

Fibromyalgia--Advances in Diagnosis and Treatment

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Abstract

Fibromyalgia syndrome is a condition characterized by chronic, widespread soft tissue pain and tenderness usually associated with fatigue. Diagnostic criteria developed by the American College of Rheumatology have helped establish fibromyalgia as a distinct clinical entity. Affected patients often suffer from co-morbid conditions, including chronic fatigue, depression, cognitive dysfunction, neuroendocrine imbalance, irritable bowel syndrome, migraine headache and sleep disturbances, among others. Treatment is generally non-specific. Pharmacological therapy with antidepressants, SSRIs and analgesics proves helpful in an estimated 30-50% of patients, but efficacy tends to diminish over time. Comprehensive multidisciplinary programs that incorporate behavior modification, relaxation, physical exercise, diet and pharmacological agents can address both the physical and psychological manifestations of fibromyalgia. In a model program for fibromyalgia rehabilitation, an interdisciplinary management team employs diagnostic indices to develop individualized protocols (including pharmacological therapy), to assess progress, and monitor compliance. Patient education emphasizes relaxation and stress management. As in the treatment of diabetes and hypertension, in which diet and nutrition are standard first-line therapy, dietary intervention plays a key role in fibromyalgia rehabilitation. Fibromyalgia patients may have a low micronutrient status, especially for selenium, zinc and B vitamins. Individualized dietary regimens increase the intake of plant foods while emphasizing a balanced diet and

taking food sensitivities into account. Nutraceuticals that have proven effective in adjunctive therapy include selected herbs and botanical extracts (Ginkgo biloba, Siberian ginseng, slippery elm, marshmallow, silymarin, carotenoids, plant polyphenols, ginger), as well as n-3 polyunsaturated fatty acids, dietary fiber, digestive enzymes, probiotics (lactobacilli and bifidobacteria) and antioxidants. The use of specific nutraceuticals is based upon the findings of scientifically designed clinical studies and related research on the treatment of fibromyalgia and co-morbid conditions.

Introduction

Fibromyalgia syndrome, or fibrositis, is a chronic rheumatic condition characterized by widespread, undifferentiated musculoskeletal pain and tenderness that is associated with fatigue. In the U.S., the prevalence of fibromyalgia is 2-3% of the overall population and increases with age.¹ Fibromyalgia is more common among women than men, and women between the ages of 60 and 79 years have the highest prevalence (7%).¹ Fibromyalgia is clearly a debilitating condition. Surveys have found that 10-30% of patients experience work impairment due to fibromyalgia, and as many as 26% of patients with fibromyalgia reported receiving disability compensation or other benefits.^{2,3}

In the past, the diffuse nature of the physical manifestations of fibromyalgia and lack of specific pathological findings in many cases led to a degree of controversy regarding this diagnosis. A major diagnostic advance was achieved in 1990, with publication of the American College of Rheumatology (ACR) Criteria for the Classification of Fibromyalgia.⁴ In developing this evidence-based, comprehensive diagnostic protocol, the 24-member Multicenter Criteria Committee of the ACR systematically studied 558 consecutive patients (293 with fibromyalgia and 265 control subjects). In the final report, the authors concluded that precise criteria are required to confirm the presence of fibromyalgia. The ACR committee reported that application of the following specific diagnostic criteria yielded 88.4% sensitivity and 81.1% specificity for fibromyalgia:

widespread, chronic musculoskeletal pain of >3 months' duration, combined with mild or greater tenderness on digital palpation at 11 or more of 19 bilateral "tender points", located at the following anatomical sites: occiput, low cervical, trapezius, supraspinatus, second rib, lateral epicondyle, gluteal, greater trochanter and knee.

Largely as a result of this important research, fibromyalgia is now recognized as a distinct clinical entity and is being more accurately diagnosed in affected patients.⁴ It should be noted that the 11 tender points identified are based on statistical analysis, and should not necessarily be considered absolute diagnostic criteria in a clinical setting, since they may identify only the most severe cases.^{5,6} In practice, fibromyalgia patients may present only 8-10 tender points, while palpation of other muscle groups can establish the presence of multiple tender points besides those designated in the ACR report.⁵

Fibromyalgia remains the most common cause of widespread pain, usually associated with muscle stiffness and increased pain intensity after exercise, and only rarely do such symptoms reflect other conditions such as polymyalgia rheumatica or bone pain due to osteomalacia or neoplasm.⁵ Fibromyalgia can mimic diseases such as Lyme disease or Raynaud syndrome and can contribute to pain associated with systemic lupus erythematosus in 10-40% of patients, and to rheumatoid arthritis in 10-30% of cases.³ Osteoarthritis and fibromyalgia may co-exist as well, and drug-induced myopathies and hypothyroidism should also be considered.

Fibromyalgia and Co-Morbid Conditions

Fibromyalgia is now considered a manifestation of a "sensory amplification" syndrome due to altered central pain mechanisms. As such, it belongs to a constellation of syndromes in which pain is not caused by peripheral damage or inflammation.⁶ Fibromyalgia frequently occurs with a number of common, vaguely defined syndromes, which can assist the clinician in focusing treatment. In the ACR committee report, the most commonly occurring symptoms included fatigue, sleep disturbances and morning stiffness (reported in 75-85% of cases), and "pain all over," paresthesias, headache and anxiety (in 45-69% of patients).⁴ Following are descriptions of those co-morbid conditions that are most frequently associated with the diagnosis of fibromyalgia.

Chronic Fatigue

Fibromyalgia is often closely associated with symptoms of so-called "chronic fatigue syndrome", characterized by persistent debilitating tiredness unrelated to physical exertion. Chronic fatigue significantly compromises the affected individual's ability to undertake normal activities of everyday living.⁷

In one published study, 52% of patients with fibromyalgia were found to have a history of chronic fatigue during their lifetime, and 33% had chronic fatigue as a current diagnosis.⁸

Altered Psychological Status

Fibromyalgia often presents with a significant psychological component.² Co-existing anxiety and depressive disorders are common in patients who suffer from fibromyalgia. Between 50% and 70% of fibromyalgia patients have been observed to have a history of depression, although only 18% were currently experiencing a major depression, similar to the rate seen in patients with rheumatoid arthritis or in controls.⁸ A lifetime history of anxiety disorders was found in 39%. Cognitive dysfunction, especially problems with memory and verbal efficiency and mental alertness, has also been noted in fibromyalgia patients.¹⁰

Fibromyalgia is also associated with primary sleep disorders, with alpha rhythm disturbances characteristic of restless sleep.¹¹ Furthermore, many patients experience feelings of anger and

hopelessness as well as difficulties with interpersonal relationships, that are exacerbated by their illness.¹²

Immune Dysfunction

Immune system imbalance and altered regulatory mechanisms for inflammation may also be implicated in fibromyalgia.¹³ The suppression of cytokines and related cell receptors may promote inflammation and enhance the pain and stiffness that are characteristic of this condition.¹⁴

It has also been suggested that fibromyalgia patients may have increased production of Interleukin-6 and Interleukin-8. These lymphokines are implicated as causative factors in sympathetic pain experienced by some patients with fibromyalgia.¹⁵

Neuroendocrine Dysfunction

Altered production of neurohormones and substance P, and disturbances in the hypothalamic-pituitary- adrenal axis and hypothalamic-pituitary-GH axis, have been reported in individuals with fibromyalgia.^{16,17} Thus, many fibromyalgia patients have low levels of IGF-1, unrelated to medications, pain level, depression, obesity or degree of physical conditioning.¹⁵ Perturbations in the sympathetic-parasympathetic nerve system balance have been documented in those with fibromyalgia as well.¹⁸

Bowel Disturbances

Irritable bowel syndrome (IBS), diarrhea or constipation are common among patients with fibromyalgia. As many as 73% of fibromyalgia patients have reported altered bowel function in comparison to healthy controls or patients with degenerative joint disease.¹⁹ In another study, 70% of fibromyalgia patients were found to have IBS, while 65% of an IBS group had fibromyalgia.²⁰ The severity of intestinal symptoms of IBS also correlated with the presence of fibromyalgia.²¹

Gut inflammation may promote altered intestinal permeability, and may play a role in associated food sensitivities. Localized immune responses in the gut are believed to increase gut permeability in IBS, thus promoting antigen uptake.²² Approximately 50% of pediatric IBS cases were shown to have increased gut permeability following food provocation, and allergy symptoms diminished after food exclusion.²³

Headache Syndromes

Patients with fibromyalgia have high lifetime rates of migraine headache, in addition to chronic fatigue, IBS and major depression.⁸ Furthermore, investigators found that the prevalence of fibromyalgia in patients with migraine headache was 35.6%.⁹

Oxidative Stress

Oxidative stress may be a factor in both fibromyalgia and chronic fatigue. Oxidative damage, as serum protein carbonyls, was found to be significantly elevated in female fibromyalgia patients compared to age-matched controls.²⁴ In another study, increased serum lipid peroxidation was shown in patients with chronic fatigue, compared to healthy matched controls. Symptom severity in terms of fatigue, cognitive impairment and musculoskeletal pain was directly correlated with oxidative stress.²⁵ In a study of patients with fatigue, the level of serum transferrin, a recognized antioxidant, decreased with a concomitant increase in susceptibility of LDL- and VLDL-cholesterol to *in vitro* peroxidation.²⁶

Treatment Modalities

Despite substantially improved diagnostic criteria and increased recognition of fibromyalgia as a distinct clinical entity, treatment for this condition continues to be relatively non-specific. Drugs such as tricyclic antidepressants, SSRIs and analgesics have been used in managing the pain associated with fibromyalgia. Among the tricyclic antidepressants, amitriptyline has been most intensively studied. However, these agents have been shown to ameliorate pain in only 30-50% of patients, and there is a tendency for efficacy to become diminished over time.³ Nonsteroidal anti-inflammatory drugs (NSAIDs), which are frequently prescribed, have generally proven ineffective.³

Non-pharmacological modalities, including massage therapy, aerobic exercise, cognitive behavior therapy, relaxation and coping techniques or biofeedback appear to offer modest improvement in terms of symptom relief. To date, however, no single therapy has been reported to provide consistent and long-term symptomatic relief for a majority of patients diagnosed with fibromyalgia, even at rheumatology clinics that specialize in its treatment.²⁷ The lack of effective modalities for treating the persistent, widespread pain and other related symptoms of fibromyalgia remains a major source of frustration for affected patients and family members, as well as physicians.

Model for Fibromyalgia Rehabilitation

A preponderance of scientific evidence demonstrates that fibromyalgia is a medically treatment-resistant syndrome, characterized by a perplexing heterogeneity of symptoms. In designing an effective treatment protocol for fibromyalgia, it is therefore important to consider the wide spectrum of overlapping conditions.²⁸ Consequently, multidisciplinary approaches that identify important clinical factors, incorporate a range of treatment options, and address specific patient issues may well be essential in achieving an effective treatment outcome for patients with fibromyalgia.^{29,30} Based on these considerations, a Canadian interdisciplinary program focusing on rehabilitation has been developed. This individualized program emphasizes the amelioration of symptoms and improvement in daily functioning at home and at work, rather than "curing" fibromyalgia. This program, which has shown promise in

fibromyalgia treatment based on preliminary findings, has achieved formal recognition from both governmental and insurance company sources in Canada.

The Fibromyalgia Rehabilitation Program relies on a team of healthcare professionals to assist the client in improving pain management, cognitive behavior, functional capacity, lifestyle and diet.

The interdisciplinary team includes social workers, nurses, medical specialists such as internists, as well as dietitians, caseworkers and pharmacists. A medical advisory board representing key specialty areas (gastroenterology, internal medicine, psychiatry, family medicine and neurology) helps to develop policy guidelines.

Typically, the prospective client is referred to the program by a family physician. The clinical impression or diagnosis of fibromyalgia is based upon completion of a comprehensive physical examination, diagnostic laboratory blood tests including thyroid function and erythrocyte sedimentation rate, and a thorough medical history.

In an initial meeting with the prospective client, the team's social worker uses psychosocial assessments and screens for anxiety and depression, and determines whether a referral for psychological counseling is indicated. Clinic staff administer a number of diagnostic measurement indices, including a Symptom Severity Rating Scale; the Fibromyalgia Impact Questionnaire;³⁰ the Fibromyalgia Health Assessment Questionnaire;³¹ the Pain Assessment and Tender Point Sensitivity scale;³² and Graphic Depiction of Pain Sites³³ (see Appendix I for a summary of the diagnostic indices used). Additional diagnostic laboratory testing includes screening for food sensitivities.

The social worker then meets with the client and family members to establish that the individual is able and willing to complete the full 6-month program. Finally, the overall screening results are reviewed by an internal medicine specialist prior to accepting the client into the rehabilitation program.

Upon admission, the client is interviewed by a dietitian who then formulates an individualized diet program based upon a 7-day food intake diary and diagnostic test results. In addition to the dietitian, nurse caseworkers assist in patient education to achieve necessary lifestyle changes, including relaxation techniques and coping skills using a stepped approach. The importance of patient education and lifestyle modification has been reported. Cognitive behavior treatment can be effective in modifying beliefs and changing coping strategies.^{6, 34} A 14- week randomized study found that either aerobic exercise or stress management, including applied relaxation, led to a significant reduction in symptoms of pain, tenderness and depression.³⁵ An interdisciplinary education program--which included patient education in coping skills and relaxation strategies, communication skills, management of anger and perfectionism-- improved pain and fibromyalgia impact questionnaire scores after a one-month follow-up.¹² Treatment of fibromyalgia is individualized, according to indications and major complaints. L-tryptophan, which has been used to treat sleep disorders and depression since the 1960s,³⁶ is prescribed for depression, pain or

sleep disorders as needed. Appropriate supplements and nutraceuticals are prescribed in accordance with each individual case, and prescriptions are filled by a pharmacy. Dosages are individualized and adjusted as needed throughout the course of treatment.

Dietary Considerations

A growing body of scientific and clinical research supports the proposal that, beyond simply emphasizing nutrient content, foods and individual food constituents play a significant role in disease treatment as well as prevention. Diet has clearly been shown to play an important role in many chronic health conditions, and fibromyalgia is no exception. Indeed, non-pharmacological approaches related to diet and nutrition have long been recognized as standard first-line and adjunctive therapy for type 2 diabetes and hypertension.^{37,38}

Accordingly, the Fibromyalgia Rehabilitation Program incorporates dietary intervention and functional foods, as well as selected "nutraceuticals" as useful adjuncts in treatment. Dietary recommendations emphasize a balanced intake of essential nutrients with increased consumption of fruits, vegetables and whole grains, and decreased intake of refined or highly processed convenience foods and hydrogenated or saturated fat. Problematic foods are excluded or rotated according to a plan developed by the dietician and based on the client's specific food sensitivities. Clients are encouraged to drink 8 glasses of water daily, and to reduce consumption of alcohol and caffeine.

Plant-Based Diets

Foods rich in fiber, carotenoids, and flavonoids are incorporated into the dietary plan. Pilot studies of plant-based diets in cases of fibromyalgia suggest that increased intake of carotenoids, vitamin C, vitamin E, fiber and flavonoids is correlated with improvement in serum peroxidation products, pain scores, stiffness and sleep quality.^{39,40} Other research suggests that a plant-based diet may be of benefit to fibromyalgia patients. In healthy elderly men and women, there was a positive correlation between improved cognitive function and an increased dietary intake of B vitamins, vitamin C, vitamin E, fiber, vegetables, fruit, carbohydrate, folate, trace minerals and polyunsaturated fatty acids. An inverse relationship was seen between cognitive function and dietary intake of saturated fat and cholesterol. ^{41,42}

Impaired Nutrient Status

Patients may benefit from daily multiple vitamin-mineral supplementation supplying physiological levels of micronutrients. In a cohort of free-living men and women between 50 and 87 years of age, 10% were found to have inadequate levels of vitamin B₆, 37% were low in vitamin C and A, and 44% were anergic.⁴³ Multivitamin supplementation of older adults who were consuming typical diets and had recommended daily vitamin intakes nonetheless improved the status of vitamin D, vitamin B₆, B₁₂, C and

E, as well as folate and riboflavin.⁴⁴ Inadequate nutrient status for individual minerals and vitamins is known to affect some patients with fibromyalgia and co-morbid conditions.

Minerals

Serum selenium levels have been shown to be significantly lower in patients with fibromyalgia compared to matching controls.⁴⁵ Selenium intake was inversely correlated with the degree of anxiety, depression and tiredness among otherwise healthy men and women. A randomized clinical trial demonstrated that supplementation with 100 µg selenium/day significantly increased mood and decreased anxiety scores.⁴⁶

In another study, migraine patients were found to have significantly lower magnesium levels within red blood cells and lymphocytes compared to controls.⁴⁷ Nearly half (47%) of patients with chronic fatigue were magnesium-deficient, and supplementation with 10 mg magnesium/kg body weight improved magnesium status, increased serum vitamin E levels, and reduced oxidative stress (lipid peroxidation).⁴⁸

Serum zinc levels were significantly lower in depressed patients than in healthy controls.⁴⁹ Some patients with IBS have reduced erythrocyte zinc levels and increased fecal excretion of zinc.⁵⁰

Vitamins

Increased levels of homocysteine were found in the cerebrospinal fluid of women outpatients with fibromyalgia. There was a significant positive correlation between increased homocysteine and fatigue and other symptoms, even though blood levels of vitamin B₁₂ were normal.⁵¹ Typically, elevated homocysteine levels reflect inadequate folate, vitamin B₆ and/or vitamin B₁₂ status. A reduced folate status was observed in 50% of patients with chronic fatigue syndrome.⁵² Chronic fatigue is also associated with functional deficiencies of vitamin B₆, riboflavin and thiamine compared to healthy controls.⁵³ Borderline or deficient folate levels in the serum or erythrocytes were detected in 15-38% of individuals with depressive disorder.⁵⁴ Depressed patients have also been found to have significantly lower serum vitamin E levels than healthy controls.⁵⁵ Women with functional gastrointestinal disorders, including irritable bowel syndrome, were shown to have a lower mean intake of folate, vitamin C, and vitamin A compared to patients with inflammatory bowel disease. Iron was low in 59% of the study subjects, the vitamin A level was low in 47%, riboflavin was deficient in 25%, and folate was low in 9% (78% were marginal for folate).⁵⁶

Food Sensitivity

Although an etiologic role for food sensitivities in fibromyalgia remains to be established, 42% of fibromyalgia patients reported aggravation of symptoms following the consumption of problematic foods.⁵⁷ Food sensitivities may be a particularly significant factor in co-morbid conditions such as IBS.⁵⁸ In seven controlled studies, symptom-provoking foods were identified in up to 71% of IBS patients, depending on

the study. In double-blind challenges, the positive response to elimination diets ranged from 6% to 58% of patients.⁵⁹ While foods and chemicals can trigger migraine and cluster headaches, elimination and rotation diets can ameliorate them.⁶⁰ Other research has found that patients with severe migraine headache, refractory to drug treatment, were allergic to certain foods as determined by exclusion diet and challenge by allergenic foods and/or protection by oral cromoglycate.⁶¹ Food sensitivity may also be associated with depression, anxiety and musculoskeletal pain. Symptomatic patients with food allergies or IBS had similarly high levels of anxiety and depression compared to controls.⁶² In patients with arthralgia, eczema or asthma, circulating immune complexes combining IgE, IgG and antigen appeared after challenge with specific foods, and formation of these complexes correlated with intensification of pain.²²

Nutraceuticals as Adjuncts in the Treatment of Fibromyalgia

Increasingly, clinical evidence suggests that certain nutritional and botanical supplements can ameliorate symptoms associated with fibromyalgia in some patients. A wide range of published studies have documented the respective roles of varying nutraceuticals in treating fibromyalgia-related symptoms. The rationale for use of specific nutraceuticals in providing symptomatic relief for patients in the Fibromyalgia Rehabilitation Program is summarized below. Drug-herb interactions and contraindications for the administration of specific botanical products dictate their use. For example, many botanical products are not recommended for use in pregnant or lactating women.⁶³ The dosage and duration of prescribed supplements are adjusted to the individual, and clinical response is continuously monitored throughout the program. The formulations used in the Fibromyalgia Rehabilitation Program are prepared by a licensed pharmaceutical facility to ensure consistency, purity and quality.

Pain

Plant-based diets were found to increase serum antioxidant concentrations, reduce pain indices, and decrease serum peroxides and plasma fibrinogen levels in pilot studies with fibromyalgia patients.³⁹ Antioxidants can help counter oxidative stress; useful antioxidant nutrients include vitamin C, vitamin E and selenium. The n-3 polyunsaturated fatty acids may help to ameliorate pain. Treatment with fish oil as a source of long chain n-3 fatty acids daily for four weeks significantly reduced pain severity, tender point counts and depression scales in a pilot study of women with primary fibromyalgia.⁶⁴

Depression and Anxiety

A number of supplemental agents have been recommended for the treatment of depressive emotional conditions and headache by The German Commission E.⁶⁵ This Commission is a regulatory body that has evaluated the safety and efficacy of botanical preparations and medicinal herbs based on the results of clinical trials, case studies and the scientific literature, and has determined specific indications and dosages for such herbal therapies. In a randomized study, patients with depression and

cerebral insufficiency treated with Ginkgo biloba leaf extract (160 mg/day) for six weeks reported that they experienced significant improvement in depression and anxiety compared to placebo.⁶⁶ Randomized studies also suggest a benefit of Panax ginseng in the treatment of depression. Ginseng therapy for 16 weeks improved well-being indices and depression scales in postmenopausal women.⁶⁷ In another study, a combination of ginseng and multiple vitamin-mineral supplements that supplied physiologic amounts of nutrients improved the quality-of-life index in healthy men and women after four months, compared to vitamin-mineral supplementation alone.⁶⁸ In addition, n-3 polyunsaturated fatty acids may be useful in treating the psychological symptoms of fibromyalgia. Individuals with major depression exhibit markedly reduced levels of n-3 fatty acids, especially docosahexaenoic acid, in phospholipids, cholesteryl esters and red blood cell membranes. The severity of depression was found to correlate negatively with dietary intake of n-3 fatty acids.^{69,70}

Bowel Disturbances (Including IBS)

Digestive enzymes may be beneficial in some patients with bowel disturbances related to fibromyalgia. Exogenous proteolytic enzymes have been employed in the treatment of functional dyspepsia, and pancreatic enzymes have long been used to counter maldigestion due to pancreatic insufficiency.^{71,72} Furthermore, maldigestion may play a role in altered gut permeability and intestinal inflammation, as there is a positive correlation between the degree of pancreatic exocrine insufficiency and increased intestinal permeability.⁷³

Randomized studies have shown that supplementation with probiotics (including beneficial strains of lactic acid bacteria and bifidobacteria) can improve such symptoms as bloating, abdominal pain and flatulence in IBS patients.⁷⁴ In animal models, lactic acid bacteria improve intestinal immune status and reduce gut inflammation. Moreover, ingestion of nondigestible fructans (fructo-oligosaccharides) promotes the intestinal proliferation of beneficial species, such as bifidobacteria.⁷⁵

Several botanical products have been found to promote intestinal health. Dietary fiber, in the form of flaxseed, glucomannan and psyllium, has been advocated for the secondary treatment of irritable bowel, improving transit time and constipation.⁶⁵ The German Commission E has recommended the use of dandelion and ginger to treat dyspepsia and flatulence.⁶⁵ Slippery elm, marshmallow and bilberry have been recommended for use in treating mild mucosal inflammation and non-specific diarrhea.^{65,76} Slippery elm promotes mucus secretion and may be useful in controlling diarrhea as well as constipation.⁷⁷

Fatigue

Siberian ginseng has been recommended for use in the treatment of fatigue by the German Commission E.⁶⁵

Immune Imbalance (Including Inflammation)

Dietary n-3 polyunsaturated fatty acids can modulate intestinal inflammation by inducing changes in the production of proinflammatory agents, as well as by influencing lymphocytes, neutrophils and antigen-presenting cells.⁷⁸ In addition, immune status can be improved in some cases with the use of specific plant-based supplements.

For example, supplementation with carotenoids, including beta carotene, was found to improve an age-related decline in lymphocyte subsets.⁷⁹ Supplemental carotenoids can also correct the effects of a low carotenoid diet.⁸⁰ Other plant-derived products influence immune function. The citrus flavonoids can inhibit inflammation via a number of different mechanisms, including inhibition of the production of proinflammatory eicosanoids.⁸¹ Proanthocyanidins, polyphenols found in grapes and other plant sources, have been shown to act as antioxidants in controlled clinical studies, and can improve lymphocyte function in animal models.^{82,83} Probiotic bacteria such as lactobacilli and bifidobacteria are generally found within the normal human gut mucosa. They support gut defenses, including immune exclusion and elimination. Clinical trials suggest that probiotic bacteria can normalize dysfunction of the intestinal mucosa by improving the immune barrier, especially secretory IgA, ameliorating gut inflammation, and degrading food antigens.⁸⁴

Memory Deficit/Cognitive Impairment

Ginkgo biloba leaf extract has been used to successfully treat cerebral insufficiency, memory deficits, disturbed concentration and depression in a number of clinical studies.^{65, 85} Treatment with Ginkgo biloba leaf extract in combination with Panax ginseng has proven effective in improving memory in healthy volunteers.⁸⁶

Impaired Liver Function

Environmental chemicals can have a significant negative impact on the fibromyalgia patient. Severe environmental chemical intolerance was noted in 20-70% of patients with fibromyalgia and/or chronic fatigue syndrome, compared with only 4-6% of the general population.⁸⁷ Serum levels of chlorinated hydrocarbons in chronic fatigue patients were 2.5-fold greater than for healthy controls.⁸⁸ Toxic chemical exposure can impair liver function, an effect which may be countered by certain herbal products. Milk thistle (silymarin) acts as a free radical scavenger, inhibiting membrane lipid peroxidation, increasing liver protein synthesis, and stabilizing mast cells.⁸⁹ The German Commission E has recommended milk thistle for treating dyspepsia and improving liver function.⁶⁵

Treatment of Chronic Fatigue Syndrome and Irritable Bowel Syndrome

The picture emerging from clinical studies underscores a substantial overlap between fibromyalgia, IBS and chronic fatigue in terms of patient populations, symptoms, time course of symptom

development and response to therapy.³ Each of these syndromes is associated with a wide range of symptoms, and it has been argued that the overlap between these three syndromes is so extensive they can be considered manifestations of a common underlying condition.³

Although treatment of fibromyalgia can alleviate symptoms of these co-morbid conditions, they may also be treated individually.³³ Improved nutrient status and diet, as well as use of specific nutraceuticals, can serve as therapeutic adjuncts. To summarize, deficiencies of B vitamins and magnesium, as well as oxidative stress, are implicated in chronic fatigue syndrome^{48, 52,53} Environmental chemical intolerance has been noted in cases of chronic fatigue, and milk thistle may help correct associated liver dysfunction.^{65, 87-89} Botanical extracts, such as Siberian ginseng, may be effective in treating fatigue.⁶⁵ Patients with IBS may have reduced vitamin and mineral status.⁵⁶ Supplementation with probiotics (e.g., lactic acid bacteria and bifidobacteria) and with dietary fiber (e.g., flaxseed, glucomannan and psyllium) may ameliorate symptoms associated with IBS.^{65, 74} Key herbal extracts, including slippery elm, marshmallow and bilberry, may also be effective for patients with IBS. ^{65, 76,77} In the Fibromyalgia Rehabilitation Program, co-morbid conditions such as IBS and migraine are usually resolved first, while subsequent steps are taken to reduce fatigue and pain on a longer-term basis.

Fibromyalgia Patient Compliance with a Multiple-Prescription Regimen

Patient compliance is a major factor in any long-term treatment regimen and certain features of the Fibromyalgia Rehabilitation Program have been developed to maximize compliance. In utilizing the case-management model, the program incorporates a 6-stage format so that conditions affecting different major organ systems can be effectively managed. According to this schedule, the first 30 days (Stage 1) entails a series of assessments and interviews, while Stage 2 (the next 30 days) initiates treatment based on these results. At 30-day intervals (subsequent stages), progress is again assessed and treatment is further individualized as needed. Experience has shown that a team comprised of a nurse, social worker and dietician can effectively encourage compliance via weekly telephone interviews. The Severity of Symptoms and Conditions Rating Scale is used to gauge progress, and clients submit weekly reports on their compliance with diet programs and nutraceutical prescriptions. The team communicates the client's progress to the referring physician, as well as recommendations for a referral to a psychiatrist or psychologist should the need arise. Multiple visits with clinic staff also build trust by enabling clients to express their concerns. Furthermore, a series of visits helps to ensure development of a more complete understanding of the program's goals and scientific rationale. Experience has also demonstrated that participation by family members in information-sharing sessions promotes a supportive home environment, which is essential for the client to fully adhere to the prescribed treatment regimen.

Patient compliance is of particular concern with the use of multiple prescriptions. To simplify the usage of supplements, formulas that combine nutrients and nutraceutical agents have been specifically developed for use in the Fibromyalgia Rehabilitation Program. Specific combinations employed include

fiber, lactobacilli, bifidobacteria, and fructans to support colon health (COLONEX™); pectin, citrus flavonoids, slippery elm and marshmallow for IBS symptoms (IBESE™); a broad spectrum of digestive enzymes (DIZUME™); a beverage mixture containing powdered vegetables such as carrot, tomato, beet, as well as ginger, green tea extract, Ginkgo biloba leaf extract, Siberian ginseng (MINEREX™); silymarin and other herbs to support liver function (HEPEX™); purified n-3 fatty acids (EFAMEG™); and mineral nutrients (ELECTROEX™).

Conclusions

Fibromyalgia is a common syndrome with well-defined diagnostic criteria. The usual treatments are relatively non-specific, including tricyclic antidepressants, SSRIs and analgesics, and no single therapy has been shown to provide long-term benefit for a majority of patients. Treatment is complicated by the wide diversity of symptoms; in particular, IBS and chronic fatigue syndrome frequently overlap with fibromyalgia. Therefore, comprehensive multidisciplinary programs that can address both the physical and psychological manifestations of this widespread condition are potentially more efficacious than any monotherapeutic approach.

Because fibromyalgia is a treatment-resistant syndrome, rehabilitation designed to achieve a measure of normal functioning in day-to-day living is a more realistic goal than complete cure. The present model encompasses a 6-month Fibromyalgia Rehabilitation Program. An interdisciplinary management team employs diagnostic indices to develop individualized protocols, including pharmacological therapy, to assess progress, make adjustments as required, and monitor compliance. Patient education in relaxation, stress management and coping skills and in developing a supportive home environment plays an important role in achieving treatment success.

In addition to lifestyle modification, the Fibromyalgia Rehabilitation Program recognizes the importance of diet in treatment. Individualized dietary regimens are designed to improve micronutrient status and increase intake of plant foods, while emphasizing a balanced diet. The regimen also takes into consideration individual food sensitivities. Specific nutraceuticals, including a select group of medicinal herbs and botanical extracts, are used as adjunctive therapy, based upon the published results of controlled trials, case reports, and other clinical studies focusing on the treatment of fibromyalgia and co-morbid conditions.

Appendix I

Summary of Principal Diagnostic Measurement Indices – Component Scales Abstracted from the Comprehensive Health Assessment Chart for the Diagnosis of Fibromyalgia

(A copy of the complete Health Assessment Chart for Fibromyalgia, © Cutler Clinics, Inc., may be obtained by request on professional letterhead to Cutler Clinics, Inc., Division of Cutler Pharmaceuticals, Inc., Windsor Health Centre, 700 Tecumseh Road East, Suite 111, Windsor, Ontario, N8X 4T2 Canada; telephone: 519-985-1010; fax: 519-985-6641.)

1. Medical History

Includes details of any current or past illnesses, and responses to 27-item listing of specific symptoms that have proven relevant to the diagnosis of fibromyalgia.

2. Fibromyalgia Impact Questionnaire (FIQ)*

Quality-of-life measures of daily activities, work-related functioning, and assessments of pain, fatigue, stiffness, anxiety/tension and depressed mood.

3. Symptom Severity Rating Scale (Developed by Cutler Clinics, Inc.)

The presence or absence of pain, and the degree of severity on a scale of 1-10 for 20 fibromyalgia-related symptoms, which include these items:

wide-spread muscular pain (including pain at rest, or with repetitive work or with exercise)
joint pain
muscle stiffness
decreased energy
sleep disturbance
anxiety
depression

decreased mental energy
memory difficulties
tension/migraine headaches
bowel disorders (including IBS, diarrhea or constipation)
frequent/urgent urination
painful/sore feet
cold weather effects
restless leg syndrome or aches

4. Fibromyalgia Health Assessment Questionnaire (FHAQ)**

A 4-point scale measuring degree of difficulty or inability to perform specific functions: bending, dressing, washing, entering/exiting from car, vacuuming, rising from seated position, reaching overhead and running errands.

5. Pain Assessment +

Assessment of present, past or occasional intense pain on right side, on left side, above waist, below waist, and in axial skeleton (cervical, thoracic, lumbar spine, and/or anterior chest).

6. Graphic Depiction of Pain Sites ++

Identification on anatomical charts of present, past or occasional intense pain on palpation with 4- kg force at each of 18 tender points.

* Burckhardt CS, Clark SR and Bennett RM: The Fibromyalgia Impact Questionnaire: Development and validation. *J. Rheumatol.* 18:728-733, 1991.

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