A Randomized, Single-Blind, Controlled, Parallel Assignment Study of Exercise Versus Education as Adjuvant in the Treatment of Peripheral Neuropathic Pain

Cory Toth, BSc, MD, FRCPC, Shauna Brady, RN, BN, MN,
Francois Gagnon, BSc, and Kellie Wigglesworth, BSc

Objective: Some forms of chronic pain are receptive to exercise therapy for maintenance of pain relief. We evaluated the impact of a balanced exercise program in the management of human peripheral neuropathic pain compared with an educational intervention.

Methods: This was a single-center, randomized, single-blind, controlled study using an intention-to-treat protocol. Patients with confirmed neuropathic pain and a pain score ≥ 4 (0 to 10 scale) on visual analog scale (VAS) continued their regular pain therapies and were randomized to 6 months of either a balanced exercise program or an educational program. VAS for pain severity was the primary outcome variable. Characteristics of pain, function, mood, anxiety, sleep, and quality of life along with Single Stage Treadmill Walking Test calculating maximal oxygen consumption (VO_2) formed the secondary outcome measures.

Results: Seventy-eight patients were screened and 54 participated, with 28 randomized to exercise and 26 randomized to education. A total of 19 (68%) and 20 patients (77%) completed exercise and education, respectively. VAS scores improved 17% for the exercise group as compared with 9% for the education group ($P = 0.08$). The only secondary outcome measure demonstrating improvement was VO_2, which improved in exercise participants (25.6 ± 4.5 mL/kg/min at baseline vs. 28.9 ± 3.8 mL/kg/min at 6 mo).

Discussion: A balanced exercise program was beneficial for exercise capacity, but produced only a medium-sized effect without statistical significance. A small sample size and unexpectedly high dropout rates may have limited our ability to demonstrate statistically significant improvement in pain relief.

Key Words: peripheral neuropathy, neuropathic pain, exercise, education

(*Clin J Pain* 2013;00:000–000)

Neuropathic pain (NeP) is a form of chronic pain resulting from a disease or lesion within the central or peripheral nervous system.[1] Because of a multitude of conditions affecting the peripheral nervous system, including

trauma or surgery, radiculoplexopathy, and central nervous system conditions, NeP is a chronic disabling condition.[2,3] Patients with NeP face comorbidities as well, including insomnia, depression, anxiety, and lost quality of life.[2,4] Although many pharmacotherapies exist for NeP management, these are frequently associated with inefficacy and inevitable, possibly intolerable, adverse effects. Even if successful, pain relief is often partial and incomplete,[5] leading to frequent attempts at complementary therapies. Therefore, studies and incorporation of nonpharmacological interventions is desirable for both patient and clinician. One particular understudied intervention is that of the role of physical exercise. Certainly, the benefits of exercise extend beyond weight loss and muscle conditioning, for which it is often recommended. For example, improvements in cardiovascular risk factors (eg, decreased blood pressure; cholesterol, triglyceride, and fasting serum glucose levels) occur in patients who adopt a moderate regular exercise program.[6] Even if only associated with minimal weight loss, obese patients with reasonable cardiorespiratory fitness levels have reduced cardiovascular mortality risk when compared with lean, but unfit, patients.[7] Not only does physical inactivity increase the risk of chronic diseases such as coronary heart disease, type 2 diabetes, and colon cancer,[8] but it also leads to generalized deconditioning that can worsen chronic illnesses. However, most adults even without presence of a chronic illness such as NeP do not currently achieve minimal levels of exercise.[8–10]

There is some evidence that targeted exercise programs can be of benefit for pain management for chronic back pain[11,12] and fibromyalgia (FM).[13,14] These clinical studies have suggested a modest efficacy for exercise to decrease pain and improve function in patients with low back pain,[11] whereas more concrete evidence that exercise programs improve symptoms and physical capacity in FM[15] exists. Exercise may alleviate peripheral NeP in preclinical rodent studies,[16] but there are no randomized controlled clinical trials examining the impact of exercise in a population of chronic, peripheral NeP patients. There were encouraging suggestions of potential benefits upon pain severity and even cutaneous innervation patterns demonstrated in an open-label study[17] in diabetic peripheral neuropathy patients. We assessed the role of an adjuvant balanced exercise program with comparison to an educational initiative in the management of peripheral NeP using a randomized single-blinded controlled trial to determine potential benefits upon pain severity and related comorbidities. Our hypothesis was that a balanced exercise program would be effective for reduction of pain severity as compared with an educational program for patients with peripheral NeP.

MATERIALS AND METHODS

Patient Assessment

This study was approved by the Conjoint Health Research Ethics Board at the University of Calgary. Patient recruitment occurred through both primary and tertiary care (Calgary Chronic Pain Centre and the Neuropathic Pain Clinic) clinics in Calgary, Alberta, Canada with an intended equal distribution of recruitment. Recruitment occurred between February 2007 and May 2010.

Patients were assessed by a single neurologist during the study. Men or women aged 18 to 80 years with NeP associated with a peripheral neuropathic process were included in the presence of chronic pain (as long as a Douleur Neuropathique (DN4)[18] questionnaire score was ≥ 4) and if presence of peripheral NeP was confirmed by a neurologist through standard history and examination. Peripheral NeP was defined as "pain caused by a lesion or disease of the peripheral somatosensory nervous system."[19] Conditions to be considered included polyneuropathy, cervical, thoracic or lumbosacral radiculopathy, peripheral nerve entrapment, postsurgical or posttraumatic neuropathy, brachial plexopathy, trigeminal neuralgia or atypical facial pain, postherpetic neuralgia, or complex regional pain syndromes I or II.

After completion of written informed consent, patients were randomized to one of a balanced exercise program or an educational program. An electronic system was used to randomize individual patients without block randomization, with envelopes used for notification of the patient. Randomization was known to patients, the clinical coordinator, and the kinesiologists, but was unknown to the assessing physician (C.T.).

Inclusion criteria consisted of the following: (1) 18 to 80 years old; (2) neurologist-provided diagnosis of a nervous system lesion and associated NeP as a primary source of pain; (3) NeP has been present for 6 months or more in duration; (4) DN4 questionnaire score of ≥ 4; (5) NeP severity of ≥ 40 mm on a VAS on the short-form McGill Pain Questionnaire[20] at study entry; (6) willingness to be enrolled in either exercise or educational sessions; (7) perceived ability to walk on a flat surface or treadmill for at least 1 km/d at time of enrollment on behalf of the patient and enrolling physician; (8) willingness to continue with regular assessments at 3 and 6 months; (9) absence of any planned trips away from Alberta of 2 weeks or more; and (10) willingness to provide informed consent. Exclusion criteria were comprised of: (1) another cause of non-NeP source of pain that is more dominant than the peripheral NeP or that cannot be separated clinically; (2) presence of NeP for 6 months or less; (3) central nervous system cause of pain; and (4) absence of other health concerns in the view of the enrolling physician that could impact upon performance, including cardiovascular or pulmonary disease, severe obesity, amputation, use of mobility assistive devices, or active neoplasia (other than forms of skin cancer). Patients with other forms of chronic pain deemed tolerable and not interfering with daily functioning (such as osteoarthritis) were not excluded if it was determined that the patient could separate the manifestations of both forms of chronic pain.

Study Design, Protocol, and Interventions

This was a single-center, parallel-group, single-blind, controlled randomized clinical trials designed to compare 6 months of an exercise intervention versus 6 months of educational intervention (selected to be a control comparator). This was an adjuvant study—patients already using other forms of therapy, including pharmacotherapy and alternative therapies, were permitted to continue as long as the quantity of the intervention remained unchanged. No discontinuation of other therapies was performed.

Before obtaining consent, patients were informed tht they would receive either the exercise or education intervention over the next 6 months. Efficacy assessments and questionnaires were completed, followed by 1 week of completion of daily pain severity and sleep disruption severity diaries. Patients were required to complete at least 75% of their daily pain diaries over this baseline week or exclusion occurred. After this baseline week, patients initiated their randomized intervention.

Exercise Program

The exercise program was designed to be individual to the patient's condition and abilities by a kinesiologist. The program consisted of moderate exercise emphasizing aerobic exercise and stretching led by the same kinesiologist who met with the patient for 2 hours each month at a gymnasium. On their first visit, an exercise capacity test was performed. In addition, a Single Stage Treadmill Walking Test calculating maximal oxygen consumption (VO_2)[21] was performed at baseline and at a final visit. An individualized program was designed and taught to each patient, followed by observation. A suggested schedule of regular exercise occurring 3 to 5 days per week over the subsequent month was proposed and provided. Diaries were given to each patient to monitor their exercise schedules over the next 6 months. Although their presence at the gymnasium was recorded by electronic key card entry, patients were permitted to exercise in another setting as desired. The patients exercised in groups of up to 5 patients for each session. Patients were provided with a 6-month pass to the gymnasium for the period of this study free of cost.

The exercise program was designed to consist of exercises for stabilizing core torso muscles as well as aerobic exercises consisting of treadmill walking or running, elliptical stairclimber, or cycling exercises, as chosen by the patient. Proper stretching techniques were taught. A target exercise heart rate (HR) was calculated by using: (maximal HR − resting HR) (intensity fraction) + resting HR (HR reserve method). It was intended for exercise intensity to start at 40% to 60% of HR reserve, with gradual progression up to approximately 85% as tolerated over the 6-month period. Heart monitoring was performed with a standard heart rate monitor during monthly visits. Perceived exertion ratings were performed using the Borg CR-10 scale[22] as a form of feedback for patients to help guide exercise intensity. The duration of exercise performed between monthly kinesiologist visits ranged between 15 and 60 minutes as individually tolerated with a schedule of 3 to 5 days per week of exercise recommended. The schedule provided encouraged performance of the same exercises between monthly sessions. Each subsequent month, patients returned for follow-up visits, which again lasted 2 hours, and during which the kinesiologist and patients discussed their program successes and hurdles. Diaries were reviewed and problems were identified with suggestions for correction through active feedback and trial and error. During the final 6-month visit, each patient performed their final kinesiologist assessment and questionnaires were

repeated followed by an exercise capacity test for comparison to their baseline test.

Educational Program

For those patients randomized to the educational protocol, they met with the kinesiologist after the baseline week. This was a monthly program designed to spend similar amounts of time with the kinesiologists as experienced in the exercise protocol. During each of the total of 6 monthly visits, an educational lecture was provided by a kinesiologist for a 2-hour session. Educational information was provided to each patient regarding maintenance of exercise, diet, and sleep habits over the next 6 months. During each of the 6 sessions, information important for overall health was provided and discussed in a group setting for the following topics: exercise, diet, sleep hygiene, pain, relaxation, and a summary/review session.

Outcome Measures

At the baseline visit and after 3 and 6 months of intervention, patients were assessed by the neurologist who was blinded to intervention allocation. Our primary outcome measure was the change in NeP severity at endpoint, determined using a standard 100 mm VAS of the short-form McGill Pain Questionnaire[20] performed over 1 week and averaged for each response. This was performed at the baseline week, during a single week at the end of 3 months of study, and at the completion of the intervention, with recording of pain severity again performed daily for 7 days. Completion of at least 75% of the daily scores for each week of assessment was required for data inclusion for each of these weeks assessed—this strategy was performed to prevent missing data imputations for ≥ 25% of the 7 daily score items, which could introduce bias where only scores representing the participant's worst or best days were analyzed. Regression imputation bias is known to be minimal when < 2 items are missing for imputation for a 7-item scale; the last observation carried forward technique was used in this scenario.

Secondary outcome measures consisted of other efficacy assessments, and questionnaires directly or indirectly related to pain were completed at baseline visit and at the 6-month final visit. These secondary efficacy assessments included the modified Brief Pain Inventory short form (MBPI),[23] the EuroQol 5 Domains (EQ-5D),[24] the Hospital Anxiety and Depression Scale (HADS),[25] the Medical Outcomes Study Sleep Scale (MOSSS)[26] based on a 1-week recall period, the Pain Treatment Satisfaction Scale (PTSS),[27] Neuropathic Pain Symptom Inventory (NPSI),[28] and the Karnofsky Performance Scale (KPS).[29] The EQ-5D has 2 sections—the first section examines 5 dimensions of the health state: mobility, self-care, usual activities, pain/complaints, and anxiety/depression. Self-recorded EQ-5D utility scores based upon overall well-being compose the second section. We used the PTSS to determine patient-related evaluation of treatment effectiveness. For patients in the exercise cohort, performances of Single Stage Treadmill Walking Test to calculate maximal oxygen consumption (VO_2) was a secondary outcome. Finally, the Patient Global Impression of Change (PGIC)[30] and the Clinician Global Impressions Scale (CGI), during which patients and clinicians, respectively, rate overall status on a 7-point scale from 1 = very much improved to 7 = very much worse, was completed at final visit. Tertiary outcomes included body weights and body mass indices (BMI) performed at baseline and final visits.

Tolerability and Safety Assessments

A full physical exam including a neurological component was completed at baseline and at endpoint for all patients. All spontaneously reported and observed adverse events were recorded by kinesiologists during monthly visits. The Medical Dictionary for Regulatory Activities (MedDRA) terminology was used to record adverse events.

Data Analysis

There are no previous trials in peripheral NeP to use for sample size estimation. On the basis of our primary endpoint of mean pain reduction based upon daily VAS scores from each of the baseline and final weeks of study, sample size calculation used an estimated difference in means on the VAS of 0.33 with a SD of 1.0, $\alpha = 0.05$, and $1-\beta = 0.5$, providing a sample size of 24 for each cohort. We estimated a 10% dropout rate, leading to a total cohort of 54 patients to be enrolled. No interim analyses were planned.

All analyses were based on the intention-to-treat population. Missing values were managed using imputation techniques using the last observation carried forward technique. We also calculated the proportions of patients with a ≥ 30% and ≥ 50% reduction in pain score between baseline and endpoint (responder analyses), compared using ANOVA testing. Mean changes from baseline to endpoint for primary, secondary, and tertiary efficacy variables (non-categorical) were also determined for each scale using ANOVA based on 2-sided testing without adjustment for testing multiple measures and with control for baseline values. Statistical significance was set to be $\alpha = 0.05$ in each case. Bonferroni corrections were applied for evaluation of multiple subsections of secondary outcome measures. We analyzed categorical variables such as with the PGIC and CGI using the Cochran-Mantel-Haenszel test. Finally, we performed post hoc linear regression analysis to determine any relationships between VAS score improvement (independent variable) and number of exercise days performed (dependent variable).

RESULTS

Patients

Our study was impacted by high discontinuation rates (Fig. 1). A total of 78 patients were assessed for eligibility in the study, with 47 of these patients recruited from tertiary care clinics in the investigators' primary institution, whereas 31 other patients were referred from primary care clinics. A total of 24 patients were excluded, due to being unable to perform exercise or education visits (n = 13) or declining to continue after the first week of baseline assessments when randomization was provided (n = 11). Thus, a total of 54 patients were enrolled in this single-blind study. Of these patients, 28 were allocated to the exercise intervention, whereas 26 were allocated to educational sessions. Although there were no patients lost to follow-up with either intervention, a total of 9 patients discontinued the exercise intervention after an average of 1.6 ± 0.7 months, whereas 6 patients discontinued the education intervention after an average of 1.3 ± 0.5 months. For those patients remaining in the exercise intervention cohort, a minimum of 3 days of exercise was recorded in diaries
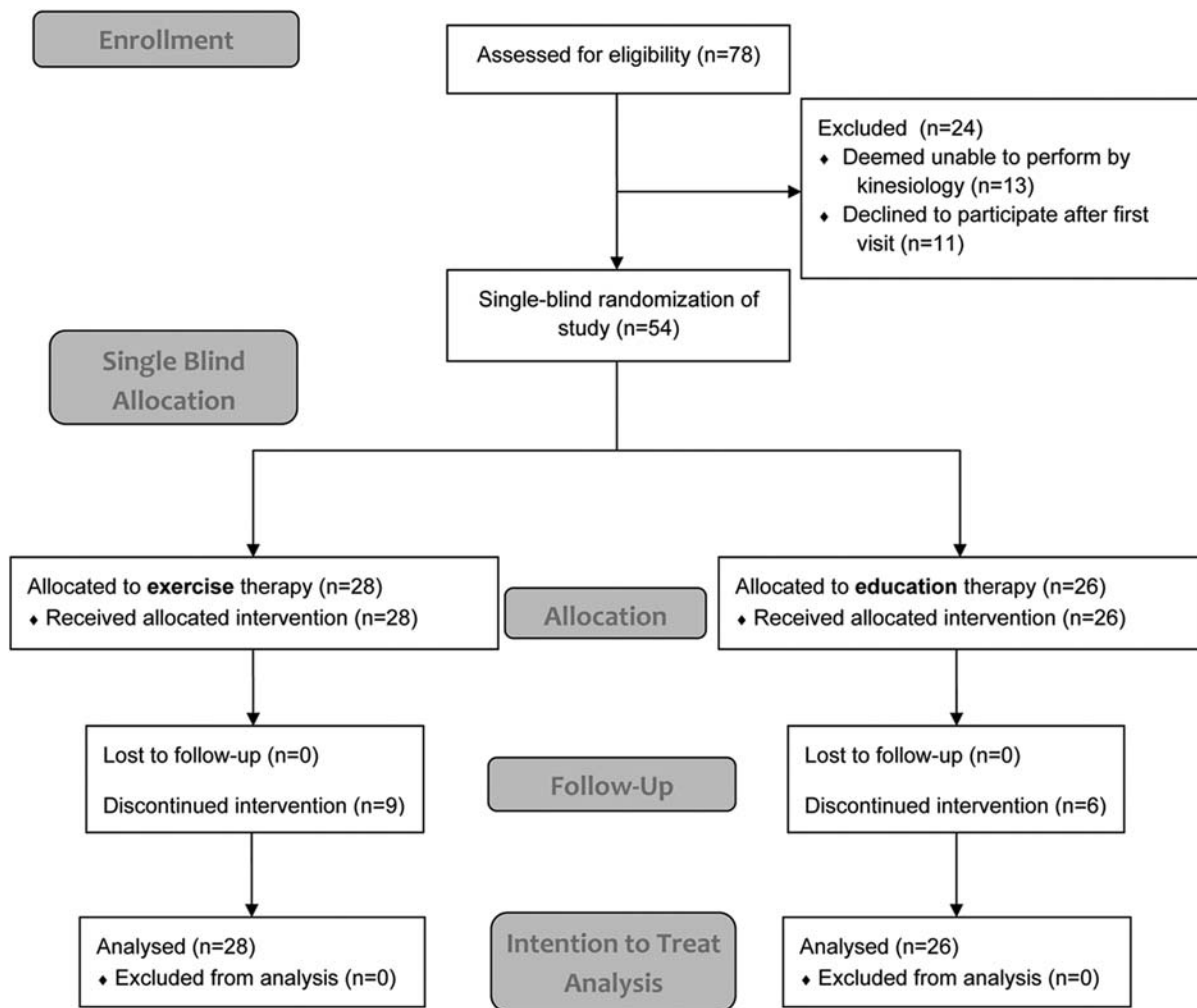
FIGURE 1. Patient disposition throughout the study using the CONSORT guidelines. This was a randomized, single-blind, controlled, parallel assignment study of exercise versus education as adjuvant in the treatment of peripheral neuropathic pain.

collected for 86% of weeks studied; only 13% of these exercise experiences were recorded as visits at the gymnasium using the keycard entry data. The mean number of exercise days was 95.1 ± 6.4 in the exercise cohort. Baseline demographic and clinical characteristics were similar between the 2 randomized treatment cohorts for sex, age, duration of disease, and number of pain medications used (Table 1).

Study Interventions

The average attendance for exercise intervention and education intervention patients was 4.3 ± 2.0 and 4.1 ± 1.7 sessions, respectively, with kinesiologist-directed sessions. Discontinuations in the exercise intervention consisted of lack of willingness to continue due to increased discomfort ($n = 7$) or lack of willingness to attend sessions at the gymnasium ($n = 2$). In the education intervention, discontinuation occurred due to lack of interest in continuing to attend sessions in all 6 patients. Analysis of all patients randomized to exercise or education interventions took place regardless of discontinuations of interventions.

Efficacy

For the primary endpoint, the exercise program cohort reduced VAS pain severity by 7.9 ± 2.8 mm ($15.2\% \pm 5.4\%$) as compared with 3.9 ± 5.4 mm ($7.3\% \pm 10.2\%$) in the education program cohort (Fig. 2). This was a nonstatistically significant difference between cohorts (ANOVA, $P = 0.08$). Despite this negative result, an effect size of 0.31 was calculated for the exercise intervention. The percentage of excluded averaged VAS scores was 6% for all patients due to completion of $\leq 75\%$ of days during the week of assessment. The number of patients with $\geq 30\%$ reduction in pain from baseline to endpoint was 0/28 (0%) in the exercise intervention group and was also 0/26 (0%) in the education intervention group.

For secondary outcome measures, the subsections of the MBPI, PTSS, and the NPSI showed no significant changes over time or between interventions. Similarly, there were no significant improvements noted with the EQ-5D for utility or index scores, MOSSS index scores, or the HADS or its subsections (Table 2). Mean KPS scores also did not show significant improvement over time. Tertiary endpoints of weight and BMI also showed no significant change at endpoint.

TABLE 1. Patient Characteristics for All Patients Enrolled to Exercise or Education

	Exercise Intervention (n = 28)	Education Intervention (n = 26)
Sex [females (%)]	16 (57)	16 (62)
Age [y (range)]	54.8 ± 6.7 (36-79)	55.4 ± 7.0 (38-80)
Duration of NeP (y)	4.6 ± 5.4 (0.6-11.9)	4.9 ± 5.9 (0.9-16.3)
No. pain medications	2.8 ± 2.4 (0-6)	2.9 ± 2.9 (0-8)
Diagnosis		
Postsurgical/posttraumatic	7	8
Diabetic polyneuropathy	9	7
Other cause for polyneuropathy	4	3
Trigeminal neuralgia/other facial pain	1	1
Cervical/lumbar radiculopathy	4	3
Postherpetic neuralgia	2	2
Complex regional pain syndrome	1	1
Inflammatory polyneuropathy	0	1

At endpoint, all patients and the blinded clinician completed the PGIC and CGI, respectively. Although leftward shifts occurred in each case, there was no significant difference between cohorts for either measure (Fig. 3). A post hoc regression analysis did not show any significant relationship between total exercise days performed and VAS pain severity score change ($F = 0.38$, $R = 0.15$, $P = 0.55$).

The maximal oxygen consumption (VO_2) was performed for all 28 patients in the exercise intervention cohort at baseline and for 19 patients at endpoint. For all 28 patients, the VO_2 was $22.8 ± 5.6$ mL/kg/min at baseline. For the 19 patients completing the exercise intervention, VO_2 was $25.6 ± 4.5$ mL/kg/min at baseline versus $28.9 ± 3.8$ mL/kg/min at the 6-month endpoint, a significant improvement for those particular patients ($P < 0.05$, ANOVA). Using imputation techniques, there was no significant improvement in VO_2 for all patients randomized to the exercise cohort.

Although discontinuations were common in both cohorts, all patients returned for 6-month endpoint assessments. Imputation of data using the last value carried forward technique was required for 4.3% of all data assessed in the study—this was required for data for patients that did not perform the 3-month follow-up visit and for some patients that declined to perform 6-month questionnaires. As mentioned, last observation carried forward techniques were used for imputation of this missing data.

Tolerability and Safety

At endpoint, no patients in the education intervention cohort reported any adverse events related to their participation. In the exercise cohort, a total of 5 patients reported transient worsening of their chronic pain, whereas 3 patients reported dizziness, and 2 patients reported muscle strain at the shoulder and hip girdle regions. All of these adverse events were described as either mild or moderate in intensity.

DISCUSSION

This is the first randomized clinical trial to examine the potential role of an exercise program in the management of peripheral neuropathic chronic pain. On the basis of our data, there were no significant improvements in pain severity, as well as for associated features of sleep efficacy, mood and anxiety, and quality of life when compared with a cohort of patients receiving educational sessions. This lack of improvement may relate to a number of issues, including the selection of the exercise program, the nature of conditions suffered by patients enrolled in the study, a small sample size, and higher than anticipated dropout rates, each of which reflected upon endpoint measures. High rates of dropouts occurring due to "lack of reported interest" in the education cohort and due to "increased discomfort" in the exercise cohort were unforeseen. The disease condition associated with higher rates of discontinuation of either exercise or education intervention was type 2 diabetes mellitus and diabetic peripheral neuropathy in nearly 50% of cases. This is in contrast with other trials studying patients with diabetes mellitus alone or fibromyalgia, which have had better retention rates.[31–33] Adverse effects were few, but overall, the exercise intervention offered failed to impact significantly upon pain severity and related measures. For those patients remaining in the exercise cohort to endpoint, there was a significant improvement in exercise capacity which is likely to contribute to other health benefits. Thus, although performance of exercise may portend other benefits, it did not seem to benefit peripheral NeP severity in our study population. The calculated effect size was in a medium range, which suggests the possibility that a larger scale study encompassing greater anticipated dropout rates and with less
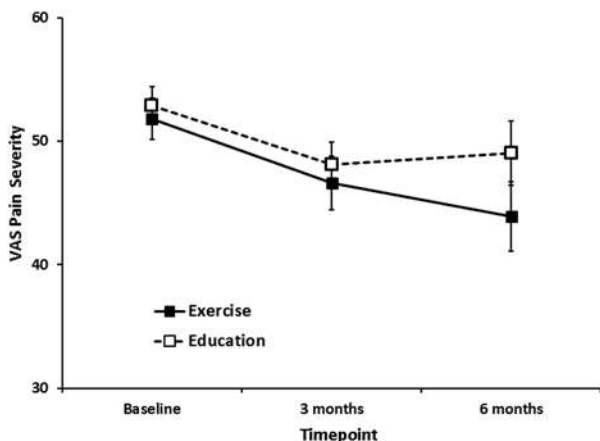

FIGURE 2. The effects of exercise or education interventions upon visual analog scoring for pain severity are demonstrated without significant difference between cohorts. Values shown are means ± SE.

TABLE 2. Secondary and Tertiary Endpoints

	Timepoint			
Characteristics	**Baseline Exercise (n = 28)**	**Baseline Education (n = 26)**	**Endpoint Exercise (n = 28)**	**Endpoint Education (n = 26)**
European Quality of Life-5 Domains (EQ-5D)				
EQ-5D utility score	64.3 ± 4.3	63.2 ± 6.2	68.6 ± 4.9	65.2 ± 7.0
EQ-5D index score	0.58 ± 0.06	0.54 ± 0.07	0.61 ± 0.07	0.56 ± 0.06
Medical Outcomes Study Sleep Scale (MOSSS)				
Characteristic MOSSS sleep problems index	32.9 ± 1.9	32.5 ± 2.3	29.8 ± 2.1	31.0 ± 2.4
Hospital Anxiety and Depression Scale (HADS)				
Characteristic HADS-A (anxiety)	7.8 ± 0.9	7.4 ± 1.2	7.4 ± 1.1	7.1 ± 1.3
HADS-D (depression)	5.6 ± 0.6	5.8 ± 1.3	5.5 ± 0.8	5.7 ± 1.4
Karnofsky Performance Scale				
Karnofsky mean Score	68.2 ± 6.5	66.7 ± 7.3	70.6 ± 7.3	65.8 ± 8.4
Weight (kg)	78.2 ± 9.8	79.7 ± 9.3	77.6 ± 10.5	79.9 ± 9.5
Body mass indices (Kg/m^2)	27.4 ± 3.5	27.7 ± 3.7	27.2 ± 3.4	27.7 ± 3.7

Values shown are means ± SE.

modest sample size calculations might find different results than our study.

There are several important strengths of this study. First, this was a randomized trial with a blinded assessor. It is hard to conceive of a double-blinded methodology for an overall exercise intervention—we chose to use a comparator of educational sessions with similar amounts of time spent with the same kinesiologists also performing the exercise portion of the study. We used pain severity as a primary outcome measure, and utilized Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations as secondary outcomes.[34] Although the overall population size studied was moderate, the anticipated sample size expectations were met. Finally, we studied exercise capacity and determined that improvements could be detected in our exercise intervention cohort for those continuing with a regular exercise program—this also suggests that the exercise program performed was sufficient to improve overall physical capabilities.

Previous studies have demonstrated the benefits of exercise for patients with conditions of chronic pain. It has been shown that aerobic exercise can reduce pain, depression, and fatigue while improving quality of life in patients with FM, although benefits seemed not to be maintained long-term, possibly due to discontinuation of exercise after the trial conclusion.[35] In addition to improving pain severity, improved function in FM patients is also possible
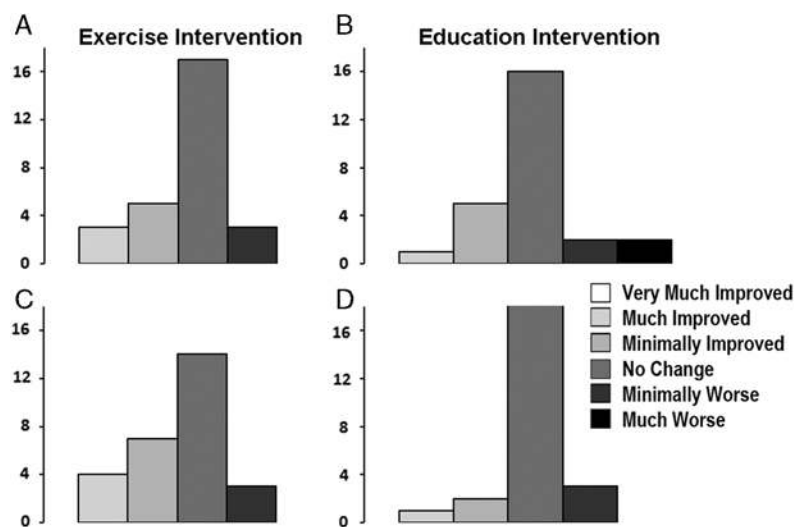

FIGURE 3. Patient Global Impression of Change (PGIC) and Clinician Global Impressions Scale (CGI) were analyzed using a Cochran-Mantel-Haenszel procedure, adjusting for center in each case. The PGIC expresses the patient's responses for each of exercise (A) and education (B) interventions. Expressing the clinician's view on overall well-being, the CGI is demonstrated for both exercise (C) and education (D) interventions. There were no significant differences between cohorts with respect to either the PGIC or the CGI measures at endpoint.

after 3 months of exercise with loss of benefit again after discontinuation of intervention.[36,37] A Cochrane review has determined that mild efficacy for pain and function may occur with exercise therapy in patients with low back pain.[11] Although positive studies certainly exist for exercise therapy in populations of low back pain patients,[38] other studies have not found improvement in pain and disability when compared with rest therapy[39] or conventional physiotherapy.[40] Most of these positive studies are limited to 12 weeks of intervention; however, a loss of sustained benefit occurs in many studies of lifestyle intervention in patients with chronic pain,[37] just as with patients having obesity and diabetes.[41,42] As a result, our long duration study may have been negative due to a loss of initial benefit; however, assessment at the 3-month timepoint also showed no positive benefit for pain severity. Peripheral NeP has been suggested to be a more severe, refractory form of chronic pain than other causes,[24] which may lead to less substantial pain relief when compared with other forms of chronic pain. It may also be possible that the location of the NeP over the feet in many participants [17/28 (61%) in exercise cohort and 15/26 (58%) in education cohort] was a limiting factor as compared with other conditions studied; most of the exercises performed required standing or walking postures, which could provide short-term exacerbation of lower limb pain due to peripheral neuropathy. Perhaps future studies should examine other forms of exercise not requiring standing or walking postures, such as with a recumbent bicycle or swimming/aqua exercises.

The rationale for exercise therapy in conditions with chronic pain is varied and uncertain. Exercise leads to improved overall well-being[15] and may lead to modifications of central neurotransmitters such as norepinephrine, important in central inhibitory pathways.[43] In addition, exercise therapy may also influence pathologic factors associated with neuropathic lesions such as reduction of inflammatory factors,[44] increasing vascular perfusion,[45] and rises in neurotrophic factors.[46] It is also conceivable that exercise promotes central synaptic plasticity and neurogenesis, as found in animal models.[47] Overall, it is likely that the benefits of exercise are multifold within the nervous system with obvious benefits upon our cardiovascular and musculoskeletal systems as well. It is plausible that exercise therapy may be beneficial in particular conditions with peripheral NeP for all of these reasons, but in our general population of patients with peripheral NeP, there were no measurable benefits upon pain or related comorbidities. NeP severity of pain may eclipse that of non-NeP chronic pain,[24] preventing the benefits of an exercise program that seems to provide at least some benefit for other conditions.

There are certainly limitations associated with this study and its results. The greatest limitation was relatively low retention in each cohort. We used a SD value of 1.0 to perform sample size calculations which was conceivably underestimated, contributing to a possibly underpowered study; we cannot rule out the possibility of a type II error as a result. As well, dropouts constituted 28% of enrolled patients, much higher than the anticipated 10% forecast. Given the calculated effect size and with consideration of this dropout rate, a study designed with power of 0.9 and $\alpha = 0.05$ and enrolling 92 participants could potentially yield a positive outcome. This was an adjuvant study, and although other therapies were maintained as constant, we cannot rule out the potential for external contributions such as that from pharmacotherapies or even performance of exercise in the education cohort. It is possible that the exercise program used was not appropriate for our patient population, although this program was similar to that used in other trials examining other chronic pain conditions.[38,39] The exposure to the exercise program portion was limited to a 6-month period, which may be inadequate but is again longer than[33] or consistent with that of other published positive studies.[48] It is possible that once-monthly sessions for assessment of exercise regimens was suboptimal, but this is again identical to protocols in other trials assessing exercise sessions.[48] On the basis of diaries reviewed, the majority of reported exercise took place outside of the chosen gymnasium, so it is possible that compliance was less than reported. It could be argued that the primary outcome measure should consist of a functional measure rather than pain severity, but functional measures including the Brief Pain Inventory were also unchanged in our population. Instead, we postulate that patients with peripheral NeP, which may be a more severe and refractory condition than other forms of chronic pain,[24] are not subject to as substantial improvement with exercise programs as do other forms of chronic pain. This may be due to pain being present over the extremities and concomitant allodynia in some cases. Finally, although patients enrolled in this study were representative of both primary care and tertiary care clinics, they may not be representative of the general population of patients with peripheral NeP.

In conclusion, we report that the impact of an exercise program for a population of patients with peripheral NeP may increase exercise capacity, but failed to impact significantly upon pain severity and other comorbid conditions. However, our findings are limited by higher than anticipated dropout rates, and the calculated effect size suggests that a larger scale study may lead to positive findings and determine an important role for exercise in this patient population. Our findings should not deter the clinical suggestion of an exercise program for this patient population, but may explain the absence of improvement in pain-related measures. The benefits of exercise extend beyond simply benefits upon pain, and could still be extolled for the patient suffering from peripheral NeP for reasons beyond that of pain relief alone. Despite the negative result, we still advocate for exercise programs to be considered for this patient population, and also suggest that larger scale studies be considered in future.

REFERENCES

1. IASP Pain Terminology. International Association for the Study of Pain. Available at: http://www.iasp-pain.org/terms-p.html. Accessed July 1, 2009.
2. Poliakov I, Toth C. The impact of pain in patients with polyneuropathy. *Eur J Pain.* 2011;15:1015–1022.
3. daCosta DiBonaventura M, Cappelleri JC, Joshi AV. A longitudinal assessment of painful diabetic peripheral neuropathy on health status, productivity, and health care utilization and cost. *Pain Med.* 2011;12:118–126.
4. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. *Clin J Pain.* 2002;18:350–354.
5. Taylor RS. Epidemiology of refractory neuropathic pain. *Pain Pract.* 2006;6:22–26.
6. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA.* 1995;273:402–407.

7. Lee CD, Blair SN, Jackson AS. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *Am J Clin Nutr*. 1999;69:373–380.

8. Chief Medical Officer, Health Do. At least five a week: evidence on the impact of physical activity and its relationship to health. London: Chief Medical Officer; 2004.

9. Sproston K, Primatesta P. Health Survey for England 2003. London: TSO (The Stationery Office); 2004. (Series HS no. 13).

10. Bromley C, Sproston K, Shelton N. The Scottish Health Survey: volumes 1 - 4, Edinburgh: Scottish Executive: 2005.

11. Hayden JA, van Tulder MW, Malmivaara A, et al. Exercise therapy for treatment of non-specific low back pain. *Cochrane Database Syst Rev*. 2005;CD000335.

12. Schaafsma F, Schonstein E, Ojajarvi A, et al. Physical conditioning programs for improving work outcomes among workers with back pain. *Scand J Work Environ Health*. 2011;37:1–5.

13. Busch AJ, Barber KA, Overend TJ, et al. Exercise for treating fibromyalgia syndrome. *Cochrane Database Syst Rev*. 2007; CD003786.

14. Hauser W, Klose P, Langhorst J, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. *Arthritis Res Ther*. 2010;12:R79.

15. Busch AJ, Schachter CL, Overend TJ, et al. Exercise for fibromyalgia: a systematic review. *J Rheumatol*. 2008;35:1130–1144.

16. Chen YW, Li YT, Chen YC, et al. Exercise training attenuates neuropathic pain and cytokine expression after chronic constriction injury of rat sciatic nerve. *Anesth Analg*. 2012; 114:1330–1337.

17. Kluding PM, Pasnoor M, Singh R, et al. The effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy. *J Diabetes Complications*. 2012;26:424–429.

18. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain*. 2005;114:29–36.

19. IASP Taxonomy. International Association for the Study of Pain, 2012. Available at: http://www.iasp-pain.org/Content/Navigation Menu/GeneralResourceLinks/PainDefinitions/default.htm#Neuro pathicpain. Accessed April 12, 2012.

20. Melzack R. The short-form McGill Pain Questionnaire. *Pain*. 1987;30:191–197.

21. Waddoups L, Wagner D, Fallon J, et al. Validation of a single-stage submaximal treadmill walking test. *J Sports Sci*. 2008; 26:491–497.

22. Borg G. Applications of the scaling methods. *Human Kinetics*. Champaign, IL: Champaign; 1988.

23. Zelman DC, Gore M, Dukes E, et al. Validation of a modified version of the Brief Pain Inventory for painful diabetic peripheral neuropathy. *J Pain Symptom Manage*. 2005;29:401–410.

24. Toth C, Lander J, Wiebe S. The prevalance and impact of chronic pain with neuropathic pain symptoms in the general population. *Pain Med*. 2009;10:918–929.

25. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*. 1983;67:361–370.

26. Hays RD, Stewart AL. Sleep measures. In: Stewart AL, Ware JE, eds. *Measuring functioning and well-being: The Medical Outcomes Study approach*. Durham, NC: Duke University Press; 1992:235–259.

27. Evans CJ, Trudeau E, Mertzanis P, et al. Development and validation of the Pain Treatment Satisfaction Scale (PTSS): a patient satisfaction questionnaire for use in patients with chronic or acute pain. *Pain*. 2004;112:254–266.

28. Bouhassira D, Attal N, Fermanian J, et al. Development and validation of the Neuropathic Pain Symptom Inventory. *Pain*. 2004;108:248–257.

29. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. *J Clin Oncol*. 1984;2:187–193.

30. Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94:149–158.

31. Ockene IS, Tellez TL, Rosal MC, et al. Outcomes of a Latino community-based intervention for the prevention of diabetes: the Lawrence Latino Diabetes Prevention Project. *Am J Public Health*. 2012;102:336–342.

32. West DS, DiLillo V, Bursac Z, et al. Motivational interviewing improves weight loss in women with type 2 diabetes. *Diabetes Care*. 2007;30:1081–1087.

33. Hooten WM, Qu W, Townsend CO, Judd JW. Effects of strength vs. aerobic exercise on pain severity in adults with fibromyalgia: a randomized equivalence trial. *Pain*. 2012; 153:915–923.

34. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113:9–19.

35. Hauser W, Thieme K, Turk DC. Guidelines on the management of fibromyalgia syndrome - a systematic review. *Eur J Pain*. 2010;14:5–10.

36. Fontaine KR, Conn L, Clauw DJ. Effects of lifestyle physical activity on perceived symptoms and physical function in adults with fibromyalgia: results of a randomized trial. *Arthritis Res Ther*. 2010;12:R55.

37. Fontaine KR, Conn L, Clauw DJ. Effects of lifestyle physical activity in adults with fibromyalgia: results at follow-up. *J Clin Rheumatol*. 2011;17:64–68.

38. Murtezani A, Hundozi H, Orovcanec N, et al. A comparison of high intensity aerobic exercise and passive modalities for the treatment of workers with chronic low back pain: a randomized, controlled trial. *Eur J Phys Rehabil Med*. 2011;47:359–366.

39. Jensen RK, Leboeuf-Yde C, Wedderkopp N, et al. Rest versus exercise as treatment for patients with low back pain and Modic changes. A randomized controlled clinical trial. *BMC Med*. 2012;10:22.

40. Chan CW, Mok NW, Yeung EW. Aerobic exercise training in addition to conventional physiotherapy for chronic low back pain: a randomized controlled trial. *Arch Phys Med Rehabil*. 2011;92:1681–1685.

41. Wing RR, Hamman RF, Bray GA, et al. Achieving weight and activity goals among diabetes prevention program lifestyle participants. *Obes Res*. 2004;12:1426–1434.

42. Pinto AM, Gokee-Larose J, Wing RR. Behavioral approaches to weight control: a review of current research. *Womens Health*. 2007;3:341–353.

43. Miyaki T, Fujikawa T, Kitaoka R, et al. Noradrenergic projections to the ventromedial hypothalamus regulate fat metabolism during endurance exercise. *Neuroscience*. 2011; 190:239–250.

44. Kadoglou NP, Iliadis F, Angelopoulou N, et al. The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus. *Eur J Cardiovasc Prev Rehabil*. 2007;14:837–843.

45. Maiorana A, O'Driscoll G, Cheetham C, et al. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. *J Am Coll Cardiol*. 2001;38:860–866.

46. Hennigan A, O'Callaghan RM, Kelly AM. Neurotrophins and their receptors: roles in plasticity, neurodegeneration and neuroprotection. *Biochem Soc Trans*. 2007;35(pt 2):424–427.

47. Vivar C, Potter MC, van Praag H. All about running: synaptic plasticity, growth factors and adult hippocampal neurogenesis. *Curr Top Behav Neurosci*. 2012. [Epub ahead of print].

48. McBeth J, Prescott G, Scotland G, et al. Cognitive behavior therapy, exercise, or both for treating chronic widespread pain. *Arch Intern Med*. 2012;172:48–57.