

Fibromyalgia

Knowns, Unknowns, and Current Treatment

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Abstract

Fibromyalgia is a chronic syndrome of diffuse musculo-skeletal pain with tenderness at specific locations, often associated with persistent fatigue, cognitive and mood disorders, joint stiffness, and insomnia. Understanding the pathophysiology of fibromyalgia and the establishment of effective treatments have been complex endeavors that have not yielded simple answers. Nevertheless, recent studies have shed light on the roles of central pain processing, genetic abnormalities, and external factors on development of the fibromyalgia syndrome (FMS). These findings have led to the use of new therapies that have shown beneficial effects on symptoms. This review discusses ideas that have become accepted as well as novel associations under consideration in regard to the pathogenesis of fibromyalgia and the current and emerging therapeutics for its treatment.

Fibromyalgia is a syndrome characterized by chronic, widespread pain in combination with tenderness to palpation at specific tender point sites on the body, in the absence of otherwise apparent organic disease. It is often associated with other symptoms, such as persistent fatigue, headaches, cognitive or memory impairment, mood disorders, joint stiffness, and insomnia.^{1,2} Despite the high prevalence of fibromyalgia (approximately 2% of the population and 3.4% of females in the United States) as well as the increasing public awareness and physician acceptance of the syndrome, understanding its pathophysiology and finding

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effective treatments continues to be a complex endeavor.^{3,4}

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Central pain processing has been shown to differ in patients with fibromyalgia, compared to those without the syndrome. Under normal circumstances, painful stimuli are transmitted to the dorsal horn of the spinal cord via primary afferent fibers (A- δ and C nerve fibers) and lead to the release of substance P and excitatory amino acids (EAAs).⁵ From there, the nociceptive information travels to the thalamus via the spinothalamic tract, where it is distributed to the somatosensory cortex and subcortical brain centers.⁶ The perception of pain is modulated through the activation of descending inhibitory pathways, and the release of neurotransmitters, such as norepinephrine, serotonin, and endorphins.⁷ However, in patients with prolonged exposure to pain, the incoming afferent signals are increased, and presynaptic release of substance P and EAAs is enhanced. An influx of calcium ions increases the production of nitric oxide, which causes nerves to become hyperexcitable and further release EAAs and substance P.⁵ Glial cells also become activated and release substances that enhance the excitability of pain transmission neurons, such as nitric oxide, reactive oxygen species, prostaglandins, proinflammatory cytokines, and nerve growth factor.⁸

Abnormal responses to pain in fibromyalgia have been documented with neuroimaging through the use of functional MRI (fMRI). Gracely and colleagues⁹ showed that painful pressure applied to the thumbnail bed increased cerebral blood flow to many common areas in patients with fibromyalgia and controls. However, these areas had increased blood flow at lower thresholds in patients with fibromyalgia syndrome (FMS). In addition, at pressures causing pain in patients with fibromyalgia but not in control subjects, there was increased blood flow to different areas

only in the control group. These locations are possibly areas involved in descending inhibitory pathways that were able to blunt the pain response in normal subjects, but not those with fibromyalgia.

Evidence for genetic abnormalities in fibromyalgia has also been elucidated, with family studies showing that first-degree relatives of individuals with FMS display an eight-fold risk of developing the syndrome as compared to family members of patients with rheumatoid arthritis (RA). Furthermore, those related to fibromyalgia patients also had lower pain thresholds and more tender points than the RA relatives.¹⁰ These familial associations have led to attempts to identify genes involved in pain transmission that may be differentially expressed in fibromyalgia. Significant genetic linkage of FMS to the HLA region has been revealed at the HLA A, B, and DRB1 loci. Other studies have examined the role of serotonergic markers, showing higher frequencies of the S/S genotype in the serotonergic transporter promoter region, as well as a decrease in the T/T polymorphism in the 5-HT_{2A} receptor gene of patients with fibromyalgia. Additional genetic markers have been discovered within the D4 dopamine gene, which showed a significant decrease in a specific 7-repeat allele in fibromyalgia patients.¹¹

External factors such as psychosocial stresses and physical injury have long been associated with widespread pain syndromes. Harkness and coworkers¹² prospectively noted the onset of diffuse pain in workers who had low job satisfaction and social support, as well as in those who had prolonged physical trauma in the workplace.¹² The effect of acute physical trauma has been less clear. Buskila and associates¹³ followed a cohort of patients with whiplash from motor vehicle accidents and noted a high percentage of development of fibromyalgia (22%). However, a more recent study followed 153 patients after whiplash injuries, and only one developed FMS.¹⁴

As with many chronic illnesses, the role of infection as a precipitating or aggravating factor in fibromyalgia is being aggressively studied. An internet survey of 2596 people with fibromyalgia found that 26.7% associated the onset of their condition with an acute illness, and 43% felt that infections worsened their FMS symptoms.¹⁵ There is data suggesting an increased prevalence of fibromyalgia in patients with Lyme disease, as well as viral infections, including HIV, HTLV-1, hepatitis B, and hepatitis C.¹⁶⁻²¹

Unknowns

Recently, increasing attention has been given to novel factors that have not classically been thought to play a role in the development of fibromyalgia. While several associations have been suggested among these factors, their role in the pathophysiology of disease has yet to be clarified.

Brain-derived neurotrophic factor (BDNF) is involved in neuronal survival and synaptic plasticity of the central and peripheral nervous system, and it appears to modulate nociceptive sensory inputs and pain hypersensitivity. In-

creased serum BDNF levels have been recently reported in fibromyalgia, suggesting an involvement in the syndrome.²²

Serum ferritin levels were found to be significantly lower in FMS patients, perhaps due to the role of iron as a cofactor in enzymes involved in neurotransmitter synthesis.²³ Levels of magnesium and zinc were also found to be decreased in 32 FMS patients (selenium was not). Association between serum zinc level and number of tender points and between fatigue and magnesium level was also found to be meaningful.²⁴ Serum IL-8 levels were elevated in fibromyalgia patients as well, and these levels were reduced to near normal levels within 6 months after brief inpatient multidisciplinary pain therapy.²⁵

The role of oxidative stress in the pathophysiology of fibromyalgia also has been studied, and Cordero and colleagues²⁶ evaluated mitochondrial function in affected patients by examining their blood mononuclear cells. They noted reduced levels of coenzyme Q10, decreased mitochondrial membrane potential, increased levels of mitochondrial superoxide, and increased lipid peroxidation, as well as increased autophagy and mitophagy. These findings may support the role of oxidative stress and mitophagy in FMS.

While studies attempting to localize the pathology in FMS to peripheral tissues have failed in showing any abnormalities in muscle tissue, Staud and coworkers did show that enhanced central pain processing can occur via continued peripheral muscle afferent input.^{27,28} Their study demonstrated that muscle lidocaine injections increased local pain thresholds and decreased remote secondary heat hyperalgesia in fibromyalgia patients, emphasizing the important role of peripheral impulse input in maintaining central sensitization.

Treatments

Given the unclear etiology of fibromyalgia, and the heterogeneous presentations of the disease, it has become clear that no one therapy is broadly efficacious. In terms of pharmacologic treatments, the tricyclic antidepressants (TCAs) were the initial drugs studied for fibromyalgia. These medicines increase synaptic concentrations of serotonin and norepinephrine in the central nervous system (CNS), reducing pain signaling. Several trials have shown short-term improvement in pain and sleep, but long-term studies have not been as efficacious.^{29,30} Adverse reactions that may limit effectiveness include fatigue, sedation, cognitive difficulties, dry mouth, and cardiac arrhythmias, although agents such as nortriptyline may have better side effect profiles at higher doses than the traditional drug used, amitriptyline.³¹

Cyclobenzaprine shares pharmacologic properties with TCAs, but acts on the brainstem to induce skeletal muscle relaxation via reduction of tonic activity of alpha and gamma neurons. Short-term studies demonstrated improvement in pain and fatigue, but longer term studies did not show an advantage over placebo.^{30,32} Tizanidine is a centrally acting alpha 2 adrenergic agonist that can be helpful for headache

and back pain; animal models have shown a reduction in substance P in the spinal fluid in treated rats.³³ All muscle relaxants are limited by side effects of fatigue and hyper-somnolence.

Selective serotonin reuptake inhibitors (SSRIs) increase serotonin availability at the neuronal synapse, and studies have shown that fluoxetine can be as effective as amitriptyline, with the two in combination having greater efficacy than either alone.³⁴ A more recent trial using higher doses of fluoxetine demonstrated a reduction in pain regardless of effect on depression.³⁵ Other SSRIs, although regularly used in practice, have not been studied effectively for FMS.^{36,37}

Serotonin-norepinephrine reuptake inhibitors (SNRIs, or dual-reuptake inhibitors) may have greater antinociceptive properties than pure SSRIs, and have provided two of the U.S. Food and Drug Administration's (FDA) approved therapies for fibromyalgia.³⁸ Arnold and associates³⁹ pooled four placebo-controlled trials using duloxetine in FMS patients, assembling 797 patients receiving treatment and 535 controls; patients were followed after a 12-week treatment period. Pain was significantly reduced in treated patients, and improvements were also noted on depression and global functioning scales.

Milnacipran is an SNRI that is somewhat selective for norepinephrine reuptake inhibition. U.S. and European studies have shown its effectiveness over placebo in pain reduction after 1 week, as well as with pain, fatigue, and cognition at 15 weeks, and with overall response [including use of the Fibromyalgia Impact Questionnaire (FIQ) total score] of FMS at 3 months.^{40,41} Patients continuing on milnacipran demonstrated a durable efficacy in pain reduction and FIQ over a 12-month period.⁴² The medication appears to be well tolerated, with headache and nausea as the most common adverse effects. On fMRI studies, milnacipran-treated patients exhibited a reduction in pain sensitivity and a parallel increase in activity in brain regions implicated in the descending pain inhibitory pathways, compared to placebo-treated patients.⁴³

Pregabalin was the first medication the FDA approved for fibromyalgia, after the drug was initially approved for diabetic neuropathy and post-herpetic neuralgia. Pregabalin disrupts neuronal signaling by binding to the α -2-delta subunit of voltage-gated calcium channels in the CNS. Multiple double-blind placebo-controlled trials have shown significant reductions in pain score, as well as decreased fatigue, improved sleep, and health related quality of life.^{44,45} Over 6 months, pregabalin retained its effectiveness in responders, compared to those who went off the drug.⁴⁶ Side effects include dizziness, somnolence, and weight gain.

Gabapentin is another centrally acting agent that is approved for multiple neurologic diseases and inhibits the same voltage-gated calcium channels as pregabalin. In a 12-week randomized controlled trial (RCT), gabapentin was more effective than placebo in improving pain scores, sleep quality, and FIQ scores at an average dose of 1800 mg per

day. The most common side effects were dizziness, sedation, and lightheadedness.⁴⁷

Although commonly prescribed, there is little objective evidence to assess the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs). In one double-blind, placebo-controlled trial, ibuprofen was no better than placebo, and, in another, naproxen led to minor but insignificant symptom improvement.^{30,48} One trial of oral corticosteroid use found no efficacy.⁴⁹

There are no short- or long-term data available to inform the use of pure opiates in fibromyalgia, but there have been some studies to support the use of the mixed opiate tramadol. The drug centrally acts at the mu-opioid receptor and also weakly inhibits norepinephrine and serotonin reuptake. In a 91-day RCT evaluating tramadol plus acetaminophen in fibromyalgia, fewer dropouts occurred in the active treatment group (48% vs 62% in the placebo arm), which was the primary end point.⁵⁰ Another study showed improvements in the FIQ using this regimen.⁵¹

Nonpharmacologic therapies in fibromyalgia have become an important part of treatment, and a review by Goldenberg and colleagues suggested strong evidence for efficacy of several interventions, including cardiovascular exercise, cognitive behavioral therapy, and patient education.⁵² However, two other reviews shed light on the fact that most studies of these interventions are of questionable quality, and no meaningful conclusions could be derived from them. Nevertheless, these investigators felt that combination approaches had better outcomes than single interventions.^{53,54}

Several novel therapeutics have been looked at lately as potential future therapies for fibromyalgia. Skrabek and coworkers performed the first RCT to assess the benefit in FMS of nabilone, a synthetic cannabinoid, and found significant decreases in pain, FIQ score, and anxiety (but not the number of tender points) in 40 patients over a 4-week period.⁵⁵ Sodium oxybate, the sodium salt of a metabolite of gamma-aminobutyric acid, was found to help FMS symptoms during its open-label trial for patients with narcolepsy. An 8-week RCT resulted in beneficial responses in composite pain, FIQ, and global health scores, as well as subjective sleep outcomes in 124 patients.⁵⁶ Naltrexone, in addition to antagonizing opioid receptors on neurons, also inhibits microglia activation. It is proposed that this mechanism may explain the improvements in fibromyalgia symptoms in a recent pilot study of 10 patients treated with the medication.⁵⁷

Conclusions

The future of fibromyalgia holds a great deal of interest for many, as its long-term effects on patients and its costs to society are becoming more clear. Current research hopefully will bear clinically useful biomarkers for FMS, to aide in diagnosis and to guide therapy. Studies of combination therapy, as well as head-to-head trials of medications will likely be forthcoming. New therapies are on the horizon, but

more trials are required in regard to symptomatic treatments, including sleep, fatigue, and cognitive disturbances. The effectiveness of multidisciplinary management also will be evaluated, in order to provide the most comprehensive care for this group of challenging and complex patients.

Disclosure Statement

The author has no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References

1. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. *Arthritis Rheum.* 1990;33:160-72.
2. Mease P, Arnold LM, Bennett R, et al. Fibromyalgia syndrome. *J Rheumatol.* 2007;34:1415-25.
3. Wolfe F, Ross K, Anderson J, et al. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum.* 1995;38:19-28.
4. Arshad A, Kong KO. Awareness and perceptions of fibromyalgia syndrome: a survey of southeast Asian rheumatologists. *J Clin Rheumatol.* 2007;13:59-62.
5. Bradley LA. Pathophysiology of fibromyalgia. *Am J Med.* 2009;122(12 Suppl):S22-30.
6. Abeles AM, Pillinger MH, Solitar BM, Abeles M. Narrative review: the pathophysiology of fibromyalgia. *Ann Intern Med.* 2007;146:726-34.
7. Gebhart GF. Descending modulation of pain. *Neurosci Biobehav Rev.* 2004;27:729-37.
8. Watkins LF, Maier SF. The pain of being sick: implications of immune-to-brain communication for understanding pain. *Annu Rev Psychol.* 2000;51:29-57.
9. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum.* 2002;46:1333-43.
10. Arnold LM, Hudson JI, Hess EV, et al. Family study of fibromyalgia. *Arthritis Rheum.* 2004;50:944-52.
11. Ablin J, Buskila D, Clauw DJ. Biomarkers in fibromyalgia. *Curr Pain Headache Rep.* 2009;13:343-9.
12. Harkness EF, Macfarlane GJ, Hahit E, et al. Mechanical injury and psychosocial factors in the work place predict the onset of widespread body pain: a two year prospective study among cohorts of newly employed workers. *Arthritis Rheum.* 2004;50:1357-9.
13. Buskila D, Neumann L, Vaisberg G, et al. Increased rates of fibromyalgia following cervical spine injury. A controlled study of 161 cases of traumatic injury. *Arthritis Rheum.* 1997;40:446-52.
14. Tishler M, Levy O, Maslakov I, et al. Neck injury and fibromyalgia – are they really associated? *J Rheumatol.* 2006 Jun;33(6):1183-5; Epub 2006 May 1.
15. Bennett R, Jones J, Turk DC, et al. An internet survey of 2,596 people with fibromyalgia. *BMC Muskuloskel Disord.* 2007;8:27-37.
16. Dinerman H, Steere AC. Lyme disease associated with fibromyalgia. *Ann Intern Med.* 1992;117:281-5.
17. Marquez J, Restrepo CS, Canida L, et al. Human immunodeficiency virus-associated rheumatic disorders in the HAART era. *J Rheumatol.* 2004;31:741-6.
18. Cruz BA, Catalan-Soares B, Prioretti F. Higher prevalence of fibromyalgia in patients infected with human T cell lymphotropic virus type I. *J Rheumatol.* 2006;33:2300-3.
19. Adak B, Tekeoglu I, Ediz L, et al. Fibromyalgia frequency in hepatitis B carriers. *J Clin Rheumatol.* 2005;11:157-9.
20. Rivera J, de Deigo A, Trinchet M, et al. Fibromyalgia-associated hepatitis C virus infection. *Br J Rheumatol.* 1997;36:981-5.
21. Buskila D, Shnaider A, Neumann L, et al. Fibromyalgia in hepatitis C virus infection. Another infectious disease relationship. *Arch Intern Med.* 1997;157:2497-500.
22. Haas L, Portela LV, Bohmer AE, et al. Increased plasma levels of brain derived neurotrophic factor (BDNF) in patients with fibromyalgia. *Neurochem Res.* 2010;35:830-4.
23. Ortancil O, Sanli A, Eryuksel R, et al. Association between serum ferritin level and fibromyalgia syndrome. *Eur J Clin Nutr.* 2010;64:308-12.
24. Sendur OF, Tastaban E, Turan Y, Ullman C. The relationship between serum trace element levels and clinical parameters in patients with fibromyalgia. *Rheumatol Int.* 2008;28:1117-21.
25. Wang H, Buchner M, Moser MT, et al. The role of IL-8 in patients with fibromyalgia: a prospective longitudinal study of 6 months. *Clin J Pain.* 2009;25:1-4.
26. Cordero MD, De Miguel M, Moreno Fernandez AM, et al. Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease. *Arthritis Res Ther.* 2010;12:R17.
27. Simms RW, Roy SH, Hrovat M, et al. Lack of association between fibromyalgia syndrome and abnormalities in muscle energy metabolism. *Arthritis Rheum.* 1994;37:794-800.
28. Staud R, Nagel S, Robinson ME, Price DD. Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: a randomized double-blind, placebo-controlled study. *Pain.* 2009;145:96-104.
29. Scudds RA, McCain GA, Rollman GB, Harth M. Improvements in pain responsiveness in patients with fibrositis after successful treatment with amitriptyline. *J Rheumatol.* 1989;19(Suppl):98-103.
30. Carette S, Bell MJ, Reynolds WJ, 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.
31. Heymann RE, Helfenstein M, Feldman D. A double-blind, randomized, controlled study of amitriptyline, nortriptyline and placebo in patients with fibromyalgia. An analysis of outcome measures. *Clin Exp Rheumatol.* 2001;19:697-702.
32. Quimby LG, Gratwick GM, Whitney CD, Block SR. A randomized trial of cyclobenzaprine for the treatment of fibromyalgia. *J Rheumatol Suppl.* 1989 Nov;19:140-3.
33. Ono H, Mishima A, Ono S, et al. Inhibitory effects of clonidine and tizanidine on release of substance P from slices of rat spinal cord and antagonism by alpha-adrenergic receptor antagonists. *Neuropharmacology.* 1991;30(6):585-9.
34. Goldenberg D, Mayskiy M, Mossey C, et al. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. *Arthritis Rheum.* 1996;39:1852-9.
35. Arnold LM, Hess EV, Hudson JI, et al. A randomized, placebo-

- controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. *Am J Med.* 2002;112:191-7.
36. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fibromyalgia- a randomized, double-blind, placebo-controlled study. *Eur J Pain.* 2000;4:27-35.
37. Patkar AA, Masand PS, Krulewicz S, et al. A randomized, controlled, trial of controlled release paroxetine in fibromyalgia. *Am J Med.* 2007;120:448-54.
38. Abeles M, Solitar BM, Pillinger MH, Abeles AM. Update on fibromyalgia therapy. *Am J Med.* 2008;121:555-61.
39. Arnold LM, Clauw DJ, Wohlreich MM, et al. Efficacy of duloxetine in patients with fibromyalgia: pooled analysis of 4 placebo-controlled clinical trials. *Prim Care Companion J Clin Psychiatry.* 2009;11:237-44.
40. Mease PJ, Clauw DJ, Gendreau RM, et al. The efficacy and safety of milnacipran for treatment of fibromyalgia. A randomized, double-blind, placebo-controlled trial. *J Rheumatol.* 2009;36:398-409.
41. Branco JC, Zachrisson O, Perrot S, Mainguy Y. A European multicenter randomized double-blind placebo-controlled monotherapy clinical trial of milnacipran in the treatment of fibromyalgia. *J Rheumatol.* 2010;37:851-9.
42. Goldenberg DL, Clauw DJ, Palmer RH, et al. Durability of therapeutic response to milnacipran treatment for fibromyalgia. Results of a randomized, double-blind, monotherapy 6-month extension study. *Pain Med.* 2010;11:180-94.
43. Mainguy Y. Functional magnetic resonance imagery (fMRI) in fibromyalgia and the response to milnacipran. *Hum Psychopharmacol.* 2009;24:S19-23.
44. Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2005;52:1264-73.
45. Mease PJ, Russel IJ, Arnold LM, et al. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *Nat Clin Pract Rheumatol.* 2008;4:514-5.
46. Crofford LJ, Simpson S, Young JP, et al. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. *Pain.* 2008;136:419-31.
47. Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum.* 2007;56:1336-44.
48. Yunus MB, Masi AT, Aldag JC. Short term effects of ibuprofen in primary fibromyalgia syndrome: a double blind, placebo controlled trial. *J Rheumatol.* 1989;16:527-32.
49. Clark S, Tindall E, Bennett RM. A double blind crossover trial of prednisone versus placebo in the treatment of fibrositis. *J Rheumatol.* 1985;12:980-3.
50. Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. *Am J Med.* 2003;114:537-45.
51. Bennet RM, Schein J, Kosinski MR, et al. Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen. *Arthritis Rheum.* 2005;53:519-27.
52. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA.* 2004;292:2388-95.
53. Karjalainen K, Malmivaara A, van Tulder M, et al. Multidisciplinary rehabilitation for fibromyalgia and musculoskeletal pain in working age adults. *Cochrane Database Syst Rev.* 2000;(2):CD001984.
54. Sim J, Adams N. Systematic review of randomized controlled trials of nonpharmacological interventions for fibromyalgia. *Clin J Pain.* 2002;18:324-36.
55. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. *J Pain.* 2008;9:164-73.
56. Russell IJ, Perkins AT, Michalek JE, et al. Sodium oxybate relieves pain and improves function in fibromyalgia syndrome: a randomized, double-blind, placebo-controlled, multicenter clinical trial. *Arthritis Rheum.* 2009;60:299-309.
57. Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study. *Pain Med.* 2009;10:663-72.