

Evaluation of a Multidisciplinary Rehabilitation Program for Fibromyalgia: A Pilot Study

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Abstract

Background. Fibromyalgia syndrome, the most common cause of widespread pain, is characterized by undifferentiated musculoskeletal pain, tenderness and fatigue. Despite improved diagnostic criteria, fibromyalgia remains resistant to conventional treatment. Modest, short-term improvement has been reported with the use of analgesics

and antidepressants, as well as non-pharmacological modalities for some patients.

Purpose. This pilot study examined the effects of a multidisciplinary fibromyalgia rehabilitation program on 21 women with fibromyalgia syndrome diagnosed by specialists and general practitioners.

Methods. The Fibromyalgia Rehabilitation Program is designed to improve patients' quality of life. Initial assessment relied on evaluation by a medical specialist. Patient and spouse education, counseling, coping strategies, dietary intervention and sound nutrition play essential roles in rehabilitation, with selected nutraceuticals, herbs and botanical extracts being employed as adjunctive therapy.

Results. Response to the individualized 6-month program was monitored by a multidisciplinary team. Significant improvement in pain and co-morbid conditions ranged from 35.9% to 78.7% ($p < 0.0001$) on a Symptom Severity Rating Scale, which assessed widespread muscle pain, joint pain, pain with repetitive movement, pain with exercise, stiffness, tender points, disturbed sleep, fatigue, depression, anxiety, irritable bowel syndrome, painful feet, and restless legs syndrome. Significant improvement was also observed for tension and memory ($p = 0.0001$), cold intolerance ($p = 0.0002$), pain at rest ($p = 0.0005$) and frequent urination ($p = 0.0005$). Monthly assessments indicated a gradual reduction in symptoms throughout treatment. The Fibromyalgia Impact Questionnaire administered at the end of treatment confirmed significant reductions in pain, fatigue, stiffness, anxiety, and depression (relative improvement: 65.6%-75.3%). Additionally, improvements were also noted in fibromyalgia impact on household activities (69.8%; $p < 0.0001$), work performance (92.1%; $p < 0.0001$) and morning tiredness (85.3%; $p < 0.0001$).

Conclusion. Patients enrolled in this pilot study of the Fibromyalgia Rehabilitation Program experienced significant improvement in muscle pain and common co-morbid conditions, such as irritable bowel syndrome and fatigue. They reported improved quality-of-life measures as well as improvement in occupational performance and household tasks. Careful monitoring indicated a high degree of patient compliance. The program was well tolerated, with few side effects reported.

Introduction

Fibromyalgia syndrome represents the most common cause of chronic generalized pain leading to reduced daily activity and increased use of healthcare services.^{1,2} Widespread muscle pain and tender point sensitivity often increase after physical activity. The prevalence of fibromyalgia syndrome has been estimated to range from 2% to 3% in the general U.S. population, and increases with age.³ Fibromyalgia affects more women than men, and >7% of women between the ages of 60 and 79 suffer from this condition.³ Morbidity associated with fibromyalgia syndrome profoundly impacts on an affected individual's quality of life and reduces worker productivity, with surveys suggesting that up to 30% of patients with fibromyalgia experience impaired work performance.⁴ Although specific diagnostic criteria for the presence of fibromyalgia are ill-defined and specific pathological findings are often lacking, an evidence-based protocol for diagnosing this condition has been developed by the American College of Rheumatology.⁵ These efforts and recent clinical research have helped to more firmly establish fibromyalgia syndrome as a distinct clinical entity.

Characteristically, fibromyalgia patients experience multiple comorbid conditions.^{3,5} These may include chronic fatigue,⁶ morning stiffness,⁵ intermittent constipation and diarrhea typical of irritable bowel syndrome,⁷ cognitive dysfunction,⁸ sleep disturbances,⁵ as well as tension headaches or migraine.⁹ Many patients with fibromyalgia also have a history of depression and/or anxiety.¹⁰ Additionally, immune dysfunction,¹¹ neuroendocrine dysfunction¹² and oxidative stress¹³ have all been implicated in the pathophysiology of fibromyalgia syndrome. This constellation of vaguely defined symptoms and co-existing conditions associated with fibromyalgia appears to be unrelated to peripheral damage or inflammation.¹⁴ As would be anticipated, the presence of multiple conditions negatively impacts affected patients, so that those who experience both fibromyalgia and chronic fatigue have a worse overall health status and greater co-morbidity than patients with fibromyalgia alone.⁶

The heterogeneity of symptoms and lack of specific pathological findings in a majority of affected patients complicate the treatment of fibromyalgia, which remains essentially non-specific. The administration of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) has been found to help ameliorate pain in only 30-50% of cases, and their effectiveness diminishes with repeated use.¹⁵

Nonsteroidal anti-inflammatory drugs (NSAIDs), which are frequently prescribed, generally prove ineffective in treating the symptoms of fibromyalgia.¹⁵ Furthermore, centers that specialize in the treatment of rheumatic conditions have also reported only marginal improvement.¹⁶ Non-pharmacological modalities such as physiotherapy, aerobic exercise, relaxation techniques, and counseling may modestly improve symptoms in selected patients.¹⁷⁻¹⁹

The multiplicity of co-morbid conditions and symptomatology makes it unlikely that any single therapy can effectively provide long-term symptom relief for a majority of fibromyalgia patients. In view of the limited success of conventional approaches in treating this syndrome, recent interest has focused on the use of a combination of treatment modalities.²⁰ An earlier communication described a new model for fibromyalgia rehabilitation, developed by a multidisciplinary Canadian team.²¹ This individualized program is designed to help ameliorate the symptoms of fibromyalgia and co-morbid conditions with the long-term goal of improving patients' quality of life. The program therefore aims to increase the patient's ability to function productively at home and in the work environment, with an overall emphasis on rehabilitative efforts.

Thus, the Fibromyalgia Rehabilitation Program is designed to assist the patient with pain management, and improve functional capacity and cognitive behavior through lifestyle and dietary modifications. To meet these goals, the program utilizes an interdisciplinary team of healthcare professionals, including medical specialists such as internists and nurses as well as dietitians, social workers and pharmacists. The present report describes the results of an open pilot study in 21 female fibromyalgia patients who have been treated in this program.

Study Patients and Methods

Patient Selection

A total of 21 women with a mean age of 51.3 years (range: 33-66 years) were enrolled in this pilot clinical trial (reflecting the fact that relatively few males have been referred for fibromyalgia rehabilitation). Most of the study patients were post-menopausal, none was pregnant, and none contemplated pregnancy. Each patient provided written

informed consent and agreed to enroll in the Fibromyalgia Rehabilitation Program. Prior to entering the program, the study patients had a history of myalgias, often associated with chronic fatigue and irritable bowel syndrome (IBS), over a period of time ranging from 2 to 22 years (mean duration: 6.5 years).

Methods

Patients were referred to the Fibromyalgia Rehabilitation Program by a family physician or medical specialist (e.g., rheumatologist, neurologist) who had made the diagnosis of fibromyalgia. This initial diagnosis was based on a comprehensive physical examination by the referring physician, a thorough medical history, appropriate blood testing, and other diagnostic criteria relevant to myalgias. During initial screening, the participating social worker made the determination as to whether a referral for psychological counseling was indicated, and met with the patient and family members to establish that she was able and willing to complete the full 6-month rehabilitation program. Overall results of the initial assessment were then reviewed by an independent specialist in internal medicine prior to acceptance of the subject into the study.

Standard components of the Fibromyalgia Rehabilitation Program include patient education; dietary modification and use of a selected combination of nutraceuticals; lifestyle changes; patient calendars and questionnaires designed to measure fibromyalgia symptoms and their impact on overall patient function; and regularly scheduled follow-up visits. Doses and intensity of use of the standard treatment components were adjusted in accordance with indications and complaints, as well as patient response to treatment.

Following a psychosocial assessment, the social worker recommended initiation of psychological counseling, participation in fibromyalgia support groups, and/or other behavior modification strategies as appropriate. Patients were also encouraged to develop or strengthen their emotional support networks. Depending upon the extent of symptoms, energy levels and responsiveness to treatment, patients could be encouraged to increase their intensity of physical activity with approval of the referring physician. The nursing staff contacted each patient monthly or bi-monthly for a follow-up interview, which included administering the Symptom Severity Rating Scale. After 6 months, the program team evaluated each individual

patient to determine whether treatment should be continued. Several patients who had experienced a less pronounced response to the rehabilitation program agreed to the continuation of treatment for up to one year.

Dietary Intervention. On being admitted to the study, the subject was interviewed by a registered dietitian, to formulate an individualized diet program based on the results of a 7-day food intake diary, food sensitivity assessments and medical history. The dietary regimen emphasizes a plant-based diet with increased consumption of whole grains, fruits, vegetables and legumes and a balanced intake of key nutrients. These recommended foods increase the intake of fiber, essential nutrients, carotenoids and flavonoids, which promote both immune and digestive health. To minimize inflammation and other disease processes, the patient was also advised to reduce the consumption of alcohol, caffeine, and hydrogenated and saturated fats. Problematic foods were excluded during the initial phases of the program, then gradually reintroduced or rotated according to individual preferences.^{22,23} Fluid intake was increased to >2 liters daily.

Nutraceuticals. The Fibromyalgia Rehabilitation Program incorporates combinations of a selected group of nutraceuticals and botanical preparations, which are prescribed as adjuncts to treatment. The clinical rationale for, and efficacy of, the specific nutraceuticals used in these combinations has been reviewed previously.²¹ These formulations, specifically developed for this program to support major body systems, are prepared by a pharmaceutically licensed facility to assure product consistency, purity and quality. The specific nutraceutical combinations and typical dosages employed in the Fibromyalgia Rehabilitation Program are summarized in Table 1.

On occasion, L-tryptophan was also prescribed as needed for depression or sleep disorders; valerian was substituted for the treatment of mild insomnia in the event that tryptophan was not well tolerated.^{24,25} Clinical response to nutraceutical therapy was monitored throughout the program, and dosages and durations of prescribed supplements were adjusted as necessary. The patient's medical history was carefully reviewed, in order to avoid any contraindications and minimize potential drug-nutrient and/or drug-herb interactions.

TABLE 1. Nutraceuticals administered in the Fibromyalgia Rehabilitation Program.

Prescribed Nutraceutical	Physiological Activity	Composition	Dosage
Hepex™	Supports normal liver function	Herbs and botanical preparations such as silymarin	5 tablespoons in 8 oz water or juice twice weekly for 3 weeks
Ibese™	For symptoms of irritable bowel syndrome	Citrus flavonoids, pectin, slippery elm and marshmallow	2 capsules t.i.d. with meals
Dizume™	Digestive aid	Hydrolytic enzymes	2 capsules t.i.d. with meals
Colonex™	Supports colonic health	Fiber, lactobacilli, bifidobacteria and fructans	1 teaspoon in 8 oz water or juice b.i.d. between meals
Parazyde™	Supports healthy gut ecology	Garlic, clove, rhubarb and pumpkin seed	3 capsules b.i.d (Weeks 1 and 3)
Immunoboost™	Supports the immune system	Siberian ginseng, Reishi mushroom, echinacea, astragalus and ashwagandha	5 ml in 8 oz water or juice b.i.d. for 3 months
Kidney Flush™	Supports normal kidney function	Herbs and botanical preparations such as horsetail, hydrangea and dandelion	2 tablespoons in 8 oz water or juice daily for 1-2 weeks
Electroex™	General nutrition	Wide range of trace minerals	5 ml in 2 L water daily
Minerex™	Beverage mixture	Powdered vegetables (e.g., carrot, tomato, beet and ginger); Siberian ginseng; extracts of Ginkgo biloba leaf and green tea; full complement of vitamins	Week 1: 2.5 ml daily in 8 oz water or juice; Week 2: 5 ml daily in 8 oz water or juice; Week 3: 5 ml between meals in water or juice

Patient Evaluation. Patient response to the program was evaluated by three measurement criteria:

- an exit interview and assessment by an independent medical evaluator;
- the Symptom Severity Rating Scale (SSRS) (see Table 2); and
- the Fibromyalgia Impact Questionnaire (FIQ), a standardized instrument widely used to study fibromyalgia syndrome.^{26,27}

The SSRS, developed by Cutler Clinics, was administered at least once a month throughout the duration of treatment and served as a primary endpoint of the study at 6 months, and at the end of treatment (up to 12 months).²¹ Each item is rated on a scale of 0 (no impairment) to 10 (the most severe or greatest impairment). The SSRS is composed of 20 questions assessing the health status of patients with fibromyalgia syndrome. Of these, 8 measure varying aspects of pain

TABLE 2. Symptom Severity Rating Scale (SSRS) items.*

1. Widespread pain in muscles
2. Pain in joints
3. Muscle pain when you are resting
4. Muscle pain with repetitive work
5. Muscle pain when exercising
6. Stiff muscles
7. Tender points
8. Decreased sense of energy at times during the day
9. Sleeping problems
10. Varying degrees of anxiety
11. Varying degrees of depression
12. Decreased mental energy
13. Memory difficulties
14. Tension headaches
15. Migraine headaches
16. IBS-related problems
17. Frequent or urgent urination
18. Painful or sore feet
19. Intolerance to cold or cold extremities
20. Restless legs syndrome or leg aches

*Patients respond to the question, “Over 7 days, on a bad day when your symptoms/ conditions are at their worst, rate their severity on a scale of 0 to 10 (10 being the most severe).”

identified in fibromyalgia patients, 2 focus on fatigue, others evaluate aspects of memory problems, symptoms of irritable bowel syndrome (IBS), tension and migraine headaches, and 4 assess other frequently reported symptoms, including restless legs/leg pain,²⁸ cold sensitivity,²⁹ painful/sore feet³⁰ and frequent urination.³¹

As a second endpoint measure, the FIQ was administered to patients upon completion of treatment. This standardized scale assesses several areas of fibromyalgia-associated impairment (depression, anxiety, generalized pain, stiffness, fatigue), as well as measuring ability to function in home activities and work performance. Both questionnaires were administered verbally by the program staff in a semi-formalized setting, to ensure the absence of any questioner influence on patients' responses.

Statistical Analysis. Primary analyses involved comparisons of baseline and 6-month symptom severity data from the SSRS, and of baseline and endpoint data on the SSRS and FIQ upon termination of patient treatment. Due to the relatively small sample size and non-parametric distribution of differences, a more conservative test, the sign test (M statistic), was employed. A significance level of 0.05 was selected. The data were analyzed in SAS version 8.12.

Results

Following completion of the study period, the medical evaluator determined that all patients showed improvement ranging from 50% to 90%, based on patients' self-assessments. Typically, subjects reported a reduction in symptoms, including a decrease in widespread and localized pain, reduced IBS symptoms, improved mood, and more restful sleep patterns. An increase in energy level was often noted as well. Improvement in day-to-day functioning and mood were corroborated by independent spouse interviews.

Symptom Severity

Baseline assessment showed that study patients reported from 13 to 20 symptoms of pain and multiple co-morbid conditions on the 20-item SSRS (mean: 17.5 symptoms/conditions per patient). In 95% of the study subjects, at least one complaint completely resolved within 6 months (mean: 5.6 complaints resolved; range: 0-15).

Figure 1 summarizes the SSRS data for representative symptoms and co-morbid conditions as mean scores at baseline and after 6 months of program participation, including levels of statistical significance for absolute differences between the pre- and post-study data. From an initial mean symptom score of 135.4 (of a possible 200), patients recorded a mean final score of 49.9. This translates into a relative overall improvement of 65.2%, with relative improvement between baseline and 6-month scores for individual symptoms ranging from 35.9% to 78.7%.

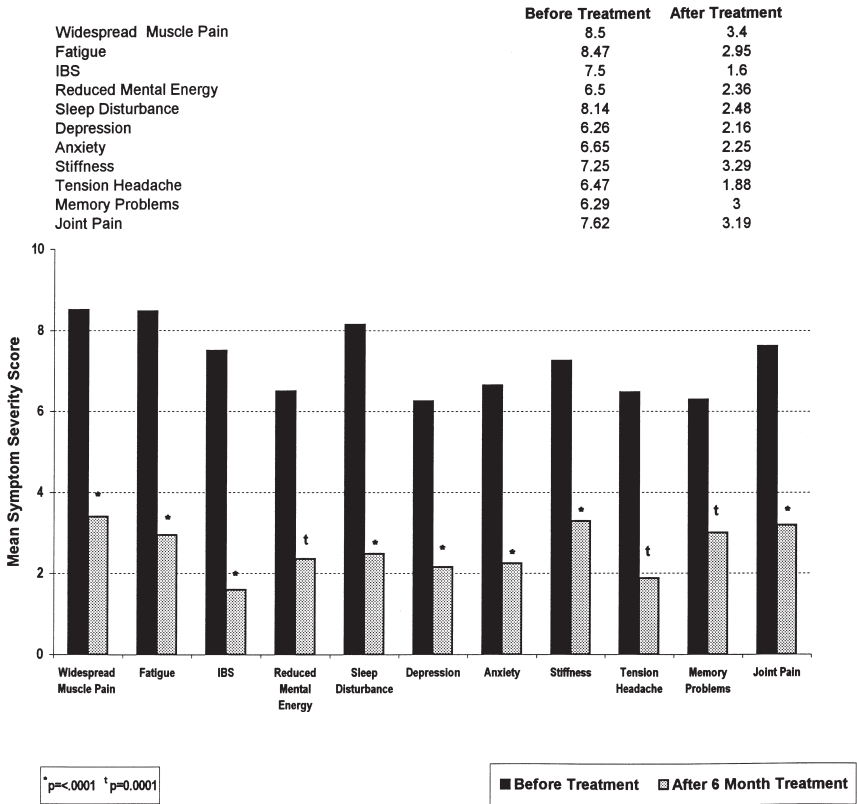


FIGURE 1. Symptom Severity Rating Scale (SSRS) scores for 11 symptom complexes, including widespread muscle pain and co-morbid conditions, in fibromyalgia patients at study entry and after completion of the 6-month Fibromyalgia Rehabilitation Program. Levels of statistical significance refer to absolute differences between pre- and post-treatment data.

Individual Measures

Widespread and Localized Pain. Eight SSRS questions focused on manifestations of general and localized pain. Consistent with the diagnosis of fibromyalgia, patients reported high initial pain scores. After 6 months of treatment, at least two of the pain scores resolved completely. Widespread muscle pain, reported by 20/21 (95%) of patients, resolved completely in 4 of the 20 cases, and the 60.0% overall improvement was highly significant ($p < 0.0001$). According to the American College of Rheumatology (ACR) report, widespread pain is the most common complaint in fibromyalgia, reported by 97% of patients.⁵ While all of the patients initially reported experiencing widespread joint pain, a highly significant ($p < 0.0001$) overall relative improvement of 58.4% was achieved following the study. Complete resolution occurred in 6/21 (28.6%) of the cases. Additional categories of widespread muscle pain—pain at rest, pain with repetitive work and pain with exercise—improved significantly, ranging between 55.9% ($p < 0.0001$) and 65.9% ($p = 0.0005$).

All of the study patients experienced muscle stiffness, which the ACR reported occurs in over three-quarters of fibromyalgia patients;⁵ this symptom improved significantly ($p < 0.0001$), and completely resolved in 4/20 (20%) of cases. Tender point sensitivity, which was reported by 19/21 (90.5%) of the study patients, showed a relative improvement of 58.3% ($p < 0.0001$) at the end of treatment. Sore/painful feet and leg pain/restless legs syndrome, previously reported in 90-95% of cases, improved by 72.6% and 73.4%, respectively ($p = 0.0001$); complete resolution of symptoms of leg pain was achieved in 52.6% of cases, and in 30% of cases of painful feet. In a previous study,²⁸ restless legs syndrome occurred in 25.8% of fibromyalgia patients; regional anatomical areas can be a source of chronic pain, and there is evidence linking joint trauma and fibromyalgia.³⁰

Fatigue. All patients in this study reported long-term chronic fatigue, which also improved significantly following treatment ($p < 0.0001$). Study patients achieved a relative improvement of 65.2% in this common symptom of fibromyalgia, with complete resolution in 7 of the 21 cases (33.3%). Low mental energy, reported by two-thirds (14/21) of the study patients, resolved in 28.6% of cases, with overall relative improvement of 63.6% ($p = 0.0001$).

Bowel Disturbances. All but one (95%) of the study group reported chronic bowel symptoms typical of IBS. The relative improvement in this complaint was 78.7% ($p<0.0001$), the highest level of relief recorded among the 20 SSRS symptoms and conditions. Bowel complaints resolved completely in 9 of 20 cases (45%).

Disturbed Sleep. All patients initially complained of sleep disorders, a problem reported by the ACR to occur in an estimated three-quarters of all fibromyalgia patients.⁵ Relative improvement of 70.3% ($p=0.0001$) was noted in this parameter, with 4 (19%) of the 21 patients returning to a normal sleep schedule.

Altered Psychological Status. In the present study, 95% of the patients initially complained of anxiety and 90.5% of minor depression, respectively. These problems resolved in over one-third of respective study patients, and overall improvement was significant—56.2% and 65.5%, respectively ($p<0.0001$). An additional 17 of the 21 study subjects reported memory problems, which resolved in 5 cases following treatment, with 52.4% relative improvement in the overall study cohort ($p=0.0001$). Problems with mental alertness and memory have been observed in fibromyalgia patients by other investigators.⁸

Headache. Tension headache, which occurred in 17/21 (80.9%) of patients, resolved in 9 (52.8%) of the cases. Relative improvement was significant ($p=0.0001$). Complete resolution was also reported by 4 of the 6 patients who initially complained of migraine headache. The ACR reported that headache occurs in more than half of all fibromyalgia patients.⁵

Other Co-Morbid Conditions. In addition to the above symptoms and conditions, frequent urination was reported by 19/21 (90.5%) of patients; relative improvement in this symptom (72.6%) was also highly significant ($p=0.0005$), and complete resolution occurred in 36.8% of cases. Cold intolerance, which has previously been reported by many fibromyalgia patients,²⁹ was a baseline complaint in 17 of the 21 study patients. This problem resolved in only 2 of the patients, with a relative improvement of 35.9% ($p=0.0002$), the lowest post-study reduction observed among the 20 symptoms and co-existing conditions evaluated.

Time Course for Improvement in Symptom Severity

Figures 2 and 3 illustrate the progressive improvement in mean symptom severity scores as measured by the SSRS at monthly intervals throughout the study. The reduction in symptoms associated with these 11 indicators of fibromyalgia can be observed throughout the 6-month study, with symptom improvement being measurable as early as 1 month after initiating treatment. The greatest relative symptomatic improvement occurred within the first 4 months of participation in the Fibromyalgia Rehabilitation Program, and was then generally maintained, but with a subsequent tapering off of further improvement.

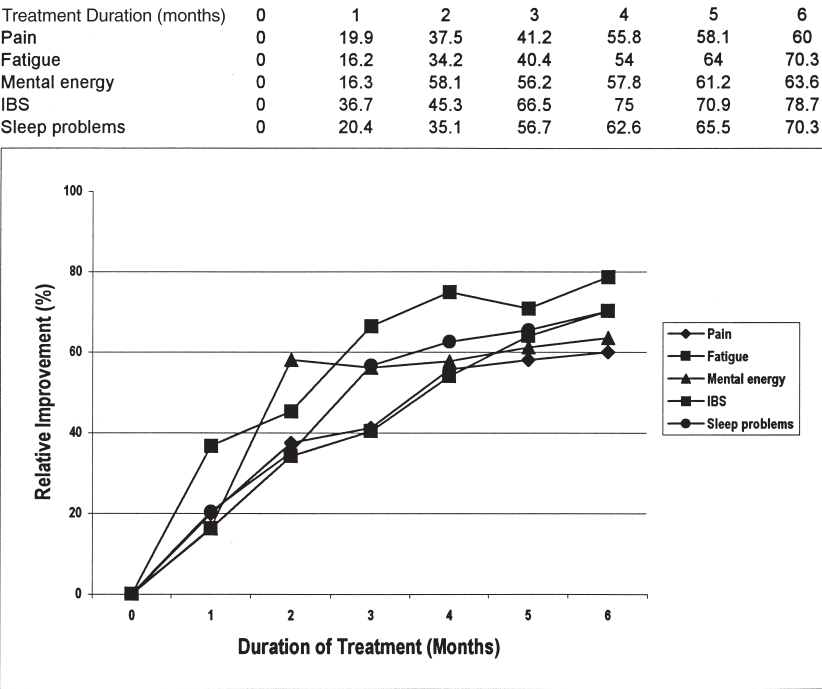


FIGURE 2. Monthly assessments of improvement in severity of widespread muscle pain, fatigue, mental energy, irritable bowel syndrome, and sleep problems for patients enrolled in the Fibromyalgia Rehabilitation Program. Mean SSRS scores are indicated.

Treatment Duration (months)	0	1	2	3	4	5	6
Stiffness	0	6.25	25.9	37	45.5	51.1	58.2
Memory Problems	0	13	29.8	35.5	47.6	47.6	52.4
Anxiety	0	35.3	44.3	47.4	52.6	57.9	56.2
Depression	0	21.8	39.5	47.9	60.5	61.3	65.5
Tension Headache	0	27.2	32.5	54.5	62.7	70	70.9
Joint Pain	0	25.0	31.0	40.0	50.6	57.5	58.4

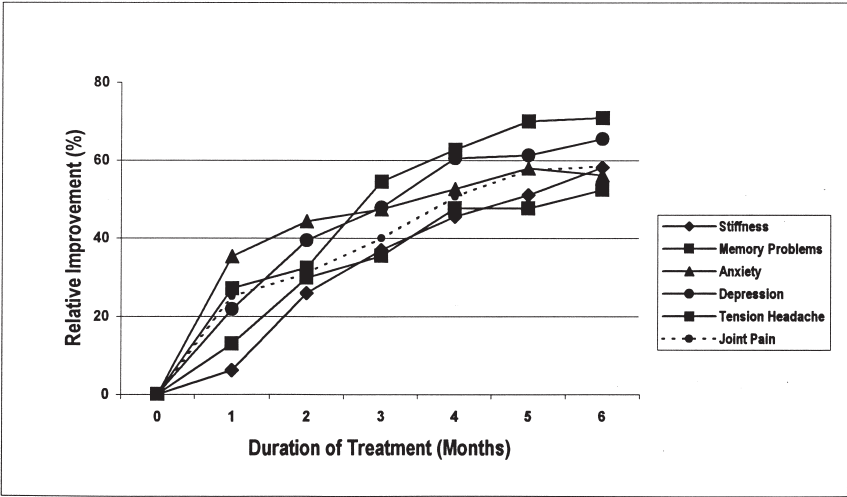


FIGURE 3. Monthly assessments of improvement in severity of stiffness, memory problems, anxiety, depression, tension headache and joint pain for patients enrolled in the Fibromyalgia Rehabilitation Program. Mean SSRS scores are indicated.

Fibromyalgia Impact Questionnaire (FIQ) Results

Table 3 summarizes study results on the FIQ, comparing mean scores at baseline and after completion of treatment (6-12 months). Significant improvement was observed in all conditions assessed by the FIQ. The impact of fibromyalgia on daily living, assessed by the first question of the FIQ, was apparent in all patients at the outset of the study. Following treatment, 8 of the 21 patients were fully able to carry out household tasks, with an overall relative improvement of 69.8% ($p<0.0001$). In addition, initial fibromyalgia symptoms affected work performance in 11 of the 21 women. Following the study, the relative improvement in work performance was 92.1% ($p= 0.0010$),

TABLE 3. Assessment of efficacy of the Fibromyalgia Rehabilitation Program using the Fibromyalgia Impact Questionnaire^{26,27} at end of treatment (6-12 months).

Question	Baseline Mean	End of Treatment Mean	Difference*	Sign Test (M)	p Value	Relative Change (%)
1. Impact of fibromyalgia on household activities.	5.06	1.53	3.53 (0.598)	9.5	<0.0001	69.8
2. Affect of symptoms on ability to do work.	6.90	0.54	6.36 (0.679)	5.5	0.0010	92.1
3. How bad has your pain been?	8.00	2.29	5.71 (0.598)	9.5	<0.0001	71.3
4. How tired have you been?	8.62	2.48	6.14 (0.518)	10.5	<0.0001	71.3
5. How tired in the morning?	8.67	1.43	7.24 (0.516)	10.5	<0.0001	83.5
6. How bad has your stiffness been?	8.09	2.00	6.09 (0.472)	10.5	<0.0001	75.3
7. How nervous or anxious?	5.94	2.00	3.94 (0.734)	8.5	<0.0001	66.3
8. How depressed or blue?	6.38	2.19	4.19 (0.743)	7.5	<0.0001	65.6

*(Standard error of the mean)

the largest percentage gain reported among all study measurements. At the end of treatment, 9 of the 11 study patients (81.8%) reported that fibromyalgia and co-morbid conditions no longer impeded their work. Finally, all of the patients reported having suffered from morning tiredness, with complete resolution occurring in 12 cases and overall relative improvement of 83.5% ($p<0.0001$).

At the end of treatment, a comparison was also made between the FIQ scores for pain and 4 co-morbid conditions that are common to both the FIQ and SSRS questionnaires. Generalized pain, reported by all study patients, improved by 71.3% ($p<0.0001$) on the FIQ and by 69.9% ($p<0.0001$) on the SSRS scale. Similarly, general tiredness showed a relative improvement of 71.3% ($p<0.0001$) on both scales, further reinforcing the significance of the overall study findings. The relative improvement in stiffness (reported by all patients) was 75.3% ($p<0.0001$) on the FIQ compared to 66.4% ($p=0.0001$) with the SSRS. Anxiety, reported by 18 of the 21 subjects, showed overall improvements of 66.3% and 66.2% on the FIQ and SSRS, respectively (both $p<0.0001$). Depression, which was reported in 16 cases, had a relative improvement of 65.6% and 70.5% on the FIQ and SSRS scales, respectively, both highly significant ($p<0.0001$).

Other Study Findings

Stability of Fibromyalgia Symptoms. In order to determine whether patients would continue to improve with extended treatment, 12 of the study subjects agreed to continue the rehabilitation program for additional periods ranging from 7 to 12 months. Evaluation of symptoms at termination of the extended treatment period showed further improvements compared to 6-month scores (mean: 12.6%; range: 0-24%). Thus, these preliminary observations suggest that some patients may derive additional benefit with continuation of the Fibromyalgia Rehabilitation Program for up to one year.

Although in general symptoms gradually improved throughout the 6-month treatment period, 2 patients (9.5%) with high initial symptom scores reported no improvement in muscle pain and minimal improvements on the SSRS scale, with a temporary increase in symptom severity over baseline for IBS and fatigue. Four other patients reported minor increases in symptom severity (1-3 symptoms per patient) that persisted for 1-2 months following partial resolution. However, extended treatment (7-12 months) led to significant reduc-

tions in symptom severity in these cases. A significant study observation was that increased severity of symptoms often corresponded to the occurrence of stressful events in patients' personal lives.

Exercise. Consistent with the general improvement in quality of life, 11 of the 21 study patients increased their physical activity during the program or upon its completion. In some cases patients began to walk regularly or increased walking duration, while others joined a gym, began or resumed aqua exercise programs, or increased their level of physical activity in the home (e.g., housework, such as washing dishes and vacuuming).

Weight Management. Although weight management was not a formal part of the study program, the increased emphasis on diet and greater intensity of physical activity resulted in 5 women reporting a weight loss, with a mean reduction of 12 pounds. Several of the patients continued their enrollment in a weight loss program. In addition, one underweight patient reported a beneficial increase in weight from 90 to 98 pounds over the 6-month study period.

Use of Prescription Drugs. Medications prescribed by the patient's primary physician or referring specialist were not under the purview of this program. However, during follow-up 5 patients indicated that, in consultation with their family doctors, they had gradually reduced or eliminated medications over the course of the study.

Adverse Effects. Mild side effects were reported with the use of four nutraceutical formulations. One patient complained of itchiness upon taking the beverage mixture. A second reported nausea with the combination supplement to support normal function of the urinary system. One patient complained of abdominal bloating and cramps with the formulation designed to help normalize immune functioning, and another experienced gastrointestinal upset following ingestion of the supplement designed to support healthy gut ecology. These patients were advised to discontinue the respective supplement for 1 week, and then to resume treatment at a reduced dosage following symptom disappearance. The dosage was then gradually increased as needed.

Discussion and Conclusion

Fibromyalgia syndrome is generally refractory to conventional treatments. Consistent with this observation, medical histories of the study patients indicated that they had experienced little improvement in fibromyalgia symptoms and associated conditions with prior use of prescribed antidepressants, analgesics, anti-inflammatory agents or sleep aids. Other modalities, including mild exercise, chiropractic treatment, acupuncture, or use of such supplements as glucosamine and chondroitin sulfate were generally ineffective or afforded at most temporary relief. It was also instructive that 11 of the study participants had experienced a worsening of symptoms following a trauma such as an automobile accident or work-related injury. Three others reported that illness (e.g., viral infection) or emotional trauma had dramatically worsened their fibromyalgia symptomatology.

Patient Assessment

Patient improvement in this pilot study was assessed by three separate criteria: evaluation by an independent medical specialist, assessment by the SSRS scale after 6 months and on completion of treatment, and by the FIQ on completing treatment. The independent medical evaluator noted that at the conclusion of the trial, patients typically had less pain, reduced fatigue and IBS, and experienced improved mood and sleep patterns. The negative impact of fibromyalgia on patients' quality of life is well recognized.³² Meaningful patient response to the Fibromyalgia Rehabilitation Program was documented by significant improvement in work performance and increased ability to perform household tasks, as well as reduced pain, chronic fatigue, IBS, disturbed sleep and other co-morbid conditions. The mean baseline FIQ score of 57.7 in the overall study cohort decreased to 14.5 at endpoint, a reduction of 74.9%. (With a maximum score of 80, an FIQ rating of 52.3 is considered indicative of moderate fibromyalgia.²⁷)

Similarly high degrees of symptomatic improvement in pain, fatigue, stiffness, anxiety and depression were observed on both SSRS and FIQ rating scales, with relative improvements of 66.4-71.3% on the SSRS and 65.6-75.3% with the FIQ. Work-related performance improved markedly. Before starting the program, 11 women had either reduced their hours, terminated employment or expressed concern that fibromyalgia might force them to reduce work hours. This

sub-group experienced over 90% improvement. Important co-morbid conditions also showed marked improvement over the study period. IBS, a frequent complaint among the study patients, improved significantly as well. Pervasive fatigue, an additional hallmark of fibromyalgia syndrome, showed similar levels of improvement on both questionnaire measures: 65.2% improvement in perceived energy level using SSRS, and 71.3% improvement on the FIQ. It has been observed that up to 52% of fibromyalgia patients report a history of chronic fatigue, and 33% have currently received this diagnosis;¹⁰ the ACR estimates that 78.2-85.2% of fibromyalgia patients suffer from persistent fatigue.⁵ Anxiety and depression, which affected most of the patients in this study cohort, also improved significantly with treatment. The ACR noted a prevalence of anxiety in as many as half of all fibromyalgia patients,⁵ with other studies concluding that depression occurs in 50-70% of affected patients¹⁰ and anxiety disorders in 39% of cases.⁸

Taken together, these results strongly suggest that this multidisciplinary rehabilitation program can be of significant clinical benefit to fibromyalgia patients. Minor adverse effects of supplemental nutraceuticals were infrequent and readily resolved with cessation and re-introduction at reduced dosage. Not all patients showed improvement in all symptoms, and patient responses to treatment varied, possibly reflecting the heterogeneity of fibromyalgia patients.^{27,33} Nonetheless, endpoint evaluations indicated significant overall improvement in all associated symptoms and co-morbid conditions, supporting the concept that a comprehensive fibromyalgia management program can be effective in treating a constellation of related conditions resistant to conventional treatment.

Symptom improvement began during the first month of treatment, with the most pronounced responses observed within the first 4 months of the study. However, further research will be needed to determine if improvement in muscle pain, IBS, depression, anxiety and other symptoms reaches a plateau at 4-6 months. It is reasonable to anticipate that a number of co-morbid conditions may improve at differing rates, and gradual improvement could be a function of the lag time needed to reflect the impact of necessary lifestyle changes, such as diet. Further improvement in pain and co-morbid conditions may occur with treatment periods >6 months, especially for those

patients who may respond more slowly. On-going patient education and reassurance also proved to be important factors in assisting patients in assuming a greater degree of individual responsibility for their own health.

Comparison of SSRS and FIQ Scores

Use of the FIQ has been recommended as a primary endpoint in clinical trials of fibromyalgia syndrome.^{26,27} While the FIQ scale is based on patients' overall impression of symptoms over the preceding week, the SSRS asks patients to evaluate the worst day of the preceding week. This reflects the finding that fibromyalgia patients typically experience "good" and "bad" days during an average week, with unpredictable frequency (unpublished observations).

The FIQ and SSRS complement each other well, as both study instruments examine such important fibromyalgia indicators as generalized pain, stiffness, fatigue, anxiety and depression. However, the FIQ also evaluates several factors that are not included in the SSRS, e.g., work performance, activities related to day-to-day living, and morning tiredness. On the other hand, the SSRS assesses 8 pain manifestations, as well as headache, tender points, disturbed sleep and 4 other indicators that do not usually appear on symptom questionnaires. Comparisons of baseline and endpoint self-assessments of pain, IBS, fatigue, sleep disturbances and related conditions are important in determining the patient's clinical status. It has been reported that commonly used measures of pain were no more effective than patients' self-assessment in evaluating therapeutic modalities.³⁴ While the SSRS represents a promising instrument for the evaluation of fibromyalgia syndrome, future studies will also examine non-symptomatic individuals and fibromyalgia patients not enrolled in the program, together with longitudinal studies of larger patient populations, in order to more effectively standardize this instrument and assess its diagnostic accuracy in greater depth.

Patient Compliance

Careful monitoring of each individual patient's progress throughout treatment is a distinctive feature of the Fibromyalgia Rehabilitation Program. Careful review of weekly calendars submitted by patients, bi-monthly or monthly interviews with nurses, and pharmacy records

suggest that patient compliance in this study was very high. This was likely due to several factors. Initial screening successfully identified those patients who were highly motivated to improve their health and return to normal daily activities. Moreover, the process of educating patients regarding the nature of fibromyalgia syndrome and the necessity for substantive lifestyle changes promoted trust between patients and the healthcare team. It was also apparent that patients with a supportive home environment were more likely to complete this multifaceted protocol. Therefore, the program also emphasizes informing spouses and other family members on all aspects of fibromyalgia and its management, in addition to educating the patient.

Post-Study Follow-Up and Other Considerations

Formal 6-month and 1-year follow-ups of the first patients to complete the Fibromyalgia Rehabilitation Program are currently in progress. Preliminary results suggest that those who adhere to the essential lifestyle changes initiated in this program can successfully maintain the improved quality of life achieved during the study. Conversely, it also appears that patients who revert to pre-treatment behaviors including previous diets, who fail to resolve complicating emotional issues, or who develop other chronic debilitating conditions may well experience a worsening of fibromyalgia symptoms. On completing the study and final assessment, patients are given the option of a 1-year after-care program, consisting of continued lifestyle and dietary changes initiated during treatment, maintenance dosage regimens of the component nutraceuticals, and monthly or bi-monthly monitoring by clinic staff.

A small sub-set of fibromyalgia patients appear to derive minimal benefit from the 6-month rehabilitation protocol, but may improve with extended treatment of up to 12 months. They may also experience a transient worsening of certain symptoms, possibly related to emotional stress. Fibromyalgia syndrome appears to be a relatively stable condition, and it has been argued that this is not a progressive disorder.²⁷ Monthly or quarterly assessments in other studies have revealed little change in most untreated patients.³⁵

In view of the high degree of personal and occupational disability experienced by patients with fibromyalgia and chronic fatigue, others have urged the development of rehabilitation programs targeted to these conditions.³⁶ The strength of a multidisciplinary program lies in

its ability to address both the physical and psychosocial manifestations of fibromyalgia and co-morbid conditions, which do not respond to monotherapies.

The Fibromyalgia Rehabilitation Program illustrates the potential of multiple treatment modalities, including nutrition and diet, for the management of fibromyalgia delivered by an interdisciplinary team.²⁰ In related research, benefits of a 12-week rehabilitation program emphasizing physiotherapy were measurable for up to 1 year after treatment.¹⁹ A controlled trial of a 4-session health education program improved quality of life and significantly reduced pain.³⁷ An interdisciplinary program featuring coping skills, relaxation techniques and communication skills successfully improved pain and FIQ scores after a one-month follow-up.³⁸

The use of dietary intervention and nutraceuticals are distinctive elements of the Fibromyalgia Rehabilitation Program. Diet clearly plays a pivotal role in many chronic health conditions, and fibromyalgia syndrome is no exception. For example, diet and nutrition have long been recognized as both standard first-line treatment and adjunctive therapy for hypertension and diabetes.^{39,40} Plant-based diets help increase antioxidant status, decrease oxidative stress and reduce pain indices. Furthermore, prudent plant-based diets have benefited selected fibromyalgia patients as well as those suffering from arthritis.⁴¹⁻⁴³ Accordingly, nutraceuticals and specific botanical preparations are used as adjunctive therapy in this rehabilitation program.²¹

Based on the results of controlled clinical trials, case studies and other investigations, The German Commission E has recommended the use of certain supplemental agents.⁴⁴ Specific nutraceuticals have been shown to support the digestive, immune and musculoskeletal systems, and indirectly benefit the nervous system and endocrine system.²¹ As integral components of a comprehensive management program, nutraceuticals, botanical preparations and a prudent diet may help to normalize digestion,⁴⁵ improve liver and kidney function,⁴⁴ ameliorate IBS symptoms,⁴⁶ reduce pain and inflammation,⁴⁷ improve memory deficits⁴⁴ and disturbed sleep,²⁵ and counter fatigue,^{44,48} among others.²¹

Another important consideration is the cost-effectiveness of fibromyalgia treatment. Fibromyalgia patients make proportionately greater use of available medical resources, placing considerable economic strain on the overall healthcare system. Canadian fibromyalgia

patients made an average of 12.1 doctor visits annually, compared with 4.3 for asymptomatic controls.⁴⁹ Fibromyalgia patients also visited specialists three times more frequently, had more hospitalizations, and required more prescription medications than control patients. Another report found that the cost of health services for fibromyalgia patients was twice that of controls without widespread pain.⁵⁰ The average annual healthcare expenditure per fibromyalgia patient was estimated to be \$2,274 in the U.S.⁵¹ Up to 30% of affected patients reported fibromyalgia-related work impairment, and 26% of patients with fibromyalgia receive disability benefits;⁴ in 1989, private insurers were estimated to be paying \$200 million/year for fibromyalgia disability claims in Canada alone.⁵² In recognition of the increased healthcare expenditures that have been documented as the result of fibromyalgia, future studies will also include appropriate cost/benefit analyses and address the cost-effectiveness of the Fibromyalgia Rehabilitation Program with respect to both direct and indirect expenditures.⁵³

In summary, patients enrolled in this pilot study of the Fibromyalgia Rehabilitation Program experienced significant improvement in such widely-recognized symptoms and co-morbid conditions as widespread soft tissue pain, IBS and chronic fatigue, with significant resulting improvements in their quality of life. This comprehensive, multidisciplinary management program was both effective and well tolerated, and future studies will also examine the potential to achieve further symptom improvement by extending the duration of treatment beyond 6 months, especially for slow treatment responders.

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References

1. Bennett RM: Fibromyalgia: The commonest cause of widespread pain. *Compr. Ther.* 21:269-275, 1995.
2. De Girolamo G: Epidemiology and social costs of low back pain and fibromyalgia. *Clin. J. Pain* 7(Suppl. 1): S1-S7, 1991.
3. Wolfe F, Ross K, Anderson J, et al.: The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum.* 38:19-28, 1995.
4. Wolfe F, Anderson J, Harkness D, et al.: Work and disability status of persons with fibromyalgia. *J. Rheumatol.* 24:1171-1178, 1997.
5. Wolfe F, Smythe HA, Yunus MB, et al.: The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia: Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 33:160-172, 1990.
6. White KP, Speechley M, Harth M and Ostbye T: Co-existence of chronic fatigue syndrome with fibromyalgia syndrome in the general population. A controlled study. *Scand. J. Rheumatol.* 29:44-51, 2000.
7. Triadafilopoulos G, Simms RW and Goldenberg D: Bowel dysfunction in fibromyalgia syndrome. *Dig. Dis. Sci.* 36:59-64, 1991.
8. Park DC, Glass JM, Minear M, et al.: Cognitive function in fibromyalgia patients. *Arthritis Rheum.* 44:2125-2133, 2001.
9. Peres MF, Young WB, Kaup AO, et al.: Fibromyalgia is common in patients with transformed migraine. *Neurobiology* 57:1326-1328, 2001.
10. Hudson JI, Goldenberg DL, Pope HG Jr, et al.: Comorbidity of fibromyalgia with medical and psychiatric disorders. *Am. J. Med.* 92:363-367, 1992.
11. Maes M, Libbrecht I, Van Hunsel F, et al.: The immune-inflammatory pathophysiology of fibromyalgia: Increased serum soluble gp130, the common signal transducer protein of various neurotrophic cytokines. *Psychoneuroendocrinology* 24:371-383, 1999.
12. Littlejohn GO, Weinstein C and Helme RD: Increased neurogenic inflammation in fibrositis syndrome. *J. Rheumatol.* 14:1022-1025, 1987.
13. Eisinger J, Zakarian H, Pouly E, et al.: Protein peroxidation, magnesium deficiency and fibromyalgia. *Magnes. Res.* 9:313-316, 1996.
14. Clauw DJ: Treating fibromyalgia: Science vs. art. *Am. Fam. Physician* 62: 1493-1494, 2000.
15. Goldenberg DL: Fibromyalgia syndrome a decade later: What have we learned. *Arch. Intern. Med.* 159:777-785, 1999.
16. Wolfe F, Anderson J, Harkness D, et al.: Health status and disease severity in fibromyalgia: Results of a six-center longitudinal study. *Arthritis Rheum.* 40:1571-1579, 1997.
17. Busch A, Schachter CL, Peloso PM and Bombardier C: Exercise for treating fibromyalgia syndrome. *Cochrane Database Syst. Rev.* 3:CD003786, 2002.
18. Sim J and Adams N: Systematic review of randomized controlled trials of non-pharmacological interventions for fibromyalgia. *Clin. J. Pain* 18:324-336, 2002.
19. Gustafsson M, Ekholm J and Broman L: Effects of a multiprofessional rehabilitation programme for patients with fibromyalgia syndrome. *J. Rehabil. Med.* 34: 119-127, 2002.

20. Sim J and Adams N: Physical and other non-pharmacological interventions for fibromyalgia. *Baillieres Best Pract. Res. Clin. Rheumatol.* 13:507-523, 1999.
21. Ronzio RA, Ripley SD and Cozad DR: Fibromyalgia—Advances in diagnosis and treatment. *Today's Therapeutic Trends* 20:135-158, 2002.
22. Haugen M, Kjeldsen-Kragh J, Nordvag BY and Forre O: Diet and disease symptoms in rheumatic diseases—Results of a questionnaire based survey. *Clin. Rheumatol.* 10:401-407, 1991.
23. Niec AM, Frankum B and Talley NJ: Are adverse food reactions linked to irritable bowel syndrome? *Am. J. Gastroenterol.* 93:2184-2190, 1998.
24. Sandyk R: L-tryptophan in neuropsychiatric disorders. A review. *Int. J. Neurosci.* 67:127-144, 1992.
25. Donath F, Quispe S, Diefenbach K, et al.: Critical evaluation of the effect of valerian extract on sleep structure and sleep quality. *Pharmacopsychiatry* 33:47-53, 2000.
26. Burckhardt CS, Clark SR and Bennett RM: The Fibromyalgia Impact Questionnaire: Development and validation. *J. Rheumatol.* 18:728-733, 1991.
27. Dunkl PR, Taylor AG, McConnell GG, et al.: Responsiveness of fibromyalgia clinical trial outcome measures. *J. Rheumatol.* 27:2683-2691, 2000.
28. Yunus MB and Aldag JC: Restless legs syndrome and leg cramps in fibromyalgia syndrome: A controlled study. *BMJ* 312:1339, 1996.
29. Jacobsen S, Petersen IS and Danneskiold-Samsøe B: Clinical features in patients with chronic muscle pain - with special reference to fibromyalgia. *Scand. J. Rheumatol.* 22:69-76, 1993.
30. White KP, Carette S, Harth M and Teasell RW: Trauma and fibromyalgia: Is there an association and what does it mean? *Semin. Arthritis Rheum.* 29:200-216, 2000.
31. Siegmeth W: Panalgesia and the fibromyalgia concept. *Wien. Med. Wochenschr.* 149:558-560, 1999.
32. Bernard AL, Prince A and Edsall P: Quality of life issues for fibromyalgia patients. *Arthritis Care Res.* 13:42-50, 2000.
33. Turk DC and Okifuji A: Pain in patients with fibromyalgia syndrome. *Curr. Rheumatol. Rep.* 2:109-115, 2000.
34. Heymann RE, Helfenstein M and Feldman D: A double blind, randomized, controlled study of amitriptyline, nortriptyline and placebo in patients with fibromyalgia. An analysis of outcome measures. *Clin. Exp. Rheum.* 19:697-702, 2001.
35. Richards SCM and Scott DL: Prescribed exercise in people with fibromyalgia: Parallel group randomised controlled trial. *BMJ* 325:185, 2002.
36. Bombardier CH and Buchwald D: Chronic fatigue, chronic fatigue syndrome, and fibromyalgia. Disability and health-care use. *Med. Care* 34:924-930, 1996.
37. Bosch RE, Saenz MN, Valls EM, et al.: Study of quality of life of patients with fibromyalgia: Impact on a health education programme. *Aten. Primaria* 15:16-21, 2002.
38. Worrel LM, Krahn LE, Sletten CD, et al.: Treating fibromyalgia with a brief interdisciplinary program: Initial outcomes and predictors of response. *Mayo Clin. Proc.* 76:384-390, 2001.

39. Florence JA and Yeager BF: Treatment of type 2 diabetes mellitus. *Am. Fam. Physician* 59:2835-2844, 1999.
40. Sacks FM, Svetkey LP, Vollmer WM, et al., for the DASH-Sodium collaborative Research Group: Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N. Engl. J. Med.* 344: 3-10, 2001.
41. Kaartinen KI, Lammi K, Hyphen M, et al.: Vegan diet alleviates fibromyalgia symptoms. *Scand. J. Rheumatol.* 29:308-313, 2000.
42. Hanninen O, Kaartinen K, Rauma AL, et al.: Antioxidants in vegan diet and rheumatic disorders. *Toxicology* 155:45-53, 2000.
43. Smith JD, Terpening CM, Schmidt SO and Gums JG: Relief of fibromyalgia symptoms following discontinuation of dietary excitotoxins. *Ann. Pharmacother.* 35:702-706, 2001.
44. Blumenthal M, Busse WR, Goldberg A, et al. (Eds.). In: The Complete German Commission E Monographs. Therapeutic Guide to Herbal Medicine. American Botanical Council, Austin, TX, 1998, pp. 88, 124, 136-138, 167-170, 192.
45. Lebenthal E, Rolston DD and Holesclaw DS Jr: Enzyme therapy for pancreatic insufficiency: Present status and future needs. *Pancreas* 9:1-12, 1994.
46. Nobaek S, Johansson ML, Molin G, et al.: Alteration of intestinal microflora is associated with reduction of abdominal bloating and pain in patients with irritable bowel syndrome. *Am. J. Gastroenterol.* 95:1231-1238, 2000.
47. Ozgocmen S, Catal SA, Ardicoglu O and Kamanli A: Effect of omega-3 fatty acids in the management of fibromyalgia. *Int. J. Clin. Pharmacol. Ther.* 38:362-363, 2000.
48. Craig T and Kakumanu S: Chronic fatigue syndrome: Evaluation and treatment. *Am. Fam. Physician* 65:1083-1090, 2002.
49. White KP, Speechley M, Harth M, et al.: The London Fibromyalgia Epidemiology Study: Direct health costs of fibromyalgia syndrome. Presented at the annual meeting of the American College of Rheumatology. Washington, DC, 1997. *Arthritis Rheum.* 40(9):S44, 1997.
50. White KP, Speechley M, Harth M and Ostbye T: The London Fibromyalgia Epidemiology Study: Direct health care costs of fibromyalgia syndrome in London, Canada. *J. Rheumatol.* 26:885-889, 1999.
51. Wolfe F, Anderson J, Harkness D, et al.: A prospective, longitudinal, multicenter study of service utilization and costs of fibromyalgia. *Arthritis Rheum.* 40:1560-1570, 1997.
52. McCain GA, Cameron R and Kennedy JC: The problem of long-term disability payments and litigation in primary fibromyalgia: The Canadian perspective. *J. Rheumatol.* 16:174-176, 1989.
53. Thomsen AB, Sorensen J, Sjogren P, et al.: Economic evaluation of multidisciplinary pain management in chronic pain patients: A qualitative systematic review. *J. Pain Symptom Manage.* 22:688-698, 2001.