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A Six-Month Randomized Controlled Trial of Exercise and Pyridostigmine in the Treatment of Fibromyalgia

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Abstract

Objective—A subset of fibromyalgia (FM) patients have a dysfunctional hypothalamic–pituitary–insulin-like growth factor 1 (IGF-1) axis, as evidenced by low serum levels of IGF-1 and a reduced growth hormone (GH) response to physiologic stimuli. There is evidence that pyridostigmine (PYD) improves the acute response of GH to exercise in FM patients. The purpose of this study was to evaluate the clinical effectiveness of 6 months of PYD and group exercise on FM symptoms.

Methods—FM patients were randomized to 1 of the following 4 groups: PYD plus exercise, PYD plus diet recall but no exercise, placebo plus exercise, and placebo plus diet recall but no exercise. The primary outcome measures were the visual analog scale (VAS) score for pain, tender point count, and total myalgic score. Secondary outcome measures were the total score on the Fibromyalgia Impact Questionnaire (FIQ) and FIQ VAS scores for individual symptoms (fatigue, poor sleep, stiffness, and anxiety), as well as quality of life (QOL) and physical fitness (lower body strength/endurance, upper and lower body flexibility, balance, and time on the treadmill).

Results—A total of 165 FM patients completed baseline measurements; 154 (93.3%) completed the study. The combination of PYD and exercise did not improve pain scores. PYD groups showed a significant improvement in sleep and anxiety in those who completed the study and in QOL in those who complied with the therapeutic regimen as compared with the placebo groups. Compared with the nonexercise groups, the 2 exercise groups demonstrated improvement in fatigue and fitness. PYD was generally well tolerated.

Conclusion—Neither the combination of PYD plus supervised exercise nor either treatment alone yielded improvement in most FM symptoms. However, PYD did improve anxiety and sleep, and exercise improved fatigue and fitness. We speculate that PYD may have improved vagal tone, thus benefiting sleep and anxiety; this notion warrants further study.

Fibromyalgia (FM) is a disorder characterized by persistent widespread pain and tender points (1). However, most FM patients have multiple symptoms (2). While the concept of central sensitization is increasingly accepted as an important pathophysiologic aberration in FM patients, the factors that contribute to its persistence are not well-characterized (3). FM patients

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have low levels of physical fitness and often experience post-exertional pain, fatigue, and delayed onset of muscle soreness (4,5). Muscle tissue may be an important source of postexertional symptom flares through the mechanism of muscle microtrauma (6,7). It has been hypothesized that reduced insulin-like growth factor 1 (IGF-1) levels may predispose some FM patients to the development of exercise-induced muscle microtrauma (8). Approximately one-third of FM patients have low levels of IGF-1 (9,10), the major effector molecule that mediates the anabolic effect of growth hormone (GH) on muscle (11).

Treatment of FM patients with GH has been reported to be of some clinical benefit (12), but GH is seldom prescribed because of its high costs and concerns regarding its long-term usage (13). GH secretion in FM patients can be acutely increased by the use of pyridostigmine (PYD; an acetylcholine esterase inhibittor) in combination with exercise (14). Regular low-grade exercise has an established role in the management of FM patients (4) and is also a stimulus for GH secretion (15,16). The aim of this study was to explore whether the long-term use of PYD and regular exercise could improve symptoms in FM patients by stimulating the hypothalamic–pituitary–IGF-1 axis.

Patients and Methods

Study design

The study was a single-center, 6-month, randomized, blinded, controlled clinical trial with a 2 × 2 × 2 design (training exercise × PYD × time). Patients were randomly assigned to 1 of 4 groups (PYD plus exercise, PYD plus diet recall but no exercise, placebo plus exercise, and placebo plus diet recall but no exercise) by the study team's statistician (NAP), who had no contact with the subjects. Age, sex, and body mass index (BMI) were block factors in the random assignment.

The laboratory portion of the study was conducted at the Clinical Translational Research Institute (CTRI) of Oregon Health & Science University. The training exercise intervention was conducted in a specially designed suspended wood-floor aerobics studio at the School of Nursing. The diet recall interviews for attention control were conducted in a private office at the School of Nursing. The Institutional Review Board and CTRI at Oregon Health & Science University approved the protocol, and all study subjects provided their written informed consent.

Study inclusion criteria

The target population consisted of adults of both sexes who were ages 18–65 years, had been diagnosed as having primary FM according to the American College of Rheumatology (ACR) criteria (1), and were medically able to engage in an exercise program. The diagnosis of FM was confirmed at the initial laboratory visit.

Study exclusion criteria

Patients with any of the following conditions were excluded from the study: 1) current or past cardiovascular, pulmonary, neurologic, endocrine, or renal disease that would preclude involvement in an exercise program (specifically, hypertension, chronic obstructive pulmonary disease, uncontrolled asthma, hypothyroidism, severe depression, pituitary disease, or surgery); 2) current use of the study drug, high-dose β-blockers (which could significantly affect the normal physiologic response to exercise), or systemic steroids (which might affect GH secretion); 3) currently exercising >30 minutes/week; 4) score of ≥29 on the revised Beck Depression Inventory (BDI-R) as modified for use in FM patients; 5) BMI >45 kg/m^2; 6) women who were pregnant or nursing; 7) planned elective surgery during the study period; or 8) ongoing, unresolved litigation.

Population sampling and setting

Participants were randomly selected from a large database of FM patients who have been seen upon referral to our university tertiary care center. The probability of adequate representation of low income and minority participants was increased by planned oversampling from the database in zip code areas known to have a higher percentage of minority populations.

Power analysis

Data from previous studies (13,16) were used to calculate the study power and sample size. In the acute exercise plus PYD study (14), serum GH was the primary outcome variable and was found to be a mean ± SD of 0.57 ± 0.82 ng/ml at rest and 4.70 ± 3.80 ng/ml after PYD plus exercise in a sample of 20 women with FM.

Assuming the same effect size for the placebo plus no exercise group as compared with the PYD plus no exercise group in our proposed study, a total of 30 participants in each group would provide statistical power >0.95 for an alpha level of 0.05. A sample size of 30 in each group would also provide adequate power for testing changes in pain, FM symptoms, and quality of life (QOL). Based on these data, we planned to enroll 144 patients (36 per group at baseline), which would allow for 18% attrition over the study period.

Study assessments

Demographic data, such as age, weight, height, BMI, estrogen status (menopause status and/or use of estrogen), current medications, and duration of FM were obtained at baseline.

Pain was the primary outcome variable. A combination of 3 pain measures was evaluated before and after the study intervention: the visual analog scale (VAS) for pain, which is a subscale of the Fibromyalgia Impact Questionnaire (FIQ), the number of tender points, and the total myalgic score. The number of tender points and the total myalgic score were measured at 18 sites as described in the ACR criteria for FM (1). The degree of tenderness at each site was based on the patient's response (scored 0–3, where 0 = no pain and 3 = withdrawal from the examiner) to digital application of pressure at a rate of 0–4 kg over a period of 4 seconds at the 18 specific tender points. This test was performed by a single examiner. The 10-cm VAS for pain (a subscale of the FIQ) rated the patient's perception of pain intensity over the previous 7 days, with anchors at 0 (no pain) and 10 (very severe pain).

Other FM symptoms were measured with the FIQ. The FIQ is a 10-item instrument that uses a 0–10-cm VAS to measure physical functioning and symptoms of pain, fatigue (0 = no tiredness and 10 = extreme tiredness), sleep (0 = awakening unrefreshed and 10 = awakening well-rested), stiffness (0 = no stiffness and 10 = very stiff), anxiety (0 = no anxiety and 10 = very anxious), and depression (0 = no depression and 10 = very depressed), along with levels of disability and overall well-being during the previous week. Total FIQ scores range from 0–100, with higher values indicating a more negative impact of FM. The FIQ has been extensively validated and has shown good sensitivity to change (17). In this study, the reliability (Cronbach's alpha) of the total myalgic score was 0.87, and the reliability (Cronbach's alpha) of the total FIQ was 0.88.

The level of depression was evaluated with the BDI-R (18). The BDI-R is a 21-item scale that measures mood and behaviors characteristic of depression. Potential participants who scored ≥29 were excluded from the study and referred for more appropriate therapy (19). In this study, the reliability (Cronbach's alpha) of the BDI-R was 0.87.

The Quality of Life Scale is a 16-item Likert-type scale that measures well-being and satisfaction in multiple domains of life. Scores for each item range from 1 (terrible) to 7

(delighted). Possible scores range from 6 to 112, with higher scores indicating better well-being and quality of life. The Quality of Life Scale has been validated in a sample of FM patients (internal consistency reliability α = 0.82–0.88; test-retest reliability r = 0.84) and is sensitive to change in FM patients (20,21). The reliability (Cronbach's alpha) of the Quality of Life Scale in this study was 0.90.

Flexibility, strength/endurance, and balance were assessed with field measures. Upper body flexibility was measured by asking participants to reach behind their head with 1 arm, extending their reach as far below the neck as possible. While that arm was extended behind them, the participants were asked to reach behind their back with the other arm, extending their reach up toward the scapula as far as possible. While both arms were behind the subject's back, the space between the extended fingertips was measured (in cm). Higher numbers indicated greater impairment of flexibility. The best of 3 attempts was recorded.

Lower body flexibility was measured by asking seated participants to extend 1 arm toward their toes on the same side of the body. The space between the fingertips and toes was measured (in cm). Higher numbers indicated greater impairment of flexibility. Negative numbers were recorded if the subject was able to reach beyond the toes. The best of 3 attempts was recorded.

Lower body strength/endurance was measured by asking participants who were seated in a wooden chair to cross their arms in front of their chest and to rise from a seated position to a standing position as many times as possible in 30 seconds. The first attempt was recorded.

Balance was measured while participants were standing with their arms at their sides and with their eyes open. They were asked to lift 1 foot no more than 3 inches from the floor and to maintain their balance in this position as long as possible. The duration was measured (in seconds). Poorer balance resulted in lower scores. The best of 3 attempts was recorded.

Study procedures

The study patients completed the treadmill testing to $\dot{V}o_2$ max and blood draws as previously described (22). Lower body strength/endurance, upper and lower body flexibility, and balance were then measured, and questionnaires were administered.

Study subjects were randomized via stratified block (age in 5-year blocks, BMI in 3-point blocks, and sex) into 4 treatment groups: PYD plus exercise, PYD plus diet recall but no exercise (exercise control group), placebo plus exercise (drug control group), and placebo plus diet recall but no exercise (drug and exercise control group). The dosage of PYD bromide (Mestinon; kindly provided by Valeant Pharmaceuticals, Costa Mesa, CA) or identical placebo tablets (also provided by Valeant Pharmaceuticals) was titrated to the full dosage of 180 mg/day over the following 11 days. The titration protocol was one-half pill on day 1, increasing by one-half pill each day until the patient was taking 1 pill (60 mg) 3 times a day. The total dose was based on our previous single-dose trial (14) and clinical experience (23). Patients were instructed to take the study drug in the morning, 1 hour prior to exercise class (based on our pilot data), and at bedtime to maximize GH release during stages 3 and 4 sleep, when 70–80% of GH is produced (24). Patients completed a monthly log, recording exercise periods, study drug intake, food intake, and any side effects they might be experiencing. Each month, information from the logs was used to confirm the dose of training exercise, to monitor for compliance with the medication regimen, to monitor for adverse events, and to document side effects of the drug.

Training exercise treatment protocol—The training exercise was supervised by an instructor certified by the American Council on Exercise as a Clinical Exercise Specialist; this instructor was not responsible for collecting outcome data. Exercises were group-based (10–

20 per group), 60-minutes in duration, and were conducted 3 times each week for 6 months. The format included low-impact, nonrepetitive cardioaerobics training for 30 minutes, strength training for 10 minutes, flexibility training for 5 minutes, balance training for 5 minutes, and relaxation for 10 minutes. The intensity goal was 40–50% of the patient's maximum heart rate or a perceived exertion of 10–12 of a total of 20, as measured by the Borg Scale.

Progressive strength training was accomplished with 3 variations of elastic bands (kindly provided by Thera-Band, Akron, OH) and free weights. All major muscle groups were exercised while minimizing work over the head, keeping movements near the midline of the body, and reducing the speed of concentric contractions compared with the speed of eccentric contractions. Weights were relaxed down or bands were slackened between contractions, allowing for delayed return to resting baseline state (25), as detailed elsewhere (26). Flexibility training to the point of gentle tension included static and nonballistic stretches. Balance training was both static and dynamic, progressing from balancing with both feet on a flat surface, balancing with 1 foot on a flat surface, and then balancing on boards/discs (kindly provided by Thera-Band) to challenge plantar proprioception.

Progressive relaxation was achieved without muscle tensing and included guided imagery with breathing awareness. The intensity of exercises were purposefully lower than the intensity described in the guidelines of the American Academy of Sports Medicine, based on our recognition of baseline physical deconditioning in FM patients that predisposes them to enhanced delayed muscle pain, symptom flare, and aggravation of FM tender point areas.

Protocol for attention control—All patients who were not randomized to an exercise group received weekly telephone calls and a 2-hour monthly visit from a registered nurse. The study subjects provided dietary data by completing objective diet recall surveys (27) and provided a narrative diet history.

All study subjects returned at the end of the 6-month study for a second treadmill test. The procedures were the same as at baseline, with 1 key difference: one half of the study subjects were given 1 60-mg tablet of PYD and the other half were given placebo, depending on their group assignment, 1 hour before stepping on the treadmill. In the event that a patient requested to withdraw from the study, the final laboratory visit was conducted within 2 weeks of withdrawal, if the patient agreed to this.

Statistical analysis

The purpose of this study was to test whether daily PYD plus supervised exercise would improve clinical symptoms of FM as a result of increased levels of IGF-1. The primary outcome measures were the FIQ pain VAS score, the tender point count, and the total myalgic score. Secondary outcome measures were scores on the total FIQ and individual VAS items of the FIQ, as well as QOL, lower body strength/endurance, balance, flexibility, and time on the treadmill. The analyses were conducted on data from patients who completed the study and not on the intent-to-treat population. Preliminary analyses included one-way analyses of variance and chi-square tests to examine statistical differences between the 4 groups at baseline. The main hypotheses of the study were tested using 2 × 2 (PYD versus placebo) × 2 (exercise versus no exercise) analysis of covariance (ANCOVA), controlling for the baseline value of the variable of interest. The adjusted means that were used for the ANCOVAs and are reported in the text are the part of the posttest scores that could not be predicted by the pretest scores or the residualized posttest scores.

Results

Characteristics of the study patients

One hundred sixty-five patients with FM completed the baseline assessments. These patients were randomized into 1 of 4 groups: 43 were randomized to PYD plus exercise, 42 to PYD plus diet recall but no exercise, 39 to placebo plus exercise, and 41 to placebo plus diet recall but no exercise. Eleven of these 164 enrolled patients failed to attend the 6-month followup visit (Figure 1).

The demographic features of the 165 patients who completed the baseline assessments are shown in Table 1. There were no statistically significant differences at baseline between the 4 groups. Estrogen status did not correlate with any symptom, fitness variable, or physiologic variable. For descriptive purposes, the raw means and SDs for all outcomes are presented in Tables 2 and 3, by drug intervention groups. The adjusted means from the ANCOVAs, which were the basis of the statistical tests, are presented in the text.

Results of the primary outcome measures

The primary aim of this study, that daily PYD plus supervised exercise would improve pain scores (as determined with the FIQ VAS scores, the number of tender points, or the total myalgic score) was not substantiated by the results. For the pain VAS score, the interaction of PYD and training exercise ($F[1,143] = 0.04$, $P = 0.849$), the main effect of PYD ($F[1,143] = 0.97$, $P = 0.325$), and the main effect of exercise ($F[1,143] = 2.39$, $P = 0.124$) failed to reach significance. For the total myalgic score, the interaction of PYD and training exercise ($F[1,146] = 0.10$, $P = 0.751$), the main effect of PYD ($F[1,146] = 1.13$, $P = 0.289$), and the main effect of exercise ($F[1,146] = 0.05$, $P = 0.831$) failed to reach significance. Additionally, for the number of tender points, the interaction of PYD and training exercise ($F[1,146] = 0.29$, $P = 0.592$), the main effect of PYD ($F[1,146] = 0.41$, $P = 0.525$), and the main effect of exercise ($F[1,146] = 1.78$, $P = 0.0184$) failed to reach significance.

Results of the secondary outcome measures

Patients who completed the study demonstrated no significant improvements in QOL, total FIQ score, FIQ stiffness VAS score, or FIQ depression VAS score. Thus, no further details on these analyses will be presented. However, there were improvements in several other outcome measures: fatigue, sleep, and anxiety levels, lower body flexibility, and balance.

Fatigue VAS scores—For fatigue, neither the interaction of PYD and training exercise nor the main effect of PYD was significant. However, the main effect of exercise training on fatigue was significant ($F[1,144] = 7.66$, $P = 0.006$). Collapsing the 4 groups into 2 according to exercise and no exercise, the groups who participated in the training exercise reported less fatigue (adjusted mean ± SEM VAS scores 6.19 ± 0.26) than did the no training exercise groups (adjusted mean ± SEM VAS scores 7.20 ± 0.26) at followup, controlling for baseline levels of fatigue.

Sleep VAS scores—For sleep, neither the interaction of PYD and training exercise nor the main effect of training exercise was significant. However, the main effect of PYD on sleep was significant ($F[1,143] = 8.38$, $P = 0.004$) (Figure 2). Collapsing the 4 groups into 2 according to PYD and placebo treatment, the PYD-treated groups reported less nonrefreshing sleep (adjusted mean ± SEM VAS scores 6.20 ± 0.26) than did the placebo-treated groups (adjusted mean ± SEM VAS scores 7.25 ± 0.25) at followup, controlling for baseline sleep values.

Anxiety VAS scores—For anxiety, neither the interaction of PYD and training exercise nor the main effect of training exercise was significant. However, the main effect of PYD on anxiety

was significant (F[1,144] = 7.02, $P = 0.009$) (Figure 3). Collapsing the 4 groups into 2 according to PYD and placebo treatment, the PYD-treated groups reported less anxiety (adjusted mean ± SEM VAS scores 3.25 ± 0.30) than did the placebo-treated groups (adjusted mean ± SEM VAS scores 4.37 ± 0.30) at followup, controlling for baseline levels of anxiety.

Lower body flexibility—For lower body flexibility, neither the interaction of PYD with training exercise nor the main effect of PYD was significant. However, the main effect of exercise training on lower body flexibility was significant (F[1,146] = 7.81, $P = 0.006$). Collapsing the 4 groups into 2 according to exercise and no exercise, the groups who participated in the training exercise had better lower body flexibility (adjusted mean ± SEM cm 5.28 ± 1.02) than did the no training exercise groups (adjusted mean ± SEM cm 1.17 ± 1.05) at followup, controlling for baseline lower body flexibility values.

Balance—For balance, neither the interaction of PYD with training exercise nor the main effect of PYD was significant. However, the main effect of exercise training on balance was significant (F[1,145] = 10.64, $P = 0.001$). Collapsing the 4 groups into 2 according to exercise and no exercise, the groups who participated in the training exercise had better balance (adjusted mean ± SEM seconds 67.93 ± 5.71) than did the no training exercise groups (adjusted mean ± SEM seconds 41.23 ± 5.87) at followup, controlling for baseline balance values.

Findings in patients who were compliant with the PYD regimen

The subjects who took ≥75% of their PYD pills (n = 133) were analyzed separately. This group was found to have a significant improvement in QOL (F[1,126] = 7.97, $P = 0.006$). Collapsing the 4 groups into 2 according to PYD and placebo treatment, the PYD-treated groups reported higher QOL scores (adjusted mean ± SEM 78.39 ± 1.37) than did the placebo-treated groups (adjusted mean ± SEM 73.26 ± 1.16) at followup, controlling for baseline QOL values.

Findings in patients who were compliant with the exercise regimen

We also examined the effect of the intervention for patients who complied with the training exercise regimen by excluding participants who attended <50% of the exercise classes (n = 123). No significant effects for the interaction or the main effect of PYD emerged in these exercise compliance analyses. However, the main effects of training exercise emerged as significant: $\dot{V}o_2$ max (F[1,114] = 7.91, $P = 0.006$), time on the treadmill (F[1,117] = 7.68, $P = 0.006$), upper body flexibility (F[1,115] = 12.31, $P = 0.001$), and lower body strength/endurance (F[1,115] = 6.81, $P = 0.010$). The training exercise groups had higher $\dot{V}o_2$ max values (adjusted mean ± SEM 21.75 ± 0.44 ml/kg) than did the no training exercise groups (adjusted mean ± SEM 20.14 ± 0.36 ml/kg) at followup, controlling for baseline $\dot{V}o_2$ max values. The training exercise groups had a longer time on the treadmill (adjusted mean ± SEM 707.01 ± 26.53 seconds) than the no training exercise groups (adjusted mean ± SEM 611.93 ± 21.71 seconds) at followup, controlling for baseline time on the treadmill. The training exercise groups had better upper body flexibility (adjusted mean ± SEM cm −4.80 ± 0.86) than did the no training exercise groups (adjusted mean ± SEM cm −8.69 ± 0.69) at followup, controlling for baseline upper body flexibility levels. The training exercise groups had better lower body strength/endurance (adjusted mean ± SEM number of rises from seated position 13.33 ± 0.45) than did the no training exercise groups (adjusted mean ± SEM number of rises from seated position 11.79 ± 0.37) at followup, controlling for baseline lower body strength/endurance.

To explore relationships between serum markers at baseline and symptoms of FM, we examined their correlations. We found no significant correlation between the total IGF-1 level or the age-adjusted IGF-1 level and any symptoms of FM. However, we did find a significant correlation between GH levels at $\dot{V}o_2$ max and the pain (r = −0.21, $P = 0.006$) and stiffness (r

= −0.27, $P = 0.001$) scores. Correlations between serum markers (GH, IGF-1, and IGFBP-3), fitness levels, and anthropomorphic measures have been described elsewhere (22).

Safety

In a previous study based on data obtained from these patients, we reported in detail on the side effects of PYD in the study participants (22). A significantly larger proportion of the PYD-treated group reported abdominal pain, diarrhea/loose stools, and muscle cramping or twitching. These effects were common, but were cited as the reason for study discontinuation in only 2 of the 11 patients who did not complete the study, perhaps indicating that the severity of the side effects was generally tolerable (22).

Discussion

The rationale for this study was that the daily use of pyridostigmine and regular exercise would stimulate the hypothalamic–pituitary–IGF-1 axis in FM patients and the resulting increase in IGF-1 levels would result in improvement in FM symptoms. As we have previously reported (22), the combination of PYD and regular exercise failed to increase IGF-1 levels, which were low for their age in 58% of the study population. As might have been predicted from this negative response, we found that the primary outcome measures of FIQ pain VAS score, tender point count, and total myalgic score did not improve in the present study. Furthermore, there was no improvement in the following secondary outcome measures: total FIQ score, FIQ fatigue VAS score, FIQ stiffness VAS score, FIQ depression VAS score, QOL, BMI, or percentage of body fat. However, there was a significant improvement in both FIQ restorative sleep VAS score and FIQ anxiety VAS score in the 2 PYD-treated groups, whereas the 2 exercise groups experienced improvements in fatigue VAS score, flexibility, balance, lower body strength/endurance, $\dot{V}o_2$ max, and time on the treadmill.

The improvements in anxiety levels and sleep quality (“awoke well rested”) in subjects taking PYD are intriguing. This is unlikely to be a spurious statistical finding resulting from multiple comparisons, since the predetermined significant P value was set at 0.01 rather than 0.05. We speculate that these improvements may be related to an augmentation of parasympathetic tone as a consequence of the daily use of PYD (28) and regular exercise (29). There is now persuasive evidence that FM patients have dysautonomia, as evidenced by results of heart rate variability studies, tilt-table testing (30), and sympathetic skin responses (31–34). Two common clinical manifestations of dysautonomia are neurally mediated hypotension and postural orthostatic tachycardia syndrome (35,36). Both of these dysautonomia syndromes have shown improvement with regular use of PYD (36). The observed improvement in restorative sleep was unexpected and may be related to recent observations that vagal stimulation can improve alertness and reduce daytime sleepiness (37,38). On the other hand, GH is known to stimulate slow-wave sleep (24), and a transient surge in GH levels related to the nighttime dose of PYD is another possibility. The observed improvement in anxiety is consistent with many reports of reduced heart rate variability in anxiety disorders (39,40) and the ability of PYD to improve heart rate variability (28,41). There is some preliminary evidence that increasing heart rate variability through biofeedback benefits some clinical features of FM (42).

This study is the first to attempt to combine training exercise and a medication in an effort to manipulate the GH–IGF-1 axis in patients with FM and to measure changes in symptoms. It is only the second study to combine a drug and exercise in a randomized controlled trial in FM patients. In an abstract published in 1992, Isomeri et al (43) reported improvement in the pain VAS score with amitriptyline and exercise in FM patients. One other exercise study reported on IGF-1 levels in a randomized controlled strength training intervention conducted for 21

weeks (44). Despite improvements in muscle mass, lower body strength/endurance, and neural recruitment, there was no improvement in IGF-1 levels.

In a previous article using data from this study group (22), we reported that strenuous exercise plus PYD promoted an acute surge in GH levels during testing, but did not increase IGF-1 levels. However, the exercise level achieved during the tri-weekly classes did have beneficial effects in terms of fatigue, flexibility, balance, lower body strength/endurance, $\dot{V}o_2$ max, and time on the treadmill. Presumably, these benefits of exercise, which have been described in many previous studies, are not a result of changes in the hypothalamic–GH–IGF-1 axis. In our previously published review of 46 other published trials of exercise in FM patients (4), fitness and physical function were most often improved as a result of aerobic or mixed-type training programs. Pain, however, was not consistently improved in these trials. At higher exercise intensity, frequency, and duration (exercise dose), there was often a worsening of pain, whereas a lower exercise dose often resulted in clinical improvements. Some of these trials had attrition rates between 30% and 87%, limiting the interpretation of the results and highlighting the difficulty in maintaining compliance in exercise trials in FM. The exercise portion of this study confirms that group-based, mixed-type exercise training in FM is possible and that the attrition rates are low (9%).

The study had several limitations. First, we may not have selected the most sensitive measurement of pain. At the time this study was funded, pain was commonly measured with a single VAS score, a total myalgic score, and a count of tender points. Newer recommendations suggest that the brief pain index and the patient's global assessment of change be used in FM intervention studies (45). Furthermore, there is increasing evidence that the number of tender points is not particularly sensitive to change in the average FM patient. Another possible limitation of the study is that the dose of PYD may not have been adequate or the duration of the trial sufficiently long. To our knowledge, there has never been a PYD dosage-escalation study or placebo comparison in FM patients. We chose the dosage of PYD based on our previous experience with a single-dose protocol and the clinical experience of other FM patient healthcare providers (23).

A future trial with PYD could use an unblinded investigator who adjusts the dosage until the IGF-1 level is normalized, along with a similar adjustment in the dosing of the placebo medication. In the previous study of injectable recombinant GH, there was normalization of the serum IGF-1 level within 4 weeks, but symptom improvements began at 4 months and were still continuing at 9 months (12). This lag time for improvement in symptoms is consistent with the known kinetics of muscle anabolism in patients taking GH (46). In general, 6 months of PYD at a dosage of 60 mg 3 times a day plus FM-tailored group exercise for 60 minutes 3 times a week was safe and well-tolerated. The side effects of the drug, including loosening of stool and increased tearing and salivation, were common, but were well-tolerated by the study subjects. The side effect of abdominal pain was somewhat problematic and was cited by 2 patients as the reason for discontinuing the study.

Overall, our study provides additional objective evidence of abnormalities in the GH–IGF-1 axis in patients with FM, but the combination of PYD and exercise at the dosage and duration tested was not able to increase IGF-1 levels or to improve most FM symptoms, except for anxiety and sleep quality. Future trials aimed toward manipulating the GH–IGF-1 axis in FM patients may include exercise and somatostatin-blocking agents, such as PYD, in combination with GH-releasing hormone secretagogues. Based on the results of this study, it would be reasonable to prospectively study the effects of long-term PYD therapy on heart rate variability and possible interactions with sleep and anxiety levels.

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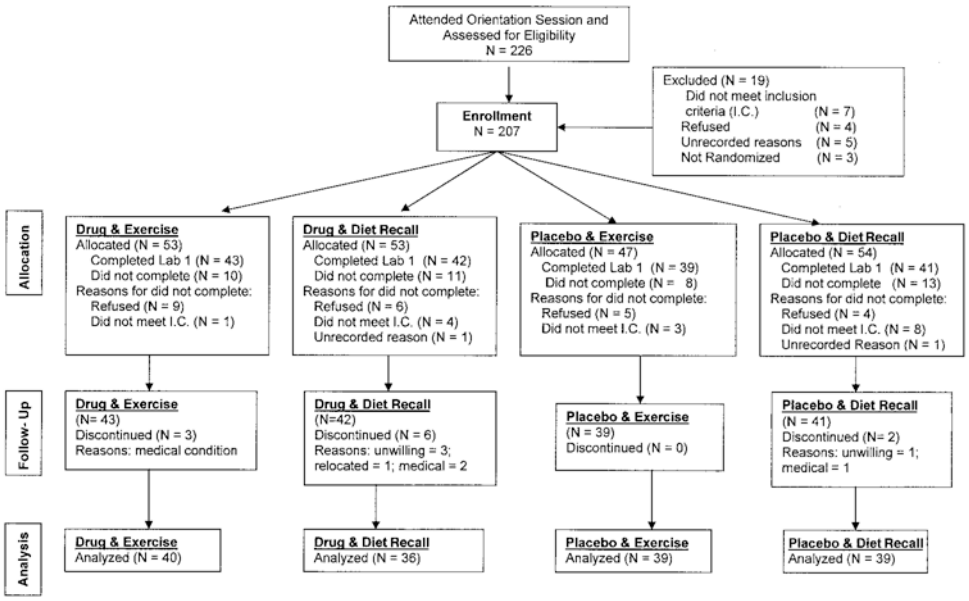

Figure 1.

Distribution of the study patients from initial contact to completion of the study. A total of 165 patients with fibromyalgia completed the baseline measurements, and 154 patients completed the study. Patients were assigned to 1 of 4 groups: pyridostigmine plus exercise, pyridostigmine plus diet recall but no exercise, placebo plus exercise, and placebo plus diet recall but no exercise (see Patients and Methods for details). Adapted, with permission, from ref. 22.

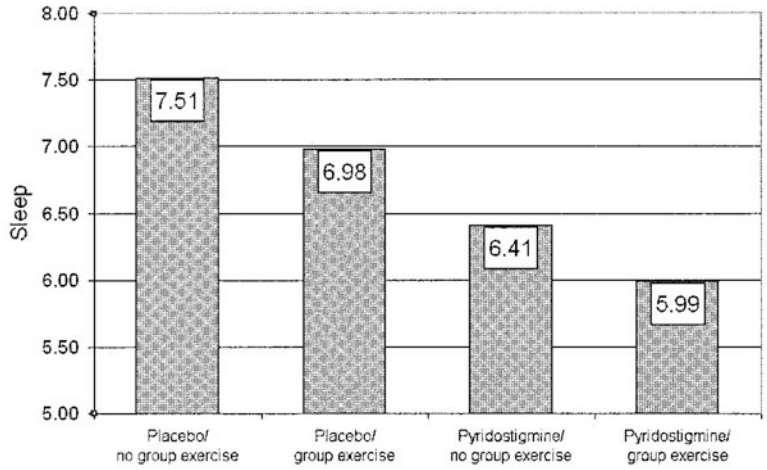

Figure 2.

Improvement in sleep quality with pyridostigmine therapy in patients with fibromyalgia. Patients were assigned to 1 of 4 groups: placebo plus diet recall but no exercise (placebo/no group exercise), placebo plus exercise (placebo/group exercise), pyridostigmine plus diet recall but no exercise (pyridostigmine/no group exercise), and pyridostigmine plus exercise (pyridostigmine/group exercise). Sleep was assessed using a 0–10-cm visual analog scale, where lower scores indicate better sleep. Values are the adjusted mean.

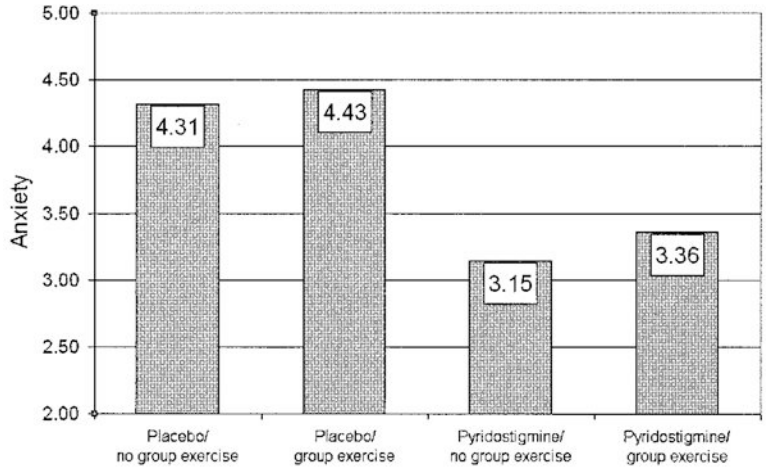

Figure 3.

Improvement in anxiety levels with pyridostigmine therapy in patients with fibromyalgia. Patients were assigned to 1 of 4 groups: placebo plus diet recall but no exercise (placebo/no group exercise), placebo plus exercise (placebo/group exercise), pyridostigmine plus diet recall but no exercise (pyridostigmine/no group exercise), and pyridostigmine plus exercise (pyridostigmine/group exercise). Anxiety symptoms were assessed using a 0–10-cm visual analog scale, where lower scores indicate less anxiety. Values are the adjusted mean.

Table 1

Baseline demographic, clinical, and laboratory data in the 165 fibromyalgia patients, by intervention group*

	Total (n = 165)	Placebo		Pyridostigmine	
		No group exercise (n = 41)	Group exercise (n = 39)	No group exercise (n = 42)	Group exercise (n = 43)
% female/male	97/3	100/0	95/5	93/7	100/0
% Caucasian/non-Caucasian	93/7	88/12	90/10	93/7	100/0
% premenopausal/postmenopausal	64/36	61/39	62/38	75/25	60/40
Age, years	49.45 ± 8.05	49.78 ± 7.87	49.62 ± 7.65	49.31 ± 7.89	49.12 ± 8.95
Duration of fibromyalgia, years	15.39 ± 10.65	14.91 ± 10.62	16.91 ± 11.94	14.81 ± 9.74	14.97 ± 10.48
Beck Depression Inventory score	9.32 ± 6.40	8.97 ± 6.51	10.58 ± 6.81	9.99 ± 5.90	7.85 ± 6.27
No. of tender points	17.2 ± 1.31	17.39 ± 0.97	17.21 ± 1.13	16.88 ± 1.70	17.00 ± 1.29
Total myalgic score	36.92 ± 8.53	38.85 ± 7.76	38.00 ± 8.88	35.17 ± 9.41	35.83 ± 7.75
Total FIQ score	58.10 ± 15.92	58.58 ± 17.80	59.64 ± 16.02	56.59 ± 14.34	57.64 ± 15.74
Pain VAS score	6.48 ± 2.20	6.46 ± 2.25	6.95 ± 2.13	5.88 ± 2.24	6.63 ± 2.14
Fatigue VAS score	7.93 ± 1.87	7.78 ± 2.24	8.16 ± 1.60	7.90 ± 1.91	7.91 ± 1.72
Sleep VAS score	8.01 ± 2.08	7.78 ± 2.15	7.82 ± 1.93	8.43 ± 2.00	8.02 ± 2.21
Stiffness VAS score	7.22 ± 2.21	7.54 ± 2.29	7.26 ± 2.23	6.95 ± 2.22	7.12 ± 2.14
Anxiety VAS score	4.88 ± 2.98	4.80 ± 2.89	5.00 ± 3.11	5.10 ± 2.87	4.63 ± 3.12
Depression VAS score	3.57 ± 2.73	3.66 ± 3.13	3.71 ± 2.67	4.05 ± 2.51	2.93 ± 2.55
BMI, kg/m^2	29.79 ± 6.25	30.22 ± 6.54	30.08 ± 6.30	28.99 ± 6.01	29.01 ± 6.12
% body fat at 7 sites, by skinfold test	34.59 ± 8.02	35.54 ± 6.89	35.32 ± 8.60	33.36 ± 8.54	34.25 ± 8.03
Vo_2 max, ml/kg	21.73 ± 4.88	20.4 ± 4.52	21.39 ± 4.91	22.95 ± 4.74	22.11 ± 5.13
Total time on treadmill, seconds	618.24 ± 282.42	533.02 ± 259.77	581.49 ± 284.23	715.0 ± 292.0	638.8 ± 270.0
Upper body flexibility, cm	8.81 ± 10.77	8.76 ± 11.50	9.71 ± 11.73	7.31 ± 10.41	9.55 ± 9.67
Lower body flexibility, cm	0.64 ± 12.42	−0.61 ± 12.43	−0.44 ± 14.07	3.07 ± 12.10	0.43 ± 11.12
Balance, seconds	29.51 ± 41.45	23.78 ± 27.62	32.85 ± 54.98	31.48 ± 43.29	30.02 ± 36.90
Lower body strength/endurance†	11.12 ± 3.70	10.59 ± 3.15	10.46 ± 4.23	12.07 ± 4.18	11.29 ± 3.00
GH at rest, ng/ml	0.67 ± 1.65	0.47 ± 0.78	0.72 ± 2.01	0.53 ± 1.14	0.94 ± 2.22
GH after treadmill exercise (at Vo_2 max), ng/ml	1.76 ± 3.53	1.41 ± 2.94	1.01 ± 1.26	2.95 ± 5.31	1.61 ± 3.09
GH at rest 1 hour after treadmill exercise, ng/ml	0.42 ± 0.80	0.63 ± 1.28	0.27 ± 0.44	0.40 ± 0.58	0.37 ± 0.62
IGF-1, ng/dl	142.10 ± 57.98	140.46 ± 52.07	126.73 ± 63.32	148.44 ± 56.26	151.5 ± 58.93
IGFBP-3, ng/dl	4.75 ± 1.18	4.97 ± 1.3	4.61 ± 1.21	4.5 ± 1.11	4.91 ± 1.06

*None of the comparisons between the placebo and pyrodistigmine groups showed a significant difference. No tests of significance were conducted for sex or race because the numbers in 1 or more cells were <5. Except where indicated otherwise, values are the mean ± SD. FIQ = Fibromyalgia Impact Questionnaire; VAS = visual analog scale (0–10 cm); BMI = body mass index; $\dot{V}o_2$ max = maximum oxygen consumption (i.e., highest rate at which oxygen can be taken up and utilized during exercise); GH = growth hormone; IGF-1 = insulin-like growth factor 1; IGFBP-3 = insulin-like growth factor binding protein 3.

†Represents the number of times subjects could rise from a seated position in 30 seconds.

Table 2

Raw means and SDs for quality of life and fibromyalgia symptoms in the fibromyalgia patients at baseline and followup, by drug intervention group*

	Baseline		Followup			
			Placebo		Pyridostigmine	
	Placebo, mean ± SD	Pyridostigmine, mean ± SD	No. of patients	Mean ± SD	No. of patients	Mean ± SD
Quality of life						
No training exercise	70.80 ± 13.87	74.62 ± 13.95	38	72.10 ± 14.14	36	77.06 ± 16.24
Training exercise	68.78 ± 15.47	75.30 ± 15.54	38	71.44 ± 15.93	39	82.00 ± 11.47
Total myalgic score						
No training exercise	38.44 ± 7.87	34.36 ± 9.25	38	34.07 ± 10.75	36	28.92 ± 12.62
Training exercise	37.87 ± 8.96	36.38 ± 7.82	38	33.47 ± 10.36	39	31.23 ± 10.04
No. of tender points						
No training exercise	17.34 ± 0.99	16.81 ± 1.77	38	16.08 ± 2.76	36	14.83 ± 4.27
Training exercise	17.24 ± 1.13	17.00 ± 1.34	38	16.29 ± 2.48	39	15.92 ± 3.25
Total FIQ score						
No training exercise	58.79 ± 18.48	56.02 ± 14.77	38	53.16 ± 19.93	35	47.80 ± 21.66
Training exercise	59.96 ± 16.10	58.25 ± 15.42	38	53.66 ± 21.29	39	44.01 ± 20.73
Pain VAS score						
No training exercise	6.42 ± 2.33	5.97 ± 2.14	38	5.84 ± 2.53	34	5.29 ± 2.73
Training exercise	6.97 ± 2.15	6.72 ± 2.05	37	5.59 ± 2.92	39	5.00 ± 2.31
Fatigue VAS score						
No training exercise	7.74 ± 2.32	7.69 ± 1.92	38	6.95 ± 2.49	35	7.23 ± 2.91
Training exercise	8.19 ± 1.61	7.87 ± 1.75	37	6.62 ± 2.69†	39	5.97 ± 2.32†
Sleep VAS score						
No training exercise	7.76 ± 2.20	8.26 ± 2.08	38	7.34 ± 2.56	35	6.66 ± 3.00†
Training exercise	7.89 ± 1.90	7.97 ± 2.32	37	6.92 ± 2.89	38	6.00 ± 2.86†
Stiffness VAS score						
No training exercise	7.47 ± 2.35	7.09 ± 2.19	38	6.84 ± 2.80	35	6.06 ± 2.85
Training exercise	7.35 ± 2.19	7.33 ± 1.77	37	6.11 ± 2.94	39	5.69 ± 2.60
Anxiety VAS score						
No training exercise	4.82 ± 2.99	4.86 ± 2.70	38	4.29 ± 2.98	35	3.14 ± 3.14†
Training exercise	5.14 ± 3.04	4.67 ± 3.17	37	4.57 ± 3.04	39	3.26 ± 2.80†
Depression VAS score						
No training exercise	3.76 ± 3.21	3.91 ± 2.65	38	2.95 ± 2.66	35	2.83 ± 2.54
Training exercise	3.76 ± 2.53	2.90 ± 2.63	37	4.32 ± 3.26	39	2.85 ± 2.86

*Of the 4 intervention groups, the 2 groups receiving pyridostigmine were analyzed separately from the 2 groups receiving placebo. FIQ = Fibromyalgia Impact Questionnaire; VAS = visual analog scale (0–10 cm).

†$P < 0.006$-0.001.

Table 3

Raw means and SDs for fitness outcomes in the fibromyalgia patients at baseline and followup, by drug intervention group*

	Baseline		Followup			
			Placebo		Pyridostigmine	
	Placebo, mean ± SD	Pyridostigmine, mean ± SD	No. of patients	Mean ± SD	No. of patients	Mean ± SD
BMI, kg/m^2						
No training exercise	30.16 ± 6.68	29.17 ± 5.77	38	30.48 ± 7.21	35	28.85 ± 5.38
Training exercise	31.08 ± 6.30	29.01 ± 6.13	39	30.62 ± 6.15	40	28.87 ± 6.25
% body fat at 7 sites, by skinfold test						
No training exercise	35.53 ± 7.05	33.66 ± 8.28	38	36.10 ± 7.55	35	33.72 ± 8.14
Training exercise	35.32 ± 8.60	33.94 ± 7.91	39	35.78 ± 8.28	39	33.89 ± 8.47
$\dot{V}o_2$ max, ml/kg						
No training exercise	20.68 ± 4.54	23.13 ± 4.84	37	19.07 ± 3.65	34	21.38 ± 4.42
Training exercise	21.39 ± 4.91	21.74 ± 4.65	38	20.83 ± 5.16	40	20.83 ± 4.22
Total time on treadmill, seconds						
No training exercise	548.95 ± 256.15	721.49 ± 282.23	38	514.89 ± 270.31	35	729.43 ± 326.11
Training exercise	581.49 ± 284.23	632.95 ± 265.92	39	630.13 ± 318.88	40	673.63 ± 239.40
Upper body flexibility, cm						
No training exercise	−8.74 ± 11.71	−8.20 ± 10.37	38	−10.13 ± 10.54	35	−6.94 ± 9.91
Training exercise	−9.71 ± 11.73	−9.23 ± 9.82	38	−7.66 ± 11.48	39	−6.77 ± 9.21
Lower body flexibility, cm						
No training exercise	−0.29 ± 12.82	3.37 ± 11.17	38	0.97 ± 13.18	35	2.66 ± 13.60
Training exercise	−0.44 ± 14.07	0.38 ± 10.97	39	4.00 ± 12.31†	39	5.46 ± 12.80†
Lower body strength/endurance‡						
No training exercise	10.62 ± 3.26	12.20 ± 4.47	37	10.95 ± 3.81	35	13.26 ± 5.31
Training exercise	10.42 ± 4.28	11.11 ± 3.01	38	12.42 ± 4.07	38	13.00 ± 3.85
Balance, seconds						
No training exercise	23.58 ± 28.27	35.20 ± 46.33	38	34.11 ± 40.84	35	48.49 ± 69.06
Training exercise	32.85 ± 54.98	25.97 ± 28.69	39	73.82 ± 78.54†	38	62.21 ± 47.96†

*Of the 4 intervention groups, the 2 groups receiving pyridostigmine were analyzed separately from the 2 groups receiving placebo. BMI = body mass index; $\dot{V}o_2$ max = maximum oxygen consumption (i.e., highest rate at which oxygen can be taken up and utilized during exercise).

†$P < 0.006–0.001$.

‡Represents the number of times subjects could rise from a seated position in 30 seconds.