

Combination Therapy in Fibromyalgia

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Abstract: Fibromyalgia is an enigmatic medical condition whose specific etiology remains undiscovered but currently plagues five million Americans [1]. Research indicates that the origin of the disease is most likely multifactorial. Treatment should therefore be tailored accordingly. Thus, it is often necessary to combine different options in order to achieve the maximum benefit in patients suffering from fibromyalgia.

Key Words: Fibromyalgia, Treatment, Pain, Sleep, Serotonin, Antidepressants, SSRIs, HPA, Estrogen.

INTRODUCTION

Fibromyalgia is characterized as a chronic, painful, non-inflammatory syndrome affecting the musculoskeletal system. This disease affects 2% of the population, 0.5% of men and 3.4% of women [2]. Clearly, this condition is far more common in females than in males. Although it may occur in any age group, fibromyalgia is most commonly diagnosed in the mid-forties, a time when women are often entering the menopausal transition. It comprises 15% of outpatient rheumatology visits and 5% of general medicine visits in the United States [3]. In order to diagnose this condition, the American College of Rheumatology recommends that patients meet two criteria, a history of widespread pain for at least three months and pain in 11 of 18 specific anatomical sites described as tender points [4]. This definition, however, does not include the large number of other symptoms commonly associated with fibromyalgia, including fatigue, non-restorative sleep, morning stiffness, headache, cognitive disturbances, anxiety, paresthesias and a sense of swelling, often located in the hands and fingers [5, 6]. The multiplicity of symptoms and chronic nature of fibromyalgia make it extremely debilitating for patients with this disorder.

Fibromyalgia has been noted to occur comorbidly with other chronic conditions such as irritable bowel syndrome, chronic fatigue syndrome, migraine headaches, restless leg syndrome, temporomandibular joint syndrome and myofascial pain syndrome. Depressive symptoms are also quite common in patients with fibromyalgia, with over half these patients having a lifetime history of depression [7, 8]. Hormonal changes, such as those occurring during pregnancy and the premenstrual period, have been associated with worsening symptoms [9], although onset often does not occur until the perimenopausal period. Obesity has also been linked with fibromyalgia; 61% of patients diagnosed with the condition have a BMI of greater than 25 [10]. Finally, fibromyalgia has been referred to as a "stress-related syndrome" because of the increase in symptoms during times of physical or emotional duress [11]. Changes in the weather or

physical activity may also bring about an increase in symptoms. As indicated above, fibromyalgia is an extraordinarily complex disorder with a wide variety of clinical components that must be accounted for in both the theories describing its origin and the combination of treatments used to ameliorate its symptoms.

ETIOLOGY

Fibromyalgia's constant pain and sleep disturbances point to a central origin of the disease [12, 13]. Biopsies of tender points have revealed no peripheral pathology [14], reinforcing the idea that this condition is caused by dysfunctional central processing. It also seems, based on the variety of symptoms that patients experience, increasingly evident that a single neurochemical dysfunction is not responsible for all the symptoms associated with fibromyalgia. There appear to be two main components that play a role in its pathology. The first is hypofunction of the serotonin (5-HT) system. Research shows decreased transcription of the short allele of the serotonin transporter in patients with fibromyalgia compared with controls [15]. Studies have also shown decreased levels of serotonin and tryptophan (the precursor to serotonin) in both the plasma and CSF of patients with fibromyalgia [16]. Tryptophan levels may also be regulated by estrogen levels, which can be disturbed in peri- and post-menopausal women [17]. Sleep EEG's of fibromyalgia patients show the intrusion of alpha waves (normally seen during wakefulness or REM sleep) into non-REM or deep sleep with infrequent progression to stage 3 and 4 sleep, a necessary part of restorative sleep [18, 19]. This abnormality is mediated by faulty central serotonergic neurotransmission [20]. It is reasonable to conclude that decreased serotonin may be responsible for the major symptoms of fibromyalgia given its importance as a neurotransmitter in both nociception and sleep.

Secondly, the hypothalamic-pituitary-end organ axis appears to be hyperactive. This is indicated by heightened cortisol levels with a flattened diurnal secretion pattern [21]. The dysfunctional activity of corticotropin releasing hormone (CRH) neurons appears to cause other hormonal perturbations. For example, CRH stimulates the production of somatostatin, which then inhibits both growth hormone and thyroid stimulating hormone [22]. Patients with fibromyalgia

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have decreased insulin growth factor (IGF) levels, another indicator of diminished growth hormone secretion. Sleep stages 3 and 4, disturbed in this patient population as cited above, are associated with hormone(s) release, growth hormone in particular [23]. There is debate over whether or not sex hormones are affected by the altered hypothalamic-pituitary axis (HPA) in fibromyalgia [22, 24], but it is suggested that they are by the preponderance of women affected by this illness. Abnormalities in CRH production may also induce hypofunction of neurotransmitters governing mood, motivation and somatic processes, alter the stress response, and modify nociception [21]. Patients with fibromyalgia have cerebrospinal fluid levels of substance P three times what is considered normal [12]. Additionally, the disturbances in the serotonin system and the HPA may cause disruptions in other neurotransmitter levels/function. Norepinephrine and dopamine are known to play a role in mood and cognition and may be dysfunctional in fibromyalgia patients [25]. Although the details have yet to be defined, it is apparent that the serotonin system and the HPA are heavily intertwined in the production of symptoms suffered by patients with fibromyalgia, and it is necessary to account for these many factors when determining the treatment plan for them.

TREATMENT

There are a number of treatments available to patients suffering from fibromyalgia, both pharmacological and non-

pharmaceutical. The wide variety of treatments attests to the complex nature of the disease. Because of this, it is often necessary to combine treatments to achieve maximum effect in patients suffering from fibromyalgia. As noted in Fig. (1), treatment aimed at one dysfunctional system may not improve a particular symptom given the other impaired systems' role in the creation of that symptom. Complete remission is exceedingly rare, so it is also of great importance that treatment be suitable for long-term use.

Antidepressants

Antidepressants are the most common class of medications used to treat fibromyalgia. Both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been studied and prescribed with great frequency. TCAs act by blocking the reuptake of serotonin and norepinephrine. They are reasonably effective in the treatment of chronic pain due to the potentiation of medullospinal antinociceptive systems. Unfortunately, they are plagued with many side effects caused by their multiple interactions with other neurotransmitter systems. In patients already suffering from fatigue, these side effects, including sedation and weight gain, can pose a real problem. These drugs are also toxic, even lethal, in overdose, a fact which must be taken into consideration when prescribing drugs to a patient population with a high rate of depression. SSRIs selectively block serotonin reuptake by the presynaptic receptors but have little effect on other neurotransmitters.

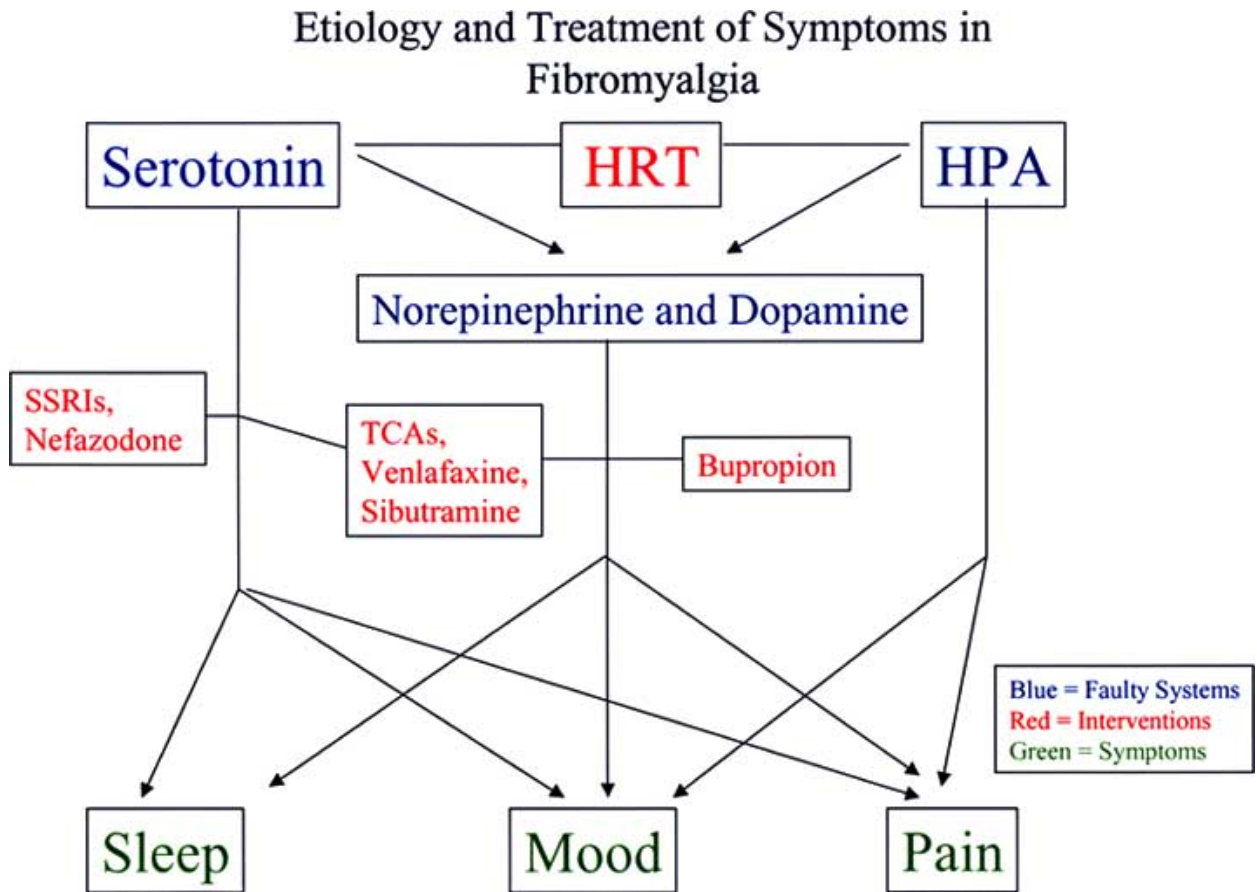


Fig. (1).

Although their side effect profile is much better, SSRIs may be limited in their usefulness in fibromyalgia due to their effect on only one neurotransmitter system.

A meta-analysis of the use of antidepressants vs. placebo to treat fibromyalgia revealed that these drugs do reduce the symptoms of the disease. It identified the number needed to treat as four; in other words, if four patients with fibromyalgia were treated with antidepressants, one would show improvement [26]. Perhaps the most promising current form of treatment is combining the two antidepressants; one trial showed that when amitriptyline and fluoxetine were taken together, they were twice as effective as when either was taken alone [27]. The dose of antidepressant required for pain relief is lower than that required to treat depression, so the patient should be started on a small dose that can be titrated upward to provide both pain relief and improvement of depressive symptoms, if that is required by the patient. These medications may also be taken at bedtime to provide some improvement in the patient's sleep. The symptoms most likely to respond to antidepressant therapy are pain, dysfunctional sleep, mood and fatigue; trigger points are the least likely to improve [28].

Several new antidepressants have recently been introduced and show potential in the treatment of fibromyalgia, combining the efficacy of TCAs and the reduced side effect profile of SSRIs. Venlafaxine blocks the reuptake of norepinephrine in addition to serotonin. Nefazodone blocks serotonin reuptake while also acting as a 5-HT₂ antagonist. There is some evidence that the 5-HT₂ receptor may be involved in the modulation of pain [29]. Both these drugs have been effective in pain management [30, 31], but they deserve more evaluation to assess their efficacy in the treatment of fibromyalgia. A serotonin/norepinephrine/dopamine reuptake inhibitor found to be helpful in treatment of fibromyalgia, sibutramine, was originally marketed in 1997 as a weight loss drug [32]. Twenty-five of thirty fibromyalgia patients (83%) given this medication reported significant pain relief after four to eight weeks of treatment [33]. Bupropion, although its exact mechanism remains unclear, is known to affect norepinephrine and dopamine, which both play a role in mood and cognition [25]. It is also known to be energizing in patients suffering from depression. This drug too warrants more investigation. Due to this population's sensitivity to medication side effects, it is best to keep the treatment regimen as simple as possible. However, due to the complex interactions of the systems involved in the illness, single drug therapy is usually not successful. Thus, if symptom control is not obtained with one medication, success has been achieved with a combination of these drugs.

Hormone Replacement Therapy (HRT)

As previously mentioned, the most common group to suffer from fibromyalgia is women in the menopausal transition. HRT can serve as an additional means of stabilization in this population if symptom control is not achieved with a combination of antidepressants. Estrogen may serve to modulate serotonin by affecting its binding, metabolism or degradation, thus improving a patient's pain and mood. Estrogen may also alter the dopamine system, enhancing

cognition. Giving estrogen in addition to antidepressants may make the side effects of the estrogen more tolerable to a group of patients highly sensitive to adverse events [34]. In general, estrogen used in this age group of women has been a hotly debated topic [35], but in the case of patients with fibromyalgia, the benefits may outweigh the potential risks.

NSAIDs and Corticosteroids

This seems like an obvious group of drugs to turn to for the relief of pain. Unfortunately, they appear to provide little relief in the patients with fibromyalgia. Several studies have compared NSAID's to tricyclic antidepressants and found no benefit with NSAIDs alone and no synergistic effect when combined with the TCAs [36, 37]. Prednisone was compared with placebo in regard to its effect on pain, sleep disturbance, morning stiffness and fatigue, and it showed no significant difference in symptom improvement [38]. Furthermore, since fibromyalgia does not appear to involve an inflammatory mechanism, these drugs have little importance in the treatment of this condition, and in fact may further contribute to a mood disturbance.

Opioids

Opioids are again another class of drugs commonly prescribed for pain relief. Due to the chronic nature of the fibromyalgia and the extremely high potential for abuse of these drugs, these medications should be avoided in patients with fibromyalgia or discontinued in those patients already taking them. In addition, opioids may negatively impact cognition, worsen associated symptoms of fibromyalgia and lead to sedation and/or fatigue.

Muscle Relaxants

The only drug in this group to show any benefit in patients with fibromyalgia is cyclobenzaprine [39-42]. This may be explained by the fact that its chemical structure is quite similar to that of amitriptyline and differs by only one double bond [43, 44]. Other drugs in this class, metaxalone and carisoprodol, are used for the treatment of acute musculoskeletal pain and are not recommended for patients with fibromyalgia [45].

Other Medications

There are a number of other medications that have been tried in the treatment of fibromyalgia. S-adenosylmethionine (SAME), an amino acid and neurotransmitter precursor, has been shown to provide improvement in the number of tender points and morning stiffness [28]. Capsaicin, an inhibitor of substance P, produced significantly less tenderness in tender points and greater grip strength [46]. Growth hormone supplementation in patients with low insulin growth factor levels produced significant pain relief and improvement in overall quality of life compared to placebo [47]. Unfortunately, this drug is very expensive. Benzodiazepines do not play a role in the treatment of fibromyalgia secondary to their sedative properties and addictive nature. However, zolpidem, a non-benzodiazepine hypnotic agent, allowed for improved sleep and daytime energy levels in fibromyalgia patients. It does not, however, alter pain levels, and this limits its usage [48].

There are other drugs that have not yet been studied as treatments for fibromyalgia. Gabapentin and pregabalin, both GABA agonists, were originally designed for management of seizures resistant to typical treatment [49]. However, studies have shown that both drugs are useful for the control of various forms of pain [50-52]; these drugs may therefore serve to modulate the pain felt by patients with fibromyalgia. Psychostimulants, which are dopamine agonists, are known to decrease daytime sleepiness, enhance cognition and temporarily improve mood. Since all these are symptoms from which fibromyalgia patients suffer, this class of drugs certainly warrants investigation in this condition. However, patient use must be carefully monitored secondary to the abuse potential and the possibility of paradoxical insomnia created by these drugs.

Cognitive Behavioral Therapy (CBT)

The main purpose of this therapy is to teach patients psychological management strategies for coping with the chronic pain and disability associated with fibromyalgia [53]. Specifically, this includes decreasing feelings of helplessness, reorganizing negative thoughts leading to pain and developing strategies for handling pain [45]. A meta-analysis of CBT in chronic pain patients drew the conclusion that this form of therapy is indeed effective in this patient population [54]. In fibromyalgia patients in particular, CBT produced decreases in pain perception and tender point measures [55-59]. The primary drawback of this intervention is the time intensive nature of the therapy and the high cost involved.

Exercise Programs

A majority of patients with fibromyalgia fall below the standards of physical fitness established by the American Heart Association [60]. Cardiovascular exercise appears to be the most effective form of exercise (as compared to flexibility [61] and relaxation [62] exercises) in which fibromyalgia patients can participate. Patients doing aerobic exercise reported reduced pain, increased energy, decreased tender point scores and increased physical and social activity [62-65]. Compliance with these exercise regimens, however, is commonly poor in this patient population.

Other Non-Pharmaceutical Treatments

There are a few other therapies not involving medications that have been tried in patients with fibromyalgia. Transcutaneous Electric Nerve Stimulation (TENS) has been attempted and shown little benefit in these patients. It is more appropriate for localized pain versus the diffuse, generalized pain typically associated with fibromyalgia; this limits its usefulness in the treatment of the disease [66]. Biofeedback, a process in which the patient is taught to control certain physiological processes, has produced improved physical activity and reduced disease severity [67]. Hypnosis [68] and chiropractic treatment [69] have also shown some benefit in patients with fibromyalgia. Perhaps more importantly, maintaining a good diet, a regular sleep schedule and a healthy lifestyle will serve to improve these patients' symptoms.

Summary of Treatments

In a complicated disorder like fibromyalgia, combination treatment is often necessary to best relieve the patient's symptoms. Antidepressants, used singly or in combination, may serve to relieve pain and improve sleep and mood. In perimenopausal women, estrogen, when used in combination with an antidepressant to improve tolerability, may contribute significantly to symptom reduction. Anti-inflammatory drugs and opioids, both commonly used to control pain, have little to no role in controlling symptoms in fibromyalgia patients. There are a number of other medications with which researchers are experimenting to provide better management of symptoms; these may play a larger role in the treatment of the disease in the future. Both cardiovascular exercise and cognitive behavioral therapy serve to improve patients' pain and can be combined with drug therapy for maximum benefit to the patient.

CONCLUSION

Fibromyalgia is a chronic, debilitating condition. The best the patient and his or her physician can expect is good control of symptoms with as few side effects from treatment as possible. Because of the broad range of symptoms from which these patients suffer, it may be necessary to combine treatment modalities to best achieve relief from the condition. Much still needs to be discovered concerning the nature of the disease, and the most appropriate means of treating it.

REFERENCES

References 70-72 are related articles recently published in *Current Pharmaceutical Design*.

- [1] Arthritis Foundation. Fibromyalgia syndrome. Atlanta, GA: The Foundation. 1996.
- [2] Wolfe F, Ross K, Anderson J, Russell IJ, Herbert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995; 38: 19-28.
- [3] Wolfe F. Fibromyalgia, the clinical syndrome. *Rheum Dis Clin NA* 1989; 15: 1-17.
- [4] Wolfe F, Smythe H, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, *et al.* The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990; 33(2): 160-172.
- [5] Wolfe F. The clinical syndrome of fibrositis. *Am J Med* 1986; 81(suppl 3A): 7-14.
- [6] Yunus M, Masi A, Aldag J. A controlled study of primary fibromyalgia syndrome: clinical features and associations with other functional syndromes. *J Rheumatol* 1989; 16(suppl 19): 62-71.
- [7] Hudson JL, Goldenberg DL, Pope HG, Keck PE, Schlesinger L. Comorbidity of fibromyalgia with medical and psychiatric disorders. *Am J Med* 1992; 92: 363-367.
- [8] Triadafilopoulos G, Simms RW, Goldenberg DL. Bowel dysfunction in fibromyalgia syndrome. *Dig Dis Sci* 1991; 36: 59-64.
- [9] Ostensen M, Rugelsjoen A, Wigers SH. The effect of reproductive events and alterations of sex hormone levels on the symptoms of fibromyalgia. *Scand J Rheumatol* 1997; 26(5): 355-360.
- [10] Yunus MB. Relationship between body mass index and fibromyalgia features. *Scand J Rheumatol* 2001; 3(2): 27-31.
- [11] Crofford LJ. Neuroendocrine abnormalities in fibromyalgia and related disorders. *Am J Med Sci* 1998; 315(6): 359-366.
- [12] Russell IJ, Orr MD, Littman B, Vipraio D, Alboukrek D, Michalek JE, *et al.* Elevated cerebrospinal fluid levels of substance P in

- patients with the fibromyalgia. *Arthritis Rheum* 1994; 37: 1593-1601.
- [13] Yunus MB. Towards a model of pathophysiology of fibromyalgia: aberrant central pain mechanisms with peripheral modulation. *J Rheumatol* 1992; 19: 846-850.
- [14] Yunus MB, Kalyan-Raman UP. Muscle biopsy findings in primary fibromyalgia and other forms of non-articular rheumatism. *Rheum Dis Clin North Am* 1989; 15: 115-133.
- [15] Offenbaecher M, Bondy B, de Jonge S, Glatzeder K, Kruger M, Schoeps P, *et al.* Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. *Arthritis Rheum* 1999; 42: 2482-2488.
- [16] Russell IJ. Neurochemical pathogenesis of fibromyalgia syndrome. *J Musculoskel Pain* 1996; 4: 61-92.
- [17] Russell IJ, Vaeroy H, Javors M, Nyberg F. Cerebrospinal fluid biogenic amines metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. *Arthritis Rheum* 1992; 35: 550-556.
- [18] Moldofsky H. Sleep and fibrositis syndrome. *Rheum Dis Clin North Am* 1989; 15(1): 91-103.
- [19] Harding SM. Sleep in fibromyalgia patients: subjective and objective findings. *Am J Med Sci* 1998; 315: 367-376.
- [20] Moldofsky H, Scarisbrick P. Introduction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. *Psychosom Med* 1975; 37: 341-345.
- [21] Neeck G, Crofford IJ. Neuroendocrine perturbations in fibromyalgia and chronic fatigue syndrome. *Rheum Dis Clin North Am* 2000; 26: 989-1002.
- [22] Neeck G, Riedel W. Hormonal perturbations in fibromyalgia syndrome. *Ann N Y Acad Sci* 1999; 876: 325-339.
- [23] Lentz MJ, Landis CA, Rothermel J, Shaver JL. Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle aged women. *J Rheumatol* 1999; 26: 1586-1592.
- [24] Korszun A, Young EA, Engleberg NC, Masterson L, Dawson EC, Spindler K, *et al.* Follicular phase hypothalamic-pituitary-gonadal axis dysfunction in women with fibromyalgia and chronic fatigue syndrome. *J Rheumatol* 2000; 27: 6.
- [25] Clayton AH, Kaltsounis-Puckett J. Combination therapy in the treatment of major depressive disorder complicated by fibromyalgia and menopause. *Psychosomatics* 2002; 43(6): 491-493.
- [26] O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants: a meta-analysis. *J Gen Intern Med* 2000; 15(9): 659-666.
- [27] Goldenberg DL, Mayskiy M, Mossey C, Ruthazar R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. *Arthritis Rheum* 1996; 39: 1852-1859.
- [28] Arnold LM, Keck Jr PE, Welge JA. Antidepressant treatment of fibromyalgia. *Psychosomatics* 2000; 41(2): 104-113.
- [29] Abbott FV, Hong Y, Blier P. Activation of 5-HT_{2A} receptors potentiates pain produced by inflammatory mediators. *Neuropharmacology* 1996; 35: 99-110.
- [30] Goodnick PJ, Breakstone K, Kumar A, Freund B, DeVane CL. Nefazodone in diabetic neuropathy: response and biology (letter). *Psychosom Med* 2000; 62: 599-600.
- [31] Dwight MM, Arnold LM, O'Brien H, Metzger R, Morris-Park E, Keck PE Jr. An open clinical trial of venlafaxine treatment of fibromyalgia. *Psychosomatics* 1998; 39: 14-17.
- [32] James WP, Astrup A, Finer N, Hilsted J, Kopelman P, Rossner S, *et al.* Effect of sibutramine on weight management after weight loss: a randomized trial. *Lancet* 2000; 356: 2119-2125.
- [33] Palangio M, Flores JA, Joyal SV. Treatment of fibromyalgia with sibutramine hydrochloride monohydrate: comment on the article by Goldenberg, *et al.* *Arthritis Rheum* 2002; 46(9): 2546.
- [34] Soares CN, Almeida OP, Joffe H, Cohen LS. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2001; 58: 529-534.
- [35] Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288(3): 321-333.
- [36] Goldenberg DL. Fibromyalgia syndrome a decade later: what have we learned?. *Arch Intern Med* 1999; 159: 777-785.
- [37] Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. *Arthritis Rheum* 1986; 29: 1371-1377.
- [38] Clark S, Tindall E, Bennett RM. A double-blind crossover trial of prednisone versus placebo in the treatment of fibrositis. *J Rheumatol* 1985; 12: 980-983.
- [39] Carette S, Bell MJ, Reynolds WJ, Haraoui B, McCain GA, Bykerk VP, *et al.* Comparison of amitriptyline, cyclobenzaprine and placebo in the treatment of fibromyalgia: a randomized, double-blind clinical trial. *Arthritis Rheum* 1994; 37: 32-40.
- [40] Bennett RM, Gatter RA, Campbell SM, Andrews RP, Clark SR, Scarola JA. A comparison of cyclobenzaprine and placebo in the management of fibrositis: a double-blind, controlled study. *Arthritis Rheum* 1988; 31: 1535-1542.
- [41] Quimby LG, Gratwick GM, Whitney CD, Black SR. A randomized trial of cyclobenzaprine for the treatment of fibromyalgia. *J Rheumatol* 1989; 16: 140-143.
- [42] Reynolds WJ, Moldofsky H, Saskin P, Lue FA. The effects of cyclobenzaprine on sleep physiology and symptoms in patients with fibromyalgia. *J Rheumatol* 1991; 18: 452-454.
- [43] Wong ECC, Koenig J, Turk J. Potential interference of cyclobenzaprine and norcyclobenzaprine with HPLC measurement of amitriptyline and nortriptyline: resolution by GC-MS analysis. *Clin Toxicol* 1995; 19: 218-224.
- [44] Poklis A, Edinboro LE. REMEDI drug profiling system readily distinguishes between cyclobenzaprine and amitriptyline in emergency toxicology urine specimens. *Clin Chem* 1992; 38: 2349-2350.
- [45] Alarcon GS, Bradley LA. Advances in the treatment of fibromyalgia: current status and future directions. *Am J Med Sci* 1998; 315(6): 397-404.
- [46] Holzer P. Capsaicin: cellular targets, mechanisms of action and selectivity for thin sensory neurons. *Am Soc Pharmacol Exp Ther* 1991; 43: 143-201.
- [47] Bennett RM, Clark SR, Burckhardt CS, Walczyk J. A double-blind placebo-controlled study of growth hormone in fibromyalgia. *J Musculoskel Pain* 1995; 3: 110.
- [48] Moldofsky H, Lue FA, Mously C, Roth-Schechter B, Reynolds WJ. The effects of zolpidem in patients with fibromyalgia: a dose ranging, double-blind, placebo-controlled, modified crossover. *J Rheumatol* 1996; 23: 529-533.
- [49] Bryans JS, Wustrow DJ. 3-substituted GABA analogs with central nervous system activity: a review. *Med Res Rev* 1999; 19: 149-177.
- [50] Tremont-Lukats IW, Megeff C, Backonja MM. Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy. *Drugs* 2000; 60: 1029-1052.
- [51] Mao J, Chen LL. Gabapentin in pain management. *Anesth Analg* 2000; 91: 680-687.
- [52] Hill CM, Balkenohl M, Thomas DW, Walker R, Mathe H, Murray G. Pregabalin in patients with postoperative dental pain. *Eur J Pain* 2001; 5: 119-124.
- [53] Bradley L. Cognitive behavioral therapy for primary fibromyalgia. *J Rheumatol* 1989; 16(suppl 19): 131-136.
- [54] Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain* 1999; 80(1-2): 1-13.
- [55] Bennett RM, Campbell S, Buckhardt C, Clark S, O'Reilly C, Weins A. Balanced approach provides small but significant gains: a multidisciplinary approach to fibromyalgia management. *J Musculoskel Med* 1991; 8: 21-32.
- [56] Bennett RM, Buckhardt CS, Clark SR, O'Reilly CA, Weins AN, Campbell SM. Group treatment of fibromyalgia: a 6 month outpatient program. *J Rheumatol* 1996; 23: 53-66.
- [57] Goldenberg DL, Kaplan KH, Nadeau MG, Brodeur C, Smith J, Schmid CH. A controlled study of a stress-reduction, cognitive-behavioral treatment program in fibromyalgia. *J Musculoskel Pain* 1994; 2:53-66.
- [58] Nielson WR, Walker C, McCain GA. Cognitive-behavior treatment of fibromyalgia syndrome: preliminary findings. *J Rheumatol* 1992; 19: 98-103.
- [59] White KP, Nielson WR. Cognitive-behavioral treatment of fibromyalgia syndrome: a follow up assessment. *J Rheumatol* 1995; 22: 717-721.

- [60] Bennett RM, Clark SR, Goldberg L, Nelson D, Bonafede RP, Porter J, *et al.* Aerobic fitness in patients with fibrositis: a controlled study of respiratory gas exchanges and ¹³⁵xenon clearance from exercising muscle. *Arthritis Rheum* 1989; 32: 454-460.
- [61] McCain G, Bell D, Mai FM, Halliday PH. A controlled study of the effects of a supervised cardiovascular fitness training program on the manifestations of primary fibromyalgia. *Arthritis Rheum* 1988; 31(9): 1135-1141.
- [62] Martin L, Nutting A, MacIntosh BR, Edworthy SM, Butterwick D, Cook J. An exercise program in the treatment of fibromyalgia. *J Rheumatol* 1996; 23: 1050-1053.
- [63] Wigers S, Stiles T, Vogel PA. Effects of aerobic exercise versus stress management treatment in fibromyalgia: a 4.5 year prospective study. *Scand J Rheumatol* 1996; 25(2): 77-86.
- [64] Nichols D, Glenn DS. Effects of aerobic exercise on pain perception, affect and level of disability in individuals with fibromyalgia. *Phys Ther* 1994; 74(4): 327-332.
- [65] Verstappen FTJ, van Santen-Hoeft HMS, Bolwijn PH, *et al.* Effects of a group activity program for fibromyalgia patients on physical fitness and well being. *J Musculoskel Pain* 1997; 5: 17-28.
- [66] Forseth KØ, Gran JT. Management of fibromyalgia: what are the best treatment choices? *Drugs* 2002; 62(4): 577-592.
- [67] Buckelew SP, Conway R, Parker J, Deuser WE, Read J, Witty TE, *et al.* Biofeedback/ relaxation training and exercise interventions for fibromyalgia: a prospective trial. *Arthritis Care Res* 1998; 11(6): 432-47.
- [68] Haanen HC, Hoenderdos HT, van Romunde LK, Hop WC, Mallee C, Terwiel JP, *et al.* Controlled trial of hypnotherapy in the treatment of refractory fibromyalgia. *J Rheumatol* 1991; 18: 72-75.
- [69] Blunt KL, Rajwani MH, Guerriero RC. The effectiveness of a chiropractic management of fibromyalgia patients: a pilot study. *J Manipulative Physiol Ther* 1997; 20: 389-399.
- [70] Eggert M, Kluter A, Zettl UK, Neeck G. Transcription factors in autoimmune diseases. *Curr Pharm Design* 2004; 10(23): 2787-96.
- [71] Hertelendy F, Zakar T. Regulation of myometrial smooth muscle functions. *Curr Pharm Design* 2004; 10(20): 2499-517.
- [72] Pacher P, Kecskemeti V. Cardiovascular side effects of new antidepressants and antipsychotics: new drugs, old concerns? *Curr Pharm Design* 2004; 10(20): 2463-75.

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