were verified and all analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

Figure 1 shows the flow of participants in the trial. As seen in Table 1, baseline characteristics were similar across treatment groups except for BMI. MI participants were slightly heavier than AC participants (p = 0.07). At study entry, 71 (33%) were taking opioids while 145 (67%) were not. Of the 71 participants taking opioids, 32 (45%) participants were taking hydrocodone, 13 (18.3%) were taking propoxyphene, 7 (9.8%) were taking oxycodone (short- and/or long-acting), 1 (1.4%) was taking morphine, and 18 (25.3%)

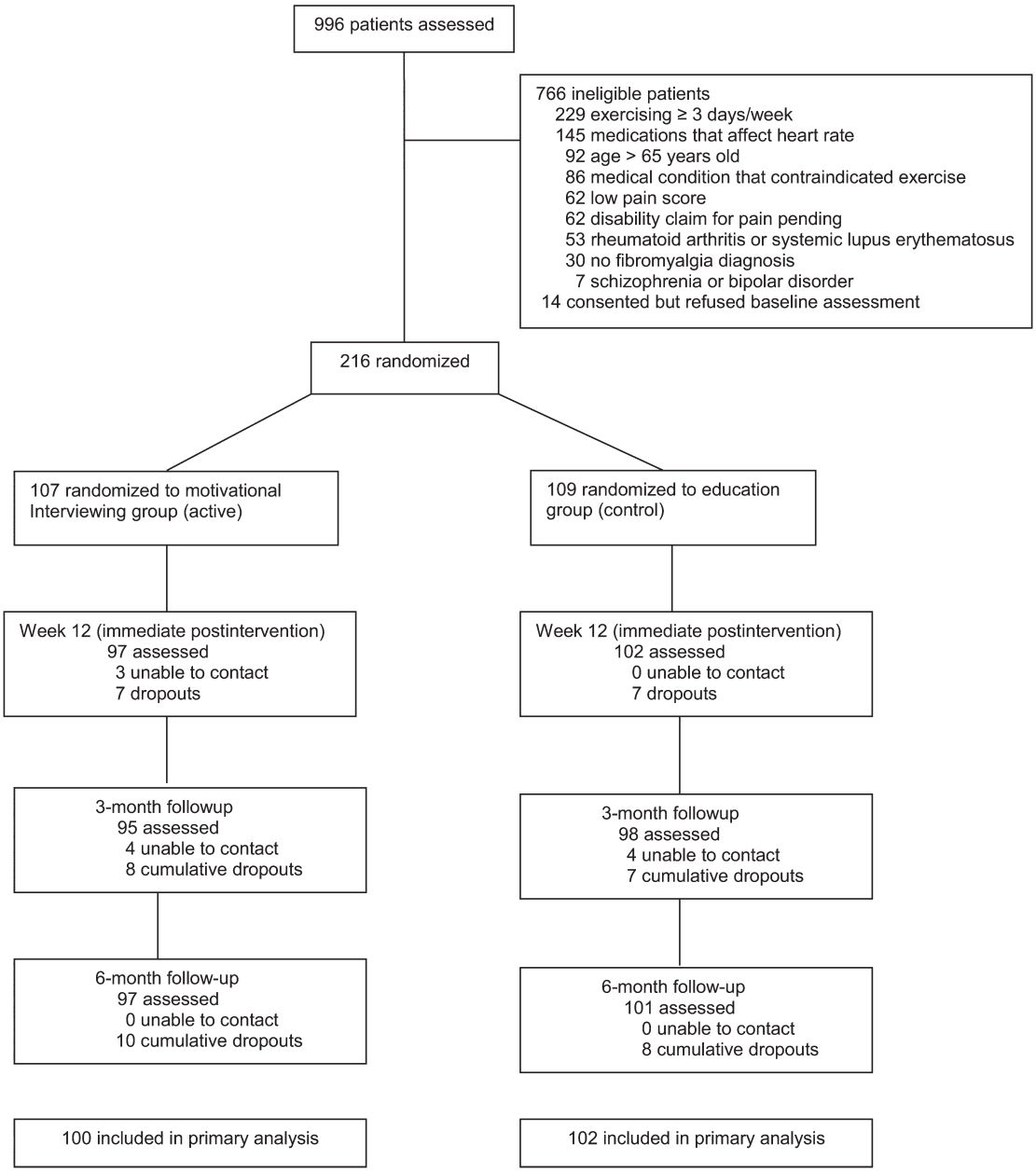

Figure 1. Flowchart of participants in the parent trial.

Table 1. Baseline characteristics. Values are the mean (SD) unless otherwise specified.

Characteristics	Motivational Interviewing, n = 107	Attention Control, n = 109
Demographics		
Age, yrs	46.0 (11.4)	45.7 (11.0)
Female, %	96	95
Non-Hispanic, %	99.1	98.2
White, %	90.7	86.2
Education, > high school, %	76.6	78.9
Married, %	57.9	64.2
Employed, %	57.9	49.5
Clinical variables		
Body mass index, kg/m^2	32.3 (7.6)	30.5 (6.6)
FM diagnosis duration, yrs	8.9 (6.4)	9.1 (7.6)
PHQ-8 depression, range 0–24*	12.4 (4.8)	12.7 (5.1)
BPI pain severity, range 0–10*	5.9 (1.2)	6.0 (1.4)
SF-36 physical function	41.36 (17.7)	40.28 (20.2)
FIQ total, range 0–100*	67.5 (12.0)	66.6 (13.5)
Prescribed medications, %		
Nontricyclic antidepressants	66.4	57.8
Anticonvulsants	31.8	27.5
Opioid analgesics	32.7	33.0
Physical activity, self-report		
CHAMPS		
LMPA, h/week	6.5 (5.6)	6.7 (7.4)

* Higher score indicates a worse state of health (except for SF-36 physical function). FM: fibromyalgia; PHQ-8: Patient Health Questionnaire 8; BPI: Brief Pain Inventory; SF-36: Medical Outcomes Study Short Form-36; FIQ: Fibromyalgia Impact Questionnaire; CHAMPS: Community Health Activities Model Program for Seniors; LMPA: light to moderate physical activity.

were taking 2 or more classes of opioids. None of the participants were receiving codeine or tapentadol. Compared with nonusers, opioid users had fewer years of education (≥ high school graduate 67.6% vs 82.8%, p = 0.012), higher mean (± SD) depression scores on the PHQ-8 questionnaire (14.08 ± 5.14 vs 11.79 ± 4.65, p = 0.001), worse physical function on the SF-36 questionnaire (36.62 ± 18.47 vs 42.96 ± 18.94, p = 0.022), and worse total scores on the FIQ (70.99 ± 12.30 vs 65.12 ± 12.53, p = 0.001). There were no statistically significant differences between nonusers and users of opioid regarding BPI pain severity [nonusers 5.86 (1.25) vs users 6.15 (1.30), p = 0.115] and the amount of LMPA [nonusers 6.58 (6.78) vs users 6.66 (5.98) h/week, p = 0.927].

Main outcomes. Table 2 shows the comparison between the MI and AC groups stratified by opioid usage. Among opioid nonusers, MI (vs AC) was associated with significantly greater improvement in SF-36 physical function, greater reduction in BPI pain and global FM severity, and a larger increase in the amount of LMPA. On the other hand, among opioid users, there were no significant treatment group differences in SF-36 physical function, BPI pain, global FM severity, and the amount of LMPA.

DISCUSSION

In our secondary analysis of a randomized controlled trial using MI to promote physical activity in FM, MI improved physical function, reduced pain and global FM severity, and increased the volume of LMPA among opioid nonusers, but not among opioid users.

MI was developed as a cognitive-behavioral strategy using a collaborative conversation approach for strengthening a person's motivation and commitment to behavior change[30]. MI has demonstrated effectiveness in nonpharmacological management of obesity[31], self-management of chronic pain[32], and medication adherence[33]. A metaanalysis found a moderate level of evidence that MI had a small effect in increasing physical activity levels in adults with obesity, CV condition, or multiple sclerosis[8]. Except for our previously completed randomized controlled trial[9], no study to date has used MI to promote physical activity in individuals with chronic pain.

Unlike other medical patient populations, patients with chronic pain are fearful that exercise might exacerbate their existing pain or result in a new injury or pain site, which may interfere with their planned physical exercise program[34]. Fear of pain is a potent inhibitor that keeps patients with chronic pain from regular exercise regimens. Most patients with FM need more than advice to exercise; they need assistance overcoming the barriers to exercise. Our MI program was designed to elicit self-motivational statements, help participants develop a plan for change, and provide strategies and plans to overcome barriers and maintain the intended behavioral changes.

Table 2. Change from baseline to Week 36. Values are means (standard errors) adjusted for baseline outcome and body mass index.

Change from Baseline to Week 36	MI	AC	p
Improvement in SF-36 physical function			
Opioid users	10.25 (1.94)	7.00 (1.87)	0.234
Opioid nonusers	14.47 (1.23)	9.66 (1.22)	0.006*
Reduction in BPI pain severity			
Opioid users	–0.80 (0.17)	–0.76 (0.16)	0.930
Opioid nonusers	–1.49 (0.12)	–0.98 (0.12)	0.004*
Improvement in global FM severity, FIQ total			
Opioid users	–9.60 (1.71)	–9.49 (1.66)	0.963
Opioid nonusers	–15.47 (1.21)	–11.85 (1.20)	0.036*
Increase in LMPA**			
Opioid users	3.64 (0.84)	3.26 (0.82)	0.746
Opioid nonusers	4.68 (0.52)	3.01 (0.51)	0.023*

* $p < 0.05$; analyses included subjects (n = 198, 92% of 216) with 6-month followup data. ** No. hours per week. MI: motivational interviewing; AC: attention control; SF-36: Medical Outcomes Study Short Form-36; BPI: Brief Pain Inventory; FM: fibromyalgia; FIQ: Fibromyalgia Impact Questionnaire; LMPA: light to moderate physical activity.

In our primary outcome paper[9], 6 months after completion of treatment, MI was not superior to AC in any of the physical activity and clinical measures. We postulate that the use of opioid may have attenuated the beneficial effects of MI to promote physical activity. One possible explanation is that opioids may impair cognition[35]. Opioids decrease activation in regions involved in cognitive control and attention, such as the dorsolateral prefrontal cortex, anterior cingulate cortex, and inferior parietal lobes, resulting in deficits in executive function[36]. Individuals who were dependent on opioids had volumetric loss in the amygdala, which is responsible for emotions, survival instincts, and memory[37]; they also showed decreased functional connectivity for the anterior insula, nucleus accumbens, and amygdala subdivisions[38]. Opioid receptors, including the mu (MOR), delta, and kappa, interact with both endogenous and exogenous opioids[39]. In animal studies, administration of a selective MOR agonist and endogenous MOR agonists impair working memory[40]. In a study of 93 opioid-dependent patients and 30 normal controls, the opioid dependents had poorer neuropsychological performance, including verbal fluency, attention, and memory. After 1 week of detoxification, the opioid-dependent group performed equally well compared with the normal controls[41]. These studies suggest that opioid usage could impair cognition that may hinder processing and retention of information delivered during an MI session.

A second possible explanation is that the common side effects (i.e., fatigue and sleep disorder) of opioids might have (indirectly) resulted in lower physical activity[42]. The association between opioid and sleep-disordered breathing is well established[43]. Among chronic opioid users who underwent overnight polysomnography, 36% had obstructive sleep apnea, 24% had central sleep apnea, 21% had combined obstructive and central sleep apnea, and only 15% did not have sleep apnea[44]. Compared with well-matched healthy controls, the chronic opioid group had a significantly higher apnea-hypopnea index (43.5/h vs 30.2/h, $p < 0.05$), indicating more sleep disturbance[45]. Opioids also reduce rapid eye movement (REM) and non-REM phases of sleep[46]. Among our study participants, opioid-induced daytime sleepiness and fatigue may have rendered exercise-based MI seemingly less effective.

Finally, the use of opioid could be a surrogate marker of patients who are more complex to treat and less likely to respond to any treatment. In our study, compared with nonusers, participants who used opioids had greater functional impairment (as measured by SF-36 physical function) and FM-related symptom burden (as measured by FIQ). The association of the use of opioids with greater psychological distress and worse health status is well reported in the literature[47,48].

Our current study has some limitations. Given that the current report was a posthoc analysis of a previously completed RCT, our study findings could have resulted from Type 1 error (i.e., false-positive findings among nonusers of opioids) and/or Type 2 error (i.e., false-negative among opioid users). Therefore, appropriate caution about the conclusions must be made. However, our study findings were consistent across all 4 outcome measures in both groups of participants. Further, there are plausible neurological, biological, and neuropsychological mechanisms[44] that support the concept that opioids may reduce the efficacy of MI. A future larger study is needed to confirm our study findings. Second, we defined opioid users and nonusers based on self-report (verified by the medication container) at the time of the enrollment. We did not consider drug changes during the study. Participants who self-reported opioid use at study entry might have discontinued the medication during the study, and vice versa. However, cross-contamination between nonusers and users would only weaken (rather than

magnify) the differential treatment effects that we observed. Third, tramadol was not considered an opioid in our study. However, the proportions of subjects taking tramadol were not significantly different between opiate nonusers and users [30 (20.7%) vs 13 (18.3%), p = 0.7], and thus it should not bias the study results. Nevertheless, our study results did not change when the 30 nonusers who were receiving tramadol were reclassified as opiate users (data not shown). Fourth, although we defined opioid users as participants who have been receiving opioids > 2 weeks, we did not distinguish chronic versus acute use of opioids. However, a previous study reported that a significant majority of patients with FM who were prescribed opioids were still taking them 1 year later[49]. Thus, our participants were likely chronic users of opioids. Nonetheless, some opioid users might have been taking them for only a short time period (e.g., 2–12 weeks). In addition, we only measured patient-reported outcomes, not performance-based outcomes, while it is known that there is disagreement between the 2 outcomes[50]. Finally, it would have been interesting to see whether the total daily dose of opioids influences the study outcome. Unfortunately, we did not collect such information to assess a possible dose-response relationship.

To our knowledge, our study is the first to show that exercise-based MI was associated with sustained benefits in increasing physical activity and improving clinical outcomes in patients with FM who were nonopioid users. In today's world of cost-conscious healthcare delivery, it is important to precisely predict treatment effect and tailor treatment to maximize effects. Clinicians may consider offering exercise-based MI among patients who are not taking opioids to enhance FM-relevant treatment outcomes. Further, our study raises an important testable hypothesis that opioids may attenuate the benefits of psychoeducational treatment intervention (i.e., MI) in patients with FM. Using brain neuroimaging and neurophysiologic tools, future investigations should seek to understand the relationships among physical activity, opioids, and the neural substrate of motivation.

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