Fibromyalgia

by KP Khalsa, D.N-C, RH (AHG)

Overview

Millions suffering the chronic pain of fibromyalgia know what it's like to wake each morning with the knowledge that they will hurt all day. Fibromyalgia syndrome (FMS) is a constellation of chronic symptoms that tend to occur in clusters, and include deep muscle aching; burning, stabbing, throbbing pains; and profound fatigue and muscular weakness.[1] Fibromyalgia is thought to be irritability of the muscles, fascia and tendons, causing pain that is widespread and migratory, and involves muscles, connective tissues (tendons, ligaments), bursae, and joints. Symptoms are transient, with periods of exacerbation and remission. Exacerbations are commonly worse during times of illness, and after heavy exercise. FMS produces no obvious laboratory signs. It is part of a large, interconnected group of disabling conditions with broadly overlapping symptom patterns. For example, up to 70% of FMS patients evince symptoms consistent with a diagnosis of irritable bowel syndrome (IBS)[2] There is almost certainly more than one form of FMS, calling into question the clinical construct of a "syndrome."

Prevalence

FMS affects an estimated 2-5% of the US population, or about 4.8 million patients.[3 4 5 6 7 8] After osteoarthritis, it is the second leading arthritic disorder, accounting for 10-30% of all rheumatology consultations in North America.[9] FMS primarily occurs in women of childbearing age, with a frequency seven times greater in women than men.[10] The median age at onset is between 29 and 37 years old, and the median age at diagnosis 34 to 53 years. Only 1% of 20-year-old women are affected, while at age 70, more than 7% develop the disease. Although no specific inheritance pattern has been identified, an increased incidence in relatives of affected patients has been noted.[11] FMS occurs worldwide and has no specific ethnic predisposition. However, the prevalence is significantly lower throughout the world, affecting only 1% of the population in Britain and Scandinavia.[12 13 14 15 16 17 18 19] The presentation in Bangladesh is essentially the same as in the West.[20]

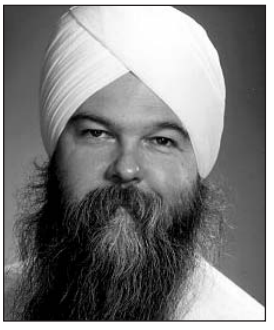
Symptoms

The pain of fibromyalgia is generally widespread, but tends to originate in one region, commonly the neck and shoulders or hips, spreading over time. Pain intensity varies with the time of the day, activity level, weather, sleep patterns, and stress levels. Up to 90% of patients experience chronic headache. Allergies, fatigue, hormonal imbalances, hypoglycemia, nasal congestion, vasomotor rhinitis, and neurotransmitter dysregulation are also associated with FMS. Almost all people with fibromyalgia have weariness, decreased endurance, or exhaustion. FMS can involve a host of other problems, including chest pain, headache, tingling, dizziness, constipation, diarrhea, gas, abdominal pain, water retention, PMS, menstrual cramps, poor memory problems, restless leg syndrome, irritable bladder, and nocturnal myoclonus. Unusual immune reactions, including skin sensitivities and allergies, contribute to the problem. Bladder spasms and irritability sometimes cause urinary urgency or frequency. Transient cognitive difficulties are common; so-called "fibro-fog" is characterized by feelings of confusion, memory lapse, language difficulties, and poor concentration.[21 22 23]

Diagnosis

FMS is diagnosed based on the presence of the following symptoms:

- A history of widespread pain in all body quadrants (pain on both sides of the body and above and below



KP Khalsa has over 30 years in the clinical herbal field. He is a nationally respected teacher, writer and lecturer who has presented at over 120 national conferences. He recently authored *Body Balance, Vitalize Your Health with pH Power and Solving the Riddle of Fibromyalgia.* Currently Khalsa is a faculty member in Bastyr University's Botanical Medicine Department in Seattle and is the Treasurer of the AHG.

Eschscholzia californica (California poppy)

the waist) that is present for at least three months
- Pain in at least 11 of 18 identified "tender-points."
- At least some points must be palpable on both sides of the body, above and below the waist, and on the midline. Some practitioners still accept a diagnosis of fibromyalgia with fewer than 11 tender points, if several of the commonly reported associated symptoms are also present.[24]

The notion of tender points has arisen because many FMS patients can identify greater pain at certain locations that appear common in the FMS population. These locations are an enigma, since their positions don't correspond to particular nerve junctions or other obvious physical landmarks. Other areas can and will most often be tender as well, but tenderness is focal rather than diffuse. In 2000, researchers found abnormal skin temperature above tender points and concluded that vasoconstriction occurs in the skin above tender points, suggesting hypoxia.[25] In 2004, German researchers looked at the connection between chronic low back pain and the prevalence of tender points and found that 39% had chronic back pain strongly associated with tender points.[26] Cabrera takes issue with diagnosis of FMS being based on the presence of tender points: "It's ridiculous to base diagnosis on 18 specific points. It's not a fair way to diagnose. It's just a good clue. A person might have 50 or 100 points, and they move around."

The FMS patient profile

The typical FMS patient is a 40-year-old female with a history of insomnia and a recent traumatic episode. The patient is commonly dry, thin, and cold, with a lifetime tendency toward constipation, corresponding with the Ayurvedic concept of excess vata. Cabrera describes these people "burning the candle at both ends and in the middle." A "health collapse" with immune involvement is commonly part of the patient's history. The criteria for chronic fatigue syndrome (CFS) and FMS overlap in about 70% of patients of either diagnosis.

Proposed etiologies

A number of events have been recognized to commonly precede, or "trigger," fibromyalgia. Trauma, both physical and psychological, dramatic hormonal changes, infection, or acute withdrawal of some medications, including steroids, are risk factors. Familial predisposition, environmental factors, and psychosocial factors seem to increase susceptibility. In a case-control study, 39% of FMS patients had significant physical trauma in the six months before the onset of their disease, compared with only 36 (24%) of controls.[27] FMS symptoms are more intense in cold weather. They improve in spring and summer. The most noteworthy climatic influence on FMS is a change in barometric pressure.[28] Ayurveda says that cold weather aggravates a basic metabolic regulatory force (vata), which is the essential cause of FMS from the Ayurvedic perspective.

Sleep disturbance

The overwhelming clinical consensus is that this disorder is a result of, or at least profoundly connected with, sleep disturbance. xxix Sleep and energy disturbances occur in about 90% of cases.[30] The usual manifestation is little or no difficulty falling asleep, but multiple awakenings. In 1975, Moldofsky published a paper that described sleep studies of patients and healthy subjects undergoing stage 4 sleep deprivation. It was surmised that FMS patients had an internal arousing mechanism, which induced alpha-delta sleep, comparable to the external stimulus they used to wake the healthy subjects.[31] [32] This non-restorative sleep syndrome was proposed to originate from central nervous system imbalances, associated with altered functions of serotonin, substance P, interleukin-1, growth hormone and cortisol.[33] Fibromyalgia patients exhibit similar dysregulated sleep physiology, that is, an alpha rhythm disturbance (7.5-11 Hz) in the EEG during deep sleep, accompanied by increased nocturnal vigilance, and light, unrefreshing sleep.[34]

Infection and immune system

There appears to be a distinct connection between immunity and FMS. FMS patients commonly have a history of viral infection, notably influenza. The general immune hypothesis posits that the immune system has become hyperresponsive, resulting in increased cytokine production. Interleukin-8 promotes sympathetic pain and Interleukin-6 induces hyperalgesia, fatigue, and depression.xxxv A 2001 study found that blood levels of antibodies to IL-receptors, and interleukin-8 were significantly higher in FMS patients. FMS patients also demonstrate increases in serum levels of immune factors stimulated by substance P.[36] A French team reports that a persistent enterovirus infection in muscles may be to blame for some cases of fibromyalgia. In 2003, they detected genetic material from enteroviruses in 20 percent of muscle biopsies from patients with chronic muscle diseases, and 13 percent of patients with FMS/CFS, but not from healthy volunteers.[37]

Hormonal causes

FMS and CFIDS, along with atypical depression and postpartum depression, are all characterized by low HPA axis and locus ceruleus-norepinephrine activity, fatigue, depressive symptoms, hyperalgesia and increased immune or inflammatory responses to stimuli.[38] Treatments that potentiate corticotropin-releasing hormone might be valuable in FMS. Pain in FMS patients has been attributed to an unusually high degree of gluconeogenesis. This increased level of muscle tissue breakdown has been hypothesized as one of the main reasons for pain, aching, and fatigue. Some research indicates that the HPA axis might be the central problem. A 1991 study found CFS patients to have significantly reduced basal evening glucocorticoid levels, and low 24-hour urinary free cortisol excretion. The patients in the study also showed elevated ACTH concentrations with an increased adrenocortical sensitivity to ACTH. Taken together, all this indicates a mild central adrenal insufficiency with a resulting mild glucocorticoid deficiency.[39]

Neuroendocrine abnormalities in both FMS and CFS may be from desynchronization of circadian systems. In 1999, scientists looked at melatonin levels in FMS and CFS patients. Nighttime melatonin levels in the blood were significantly higher in FMS patients compared to controls, but there was no significant difference in melatonin levels between CFS patients and controls. The scientists concluded that increased melatonin levels may represent a marker of increased susceptibility to stress induced hypothalamic disruptions.[40]

Myristica fragrans (nutmeg)

© Martin Wall

Herbal pain treatment

Botanical treatment of FMS incorporates the use of analgesics and anti-inflammatory herbs, the latter seeming to offer benefit in spite of a lack of inflammatory involvement in FMS. The herbs below are presented alphabetically.

Algae

Chlorella algae has demonstrated positive effects for FMS.[41] A pilot study, followed by a larger trial, showed relief of pain. In the first study, participants consumed 2 commercially available Chlorella-based products, 10 g in tablets and 100 mL of liquid daily for 2 months. The average tender point index decreased from 32 to 25 by the end of the treatment period. This decrease was statistically significant, representing a 22% decrease in pain intensity. A second study by the same group, published in 2001, was a double-blind, placebo-controlled, randomized clinical trial and also showed a positive outcome. [42]

Bacopa monniera (Brahmi)

Brahmi is outstanding for the treatment of fibro-fog. Because it increases the ability to solve problems effectively, it is often found in Ayurvedic formulas for stress prevention.[43] [44] The active constituents enhance nerve impulse transmission, strengthening memory and general cognition.[45] [46] Australian researchers gave Bacopa to seventy-six adults, aged 40 to 65 years, in a double-blind randomized, placebo control study in which various memory functions and anxiety levels were evaluated. Tests showed that the herb significantly improved the retention of new information.[47] Researchers ran an open trial with 35 anxiety neurosis patients. The dose was 12g per day of the dried plant for four weeks. Concentration and immediate memory span were both upped significantly. Nervousness, palpitation, insomnia, headache, tremors, and irritability improved significantly. Some disabled by anxiety overcame their disorder.[48] One hundred and seventy two patients with mild, moderate or severely impaired mental abilities took Bacopa. The herbal medicine significantly increased concentration ability, memory and overall mental performance of the subjects.[49] The typical dose is 2 grams of the whole herb, in capsules or tea, twice a day with warm water.

Corydalis yanhusuo (corydalis)

Corydalis tuber ("yan hu suo") is the main herb used in TCM for pain. It contains isoquinoline alkaloids, mainly tetrahydropalmatine. The raw herb is about 1% the strength of opium.[50] Its warming energy is suited to many FMS patients, and it treats insomnia and stiffness.[51] [52] [53] To start, decoct 14 grams of dry root. Drink this decoction at intervals throughout the day. If more pain analgesic and anxiolytic effect is needed, gradually increase the daily amount that is decocted and consumed.

Curcuma longa (turmeric root)

The author has found turmeric to be successful in treating FMS. It is analgesic, anti-inflammatory, antioxidant, and tissue healing.[54] Curcumin has nonsteroidal anti-inflammatory effects comparable to cortisone and phenylbutazone,[55] [56] [57] [58] Curcumin depletes nerve endings of substance P.[59] Research shows that curcumin and related compounds suppress pain through COX-I and COX-II enzyme mechanisms.[60] A relatively large dose of up to 4 tablespoons of powder may be required for efficacy.

Eschscholtzia californica (California poppy)

California poppy contains isoquinoline alkaloids, a class of pain relieving chemicals, common to the poppies, which bind to opioid receptors.[61] [62] [63] Another key alkaloid (chelerthyrine) inhibits kinase C, a substance that contributes to persistent pain.[64] [65] German Commission E lists it as an antispasmodic and sedative, for anxiety and depression.[66] A French animal study indicated a definite anti-anxiety effect. Mice sedated with California poppy were more relaxed than controls.[67] In mice, the tincture prolongs the duration of induced sleep.[68] In Germany, an herbal preparation that is 80% California poppy and 20% corydalis root is used to treat mood disorders.[69] It is shown to inhibit the body's production of adrenaline and to inhibit monoamine oxidase (MAO), allowing prolonging catecholamines activity.[70] A 2001 study found that the herb extract bonded to the benzodiazepine receptor, so other sedative mechanisms are likely.[71] As tea, a usual dose is 3-5 tsp. of chopped dry herb, brewed, taken when necessary. As a tincture, 5 mL is used when pain begins, and adjusted as needed.

***Ginkgo biloba* (ginkgo)**

Some patients with FMS claim to have experienced benefit from ginkgo and Coenzyme Q10. A very small pilot study tested this combination in 2002. Patients took 200 mg of Coenzyme Q10 and 200 mg Ginkgo biloba extract daily for 84 days, with 64% reporting symptom improvement.[72]

***Myristica fragrans* (nutmeg)**

This warming digestive herb is one of the best all-around anti-vata herbs for FMS treatment. It treats anxiety, relaxes muscle tension, and is a potent sleep inducer. Nutmeg is appropriate for nighttime waking.[73] Begin with a dose of one gram at 6:00 pm and adjust the dose and time for the desired depth of sleep. Nutmeg extracts potentiated pentobarbitone-induced sleeping time in animals.[74] Whole oil of nutmeg increased the duration of sleep induced by ethanol in chickens.[75] A typical dose for insomnia, given as one unit in the evening, is 3 grams. Administering nutmeg at bedtime with California poppy will reliably produce 12 hours of sound sleep. The maximum safe dose is 15 grams per day.

***Panax ginseng* (ginseng)**

Donald Brown, ND reports successful treatment of HPA dysfunction in CFS, a condition with similar symptoms and possible etiology, using *Panax ginseng* and *Eleutherococcus senticosus*. Numerous studies support the use of adaptogens for HPA dysregulation, fatigue, stress, anxiety, poor concentration, and diminished endurance.[76] [77]

***Petasites hybridus* (butterbur)**

In the last thirty years, studies have shown that petasites inhibits the body's production of leukotrienes, resulting in antispasmodic and anti-inflammatory activity.[78] [79] Butterbur supplements are often standardized to contain a minimum of 7.5 mg of petasin and isopetasin per tablet. Adults usually take 50-100 mg twice daily with meals. Petasites contains hepatotoxic pyrrolizidine alkaloids, thus only PA-free products are recommended for regular intake.

***Withania somnifera* (Ashwaganda root)**

Studies confirm that Ashwadanda increases stress tolerance, performance, endurance, and memory.[80] [81] [82] [83] Ayurvedic medicine considers it an herb that nourishes and regulates metabolic processes, and stabilizes mood. In one study, the researchers concluded, "The investigations support the use of *Withania somnifera* as a mood stabilizer in clinical conditions of anxiety and depression."[84] Ayurvedic herbalists use the herb to reestablish long-term sleep rhythms. Recent studies show ashwaganda to have immune enhancing action.[85] A typical dose of ashwaganda is about 1 gram per day, taken over long periods, up to many years, as a rejuvenator. Larger quantities (1- 10 grams per day) are often used in Ayurveda for acute conditions.

Adjunct Therapies for FMS

Diet and nutritional supplements

Vegetarian diet has been studied in FMS, to good effect in general.[86] [87] FMS patients were put on a strict vegan diet. These patients reported substantial reduction in joint stiffness and pain, as well as improved self reported health. Blood and urine measurements showed that antioxidant levels were markedly increased, compared with patients on an omnivorous diet. Quercetin, myricetin, and kaempherol levels were much higher in test subjects. Serum levels of antioxidants are consistently low in FMS patients and those with other joint and connective tissue disorders.[88] [89] [90] Most studies using antioxidant supplementation have not demonstrated positive results with joint disorders, while whole food diet studies consistently do.[91] A Norwegian study tested the effects of a three-week vegetarian diet for people with FMS. Serum peroxide, plasma fibrinogen, total cholesterol and high-density lipoprotein cholesterol all reduced.[92]

FMS patients are usually very low in magnesium, which leads to increased pain perception.[93] [94] Michael Murray, ND highly suggests says that magnesium deficiency in the muscle cell may be a key factor in FMS.[95] Herbalist Alan Tillotson relies on magnesium supplementation for FMS pain relief.[96] It is required for the synthesis of adenosine triphosphate. Deficiency can increase anaerobic glycolysis and lactic acid formation in the muscles (causing pain). Magnesium produces loose stool. Most people reach bowel tolerance at about 1200 - 1500 mg per day. Titrate to bowel tolerance dose.

Twenty-five FMS patients, mean age of 44.5 years, all living in Ontario, were studied between January and

March 2000. Twelve of the women (48%) had serum vitamin D levels below that considered the threshold for deficiency.[97] Marginal vitamin D deficiency is common among women with FMS living in a northern latitude. Vitamin D status should be suspected in people who have inadequate sun exposure, low intake of vitamin D-fortified foods (such as milk), or malabsorption, malnutrition, or chronic renal failure.

Massage

Thirty minutes of massage, twice weekly, can decrease pain and stiffness, and promote sleep.[98] In a 2003 study, researchers reported that movement and massage therapy reduce fibromyalgia pain.[99] In contrast to a relaxation control group, the movement/massage therapy group showed decreased depressed mood, state anxiety and regional pain immediately after the first and last sessions of the study, and a decrease in depressed mood, state anxiety and regional pain at baseline from the first to the last session.

Multidisciplinary approaches

In a presentation at the 20th Annual Meeting of the American Academy of Pain Medicine (March 2004), *Fibromyalgia Patients May Respond Well to an Interdisciplinary Approach*, Cynthia Van Keuren, PsyD, of the Cleveland (OH) Clinic Foundation spoke about the concept that patients suffering with fibromyalgia may benefit from an interdisciplinary approach that includes medication, exercise, and relaxation.[100] Van Keuren and her team from the Chronic Pain Rehabilitation Program evaluated 178 patients diagnosed with chronic low back pain, neuropathic pain, or fibromyalgia. With regard to self-perceived disability, patients with fibromyalgia showed a greater response to treatment.

In conclusion, it is clear that there is no magic bullet for FMS, and that a multifactorial approach to treatment is required.

Signs and Symptoms of Fibromyalgia

Signs and Symptoms	% of patients
Widespread pain	97.6
tenderness in > 11/18 tender points	90.1
Fatigue	81.4
morning stiffness	77.0
sleep disturbance	74.6
Paresthesias	62.8
Headache	52.8
Anxiety	47.8
dysmenorrhea history	40.6
sicca symptoms	35.8
prior depression	31.5
irritable bowel syndrome	29.6
urinary urgency	26.3
Raynaud's phenomenon	16.7

Source: The American College of Rheumatology 1990 [101]
Other commonly reported symptoms include dizziness, trouble with memory and concentration, rashes, and chronic itching.

Conditions Associated with Fibromyalgia

- Fatigue
- Irritable bowel syndrome
- Anxiety
- Depression
- Hyperventilation
- Hypermobility
- Cold intolerance and Raynaud's
- Allergy

Other Additional Associated Conditions

- Premenstrual tension syndrome
- Migraine
- Menstrual cramping
- Hypoglycemia
- Candida (Yeast overgrowth)
- Leaky gut
- Restless leg syndrome
- Interstitial cystitis

References

1 *The Merck Manual of Medical Information*. 1997, Home Edition, Merck and Co., West Point, PA, p 250

2 Barton A, Pal B, Whorwell PJ, Marshall D 1999, Increased prevalence of sicca complex and fibromyalgia in patients with irritable bowel syndrome *Am J Gastroenterol*. 94(7):1898-901

3 American College of Rheumatology, *Fibromyalgia Fact Sheet*, Online. Available at http://www.rheumatology.org/public/factsheets/fibromya.asp

4 Arthritis Foundation, *What is Fibromyalgia?* Online. Available at http://www.arthritis.org/AFStore/StartRead.asp?idProduct=3322

5 U.S. Census Bureau, *U.S. and World Population Clocks*, Online. Available at

http://www.census.gov/main/www/popclock.html
6 Andrew Weil, *Fibromyalgia*, Online. Available at http://www.drweil.com/app/cda/drw_cda.html-command=healthConditionDetail-pt=Conditions-articleId=23
7 White KP & M Harth 2001, Classification, epidemiology, and natural history of *fibromyalgia Curr Pain Headache Rep*. 5(4):320-9
8 Campbell SM, Clark S, Tindall EA, Forehand ME, Bennett RM 1983, Clinical characteristics of fibrositis. I. A "blinded," controlled study of symptoms and tender points *Arthritis Rheum* 26(7):817-24
9 Bennett RM 1989, Beyond fibromyalgia: ideas on etiology and treatment J *Rheumatol Suppl*. 19:185-91
10 Zimmerman M 1999, Persistent *Pain Nutrition Science* News. Online. Available at http://www.newhope.com/nutritionsciencenews/NSN_backs/Oct_99/fibromyalgia.cfm?path=ex
11 Pellegrino MJ et al. 1989, Familial occurrence of primary fibromyalgia *Arch Phys Med Rehab*. 70:61
12 Schiel WC, *Fibromyalgia*, Online. Available at http://www.medicinenet.com/script/main/art.asp?articlekey=363&pf=3&track=qpa363
13 Prescott E, Kjller M, Jacobsen S, Bulow PM, Danneskiold-Samsë B, Kamper-Jorgensen F 1993, Fibromyalgia in the adult Danish population: A prevalence study *Scand J Rheumatol*. 22:233-237
14 Makela M, Heliovaara M 1991, Prevalence of primary fibromyalgia in the Finnish population *BMJ*. 303:216-219
15 Middleton GD, McFarlin JE, Lipsky PE 1994, The prevalence and clinical impact of fibromyalgia in systemic lupus erythematosus *Arthritis Rheum*. 37:1181-1188
16 Borenstein D 1995, Prevalence and treatment outcome of primary and secondary fibromyalgia in patients with spinal pain *Spine*. 20:796-800
17 Lindell L, Bergman S, Petersson IF, Jacobsson LT, Herrstrom P 2000, Prevalence of fibromyalgia and chronic widespread pain *Scand J Prim Health Care*. 18(3):149-53
18 Forseth KO, Gran JT 19912 The prevalence of fibromyalgia among women aged 20-49 years in Arendal, Norway *Scand J Rheumatol*. 21(2):74-8
19 Forseth KO, Gran JT, Husby G 1997, A population study of the incidence of fibromyalgia among women aged 26-55 yr *Br J Rheumatol*. 36(12):1318-23
20 Choudhury AK, Yunus MB, Syed AH, Alam MN, Sebrina F, Aldag JC 2001, Clinical Features of Fibromyalgia Syndrome in a Bangladeshi Population *Journal of Musculoskeletal Pain*. 9(1), pp. 25-33
21 Standanyl D, Copeland, ME 2001, *Fibromyalgia and Chronic Myofascial Pain*. New Harbinger Publications, Oakland, CA
22 Glass JM, Park DC 2001, Cognitive dysfunction in fibromyalgia *Curr Rheumatol Rep*. 3(2):123-7
23 Park DC, Glass JM, Minear M, Crofford LJ 2001, Cognitive function in fibromyalgia patients *Arthritis Rheum*. 44(9):2125-33
24 Wolfe F1989, Fibromyalgia: the clinical syndrome *Rheum Dis Clin North Am*. 15(1):1-18
25 Jeschonneck M, Grohmann G, Hein G, Sprott H 2000, Abnormal microcirculation and temperature in skin above tender points in patients with fibromyalgia *Rheumatology* (Oxford). 39(8):917-21
26 Huppe A, Brockow T, Raspe H 2004, Chronic widespread pain and tender points in low back pain: a population-based study Z *Rheumatol*. 63(1):76-83
27 Al-Allaf AW, Dunbar KL, Hallum NS, Nosratzadeh B, Templeton KD, Pullar T 2002, A case-control study examining the role of physical trauma in the onset of fibromyalgia syndrome *Rheumatology* (Oxford). 41(4):450-3
28 Guedj D, Weinberger A 1990, Effect of weather conditions on rheumatic patients *Ann Rheum Dis*. 49(3):158-9
29 Hauri P, Hawkins DR 1973, Alpha-delta sleep *Electroencephalogr Clin Neurophysiol*. 34(3):233-7
30 The Arthritis Foundation, *Fibromyalgia* - What are the Symptoms? Online. Available at http://www.arthritis.org/conditions/DiseaseCenter/Fibromyalgia/fibromyalgia_symptoms.asp
31 Moldofsky H, Scarisbrick P, England R, Smythe H 1975, Musculosketal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects *Psychosom Med*. 37(4):341-51
32 Campbell SM, Clark S, Tindall EA, Forehand ME, Bennett RM 1983, Clinical characteristics of fibrositis. I. A "blinded," controlled study of symptoms and tender points *Arthritis Rheum*. 26(7):817-24
33 Chaitow L 2003, *Fibromyalgia Syndrome: A Practitioner's Guide to Treatment*. Churchill Livingstone, London
34 Moldofsky H 1993, Fibromyalgia, sleep disorder and chronic fatigue syndrome *Ciba Found Symp*. 173:262-71, discussion 272-9
35 Moldofsky H 1993, Fibromyalgia, sleep disorder and chronic fatigue syndrome *Ciba Found Symp*. 173:262-71, discussion 272-9
36 Wallace DJ, Linker-Israeli M, Hallegua D, Silverman S, Silver D, Weisman MH 2001, Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study *Rheumatology* (Oxford). 40(7):743-9
37 Douche-Aourik F, Berlier W, Feasson L, Bourlet T, Harrath R, Omar S, Grattard F, Denis C, Pozzetto B 2003, Detection of enterovirus in human skeletal muscle from patients with chronic inflammatory muscle disease or fibromyalgia and healthy subjects *J Med Virol*. 71(4):540-7
38 Tsigos C, Chrousos GP 2002, Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress *J Psychosom* Res. 53(4):865-71
39 Demitrack MA, Dale JK, Straus SE, Laue L, Listwak SJ, Kruesi MJ, Chrousos GP, Gold PW 1991, Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome *J Clin Endocrinol Metab*. 73(6):1224-34
40 Korszun A, Sackett-Lundeen L, Papadopoulos E, Brucksch C, Masterson L, Engelberg NC, Haus E, Demitrack MA, Crofford L 1999, Melatonin levels in women with fibromyalgia and chronic fatigue syndrome *J Rheumatol*. 26(12):2675-80
41 Merchant RE, Carmack CA, Wise CM 2000, Nutritional supplementation with Chlorella pyrenoidosa for patients

with fibromyalgia syndrome: a pilot study *Phytother Res*. 14(3):167-73
42 Merchant RE, Andre CA 2001, A review of recent clinical trials of the nutritional supplement Chlorella pyrenoidosa in the treatment of fibromyalgia, hypertension, and ulcerative colitis *Altern Ther Health Med*. 7(3):79-91
43 Rai D, Bhatia G, Palit G, Pal R, Singh S, Singh HK 2003, Adaptogenic effect of Bacopa monniera (Brahmi) *Pharmacol Biochem Behav*. 75(4): 823-30
44 Chowdhuri DK, Parmar D, Kakkar P, Shukla R, Seth PK, Srimal RC 2002, Antistress effects of bacosides of Bacopa monnieri: modulation of Hsp70 expression, superoxide dismutase and cytochrome P450 activity in rat brain *Phytother Res*. 16(7): 639-45
45 Kidd PM 1999,.A review of nutrients and botanicals in the integrative management of cognitive dysfunction *Altern Med Rev*. 4(3):144-61
46 Ashok DBV 1997, The Status And Scope Of Indian Medicinal Plants Acting On Central Nervous System *Indian J Pharmacol*. 29: S340-S343
47 Roodenrys S, Booth D, Bulzomi S, Phipps A, Micallef C, Smoker J 2002, Chronic effects of Brahmi (Bacopa monnieri) on human memory *Neuropsychopharmacology*. 27(2): 279-81
48 Singh RH, Singh L 1980, Studies on the anti-anxiety effect of the Medhya Rasayana drug Brahmi (*Bacopa monniera* Wet.) Part 1 *J Res Ayurveda and Siddha*. 1:133-148
49 Agrawal A, Gupta U, Dixit SP, Dubey GP 1993, Management of mental deficiency by an indigenous drug Brahmi. *Pharmacopsychoecologia*. 6(1):1-5
50 Bensky D, Gamble A 1986, *Chinese Materia Medica*. Eastland Press, Seattle
51 Kubo M, Matsuda H, Tokuoka K, Ma S, Shiomoto H 1994, Anti-inflammatory activities of methanolic extract and alkaloidal components from Corydalis tuber *Biol Pharm Bull*. 17(2):262-5
52 Liu L, Li G, Zhu F, Wang L, Wang Y 1990, Comparison of analgesic effect between locally vinegar-processed preparation of fresh rhizoma Corydalis and traditionally vinegar-processed rhizoma Corydalis *Chung Kuo Chung Yao Tsa Chih*. 15(11):666-7, 702
53 Wei F, Zou S, Young A, Dubner R, Ren K 1999, Effects of four herbal extracts on adjuvant-induced inflammation and hyperalgesia in rats *J Altern Complement Med*. 5(5):429-36
54 Fetrow CW, Avila JR 1999, *Complementary & Alternative Medicines*. Springhouse Publishing, Springhouse, PA, p 646
55 Srimal RC, Dhawan BN 1973, Pharmacology of diferuloyl methane (curcumin), a non-steroidal anti-inflammatory agent *J Pharm Pharmacol*. 25(6):447-52
56 Mukhopadhyay A, Basu N, Ghatak N, Gujral PK 1982, Anti-inflammatory and irritant activities of curcumin analogues in rats *Agents Actions*. 12(4):508-15
57 Ghatak N, Basu N 1972, Sodium curcuminate as an effective anti-inflammatory agent *Indian J Exp Biol*. 10(3):235-6
58 Murray M, Pizzorno J 1998, *Encyclopedia of Natural Medicine*. Prima, Rocklin, CA
59 Patacchini R, Maggi CA, Meli A 1990, Capsaicin-like activity of some natural pungent substances on peripheral endings of visceral primary afferents *Naunyn Schmiedebergs Arch Pharmacol*. 342(1):72-7
60 Ramsewak RS, DeWitt DL, Nair MG 2000, Cytotoxicity, antioxidant and anti-inflammatory activities of curcumins I-III from Curcuma longa *Phytomedicine*. 7(4):303-8
61 Bruneton J 1999, *Pharmacognosy: Phytochemistry, Medicinal Plants*. Intercept, p 918
62 *PDR for Herbal Medicines* 1998, Medical Economics Company, Montvale, NJ
63 Reimeier C, Schneider I, Schneider W, Schafer HL, Elstner EF 1995, Effects of ethanolic extracts from Eschscholtzia californica and Corydalis cava on dimerization and oxidation of enkephalins *Arzneimittelforschung*. 45(2):132-6
64 Herbert JM, Augereau JM, Gleye J, Maffrand JP 1990, Chelerythrine is a potent and specific inhibitor of protein kinase C *Biochem Biophys Res Commun*. 172(3):993-9
65 Fundytus ME, Coderre TJ 1996, Chronic inhibition of intracellular Ca2+ release or protein kinase C activation significantly reduces the development of morphine dependence *Eur J Pharmacol*. 300(3):173-81
66 Blumenthal M 1998, *The Complete Commission E Monographs*. The American Botanical Council, Austin, TX
67 Rolland A, Fleurentin J, Lanhers MC, Younos C, Misslin R, Mortier F, Pelt JM 1991, Behavioural effects of the American traditional plant *Eschscholzia californica*: sedative and anxiolytic properties Planta Med. 57(3):212-6
68 Bruneton J 1999, *Pharmacognosy: Phytochemistry, Medicinal Plants*. Intercept, p 918
69 Schafer HL, Schafer H, Schneider W, Elstner EF 1995, Sedative action of extract combinations of *Eschscholtzia californica* and *Corydalis cava Arzneimittelforschung*. 45(2):124-6
70 Kleber E, Schneider W, Schafer HL, Elstner EF 1995, Modulation of key reactions of the catecholamine metabolism by extracts from *Eschscholtzia californica* and *Corydalis cava Arzneimittelforschung*. 45(2):127-31
71 Rolland A, Fleurentin J, Lanhers MC, Misslin R, Mortier F 2001, Neurophysiological effects of an extract of *Eschscholzia californica* Cham. (Papaveraceae) *Phytother Res*. 15(5):377-81
72 Lister RE 2002 An open, pilot study to evaluate the potential benefits of coenzyme Q10 combined with *Ginkgo biloba* extract in fibromyalgia syndrome *J Int Med Res*. 30(2):195-9
73 Bhajan Y 1982, *The Ancient Art of Self Healing*. West Anandpur, Eugene, p 57
74 Grover JK, Khandkar S, Vats V, Dhunnoo Y, Das D 2002,. Pharmacological studies on Myristica fragrans—antidiarrheal, hypnotic, analgesic and hemodynamic (blood pressure) *parameters Methods Find Exp Clin Pharmacol*. 24(10):675-80
75 Sherry CJ, Burnett RE 1978, Enhancement of ethanol-induced sleep by whole oil of nutmeg *Experientia*. 34(4):492-3
76 Singh A, Saxena E, Bhutani KK 2000, Adrenocorticosterone alterations in male, albino mice

treated with *Trichopus zeylanicus, Withania somnifera* and *Panax ginseng preparations Phytother Res*. 14(2):122-5

77 *Phytotherapy Research*. 1996, 10:1

78 Grossman W, Schmidramsl H 2001, An extract of *Petasites hybridus* is effective in the prophylaxis of migraine *Altern Med Rev*. 6(3):303-10

79 Monograph 2001, *Petasites hybridus*. *Altern Med Rev* 6(2):207-9

80 Archana R, Namasivayam A 1999, Antistressor effect of *Withania somnifera J Ethnopharmacol*. 64(1):91-3

81 Singh B, Saxena AK, Chandan BK, Gupta DK, Bhutani KK, Anand KK 2001, Adaptogenic activity of a novel, withanolide-free aqueous fraction from the roots of *Withania somnifera* Dun. *Phytother Res*. 15(4):311-318

82 Jain S, Shukla SD, Sharma K, Bhatnagar M 2001, Neuroprotective Effects of *Withania somnifera* Dunn. in Hippocampal Sub-regions of Female Albino Rat *Phytother Res* .15(6):544-548

83 Dhuley JN 2000, Adaptogenic and cardioprotective action of ashwagandha in rats and frogs *J Ethnopharmacol*. 70(1):57-63

84 Bhattacharya SK, Bhattacharya A, Sairam K, Ghosal S 2000, Anxiolytic-antidepressant activity of *Withania somnifera glycowithanolides*: an experimental study *Phytomedicine*. 7(6):463-9

85 Davis L, Kuttan G 2000, Immunomodulatory activity of *Withania somnifera J Ethnopharmacol*. 71(1-2):193-200

86 Hanninen, Kaartinen K, Rauma AL, Nenonen M, Torronen R, Hakkinen AS, Adlercreutz H, Laakso J 2000, Antioxidants in vegan diet and rheumatic disorders *Toxicology*. 30;155(1-3):45-53

87 Kaartinen K, Lammi K, Hypen M, Nenonen M, Hanninen O, Rauma AL 2000, Vegan diet alleviates fibromyalgia symptoms *Scand J Rheumatol* 29(5):308-13

88 Comstock GW, Burke AE, Hoffman SC, Helzlsouer KJ, Bendich A, Masi AT, Norkus EP, Malamet RL, Gershwin ME 1997, Serum concentrations of alpha tocopherol, beta carotene, and retinol preceding the diagnosis of rheumatoid arthritis and systemic lupus erythematosus *Ann Rheum Dis*. 56(5):323-5

89 Heliovaara M, Knekt P, Aho K, Aaran RK, Alfthan G, Aromaa A 1994, Serum antioxidants and risk of rheumatoid arthritis *Ann Rheum Dis* 53(1):51-3

90 Knekt P, Heliovaara M, Aho K, Alfthan G, Marniemi J, Aromaa A 2000, Serum selenium, serum alpha-tocopherol, and the risk of rheumatoid arthritis *Epidemiology*. 11(4):402-5

91 Mangge H, Hermann J, Schauenstein K 1999, Diet and rheumatoid arthritis—a review *Scand J Rheumatol*. 28(4):201-9

92 Hostmark AT, Lystad E, Vellar OD, Hovi K, Berg JE 1993, Reduced plasma fibrinogen, serum peroxides, lipids, and apolipoproteins after a 3-week vegetarian diet *Plant Foods Hum Nutr*. 43(1):55-61

93 Ng SY 1999, Hair calcium and magnesium levels in patients with fibromyalgia: a case center study J *Manipulative Physiol Ther*. 22(9):586-93

94 *Functional Medicine Applications: Reversing Eight Vicious Cycles that Block Fibromyalgia and CFS Healing (and also normal healing in many other forms of illness)*. The Podell and King Medical Practice. Online. Available at http://www.drpodell.org/reversing.shtml

95 Murray MT 1996, *Encyclopedia of Nutritional Supplements*. Prima, Rocklin, CA, p 171

96 Tillotson A 2001, *The One Earth Herbal Sourcebook*. Kensington, New York, p 478

97 Huisman AM, White KP, Algra A, Harth M, Vieth R, Jacobs JW, Bijlsma JW, Bell DA 2001, Vitamin D levels in women with systemic lupus erythematosus and fibromyalgia *J Rheumatol*.

98 Weil A 1996, Living Better with Fibromyalgia, *Dr. Andrew Weil's Self Healing*. 1(6)

99 Field T, Delage J, Hernandez-Reif M 2003, Movement and massage therapy reduce fibromyalgia pain *Journal of Bodywork and Movement Therapies*. 7(1), p 49-52

100 Ingram J, *AAPM: Fibromyalgia Patients May Respond Well to an Interdisciplinary Approach*. Doctor's Guide. Online. Available at http://www.docguide.com/news/content.nsf/news/8525697700573E1885256E52005E6D88?OpenDocument&c=Pain&count=10

101 Wolfe F et al. 1990, The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee *Arthritis Rheum*. 33:160