Fibromyalgia Syndrome: Approach to Management

By I. Jon Russell, MD, PhD

ABSTRACT

The management of fibromyalgia syndrome (FMS) has traditionally been multimodal and multidisciplinary, including education, physical modalities, and medication. In this article, an acronym is offered to help the clinician remember the important components of management. An improved understanding of the pathogenesis of FMS has allowed substantial refinements in its treatment. This is particularly true for medications that target specific symptom domains, allowing individualization of therapy. Since all FMS patients experience pain, there has been emphasis on that domain although medications are now available to address two or more domains with monotherapy. In addition, a logical basis is provided to help the clinician design strategic polypharmacy.

CNS Spectr. 2008;13:3(Suppl 5):27-33.

INTRODUCTION

The objectives of treatment for patients with the fibromyalgia syndrome (FMS) are to reduce pain, improve sleep, restore physical function, maintain social interaction, and reestablish emotional balance. Since pharmacotherapy can now be focused on the biochemical and neurophysiologic abnormalities of the disorder, the clinician's first thought may be to offer a medication; however, it is important to provide a therapy that

Needs Assessment

It is commonly stated that fibromyalgia syndrome (FMS) is very difficult to treat. While that has been true in the past, new approaches are available, including mechanism-focused medications. It is now possible to effectively manage the majority of FMS patients, but physicians who have not followed the topic closely will be unaware of these innovations. Increased awareness of the diagnosis predicts an even greater need for effective therapy.

Learning Objectives

At the end of this activity, the participant should be able to:

- Recognize that successful management of the fibromyalgia syndrome (FMS) is possible.
- Recall the components of a multimodal therapy for FMS through a simple acronym.
- Identify successful medications for FMS symptoms by name and mechanism of action.
- Predict which combinations of drugs might be successful based on drug mechanisms of action as well as the individual patient's symptoms.

Target Audience: Psychiatrists

CME Accreditation Statement

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Mount Sinai School of Medicine and MBL Communications, Inc. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation

The Mount Sinai School of Medicine designates this educational activity for a maximum of 4 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This activity has been peer-reviewed and approved by Eric Hollander, MD, chair at the Mount Sinai School of Medicine. Review date: February 15, 2008. Dr. Hollander does not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

To Receive Credit for This Activity

Read the five articles in this supplement, reflect on the information presented, and then complete the CME posttest and evaluation on pages 34 and 35. To obtain credits, you should score 70% or better. Early submission of this posttest is encouraged. Please submit this posttest by March 1, 2010, to be eligible for credit. The estimated time to complete all five articles and the posttest is 4 hours. Release date: March 1, 2008. Termination date: March 31, 2010.

Dr. Russell is associate professor of medicine and director of the University Clinical Research Center at the University of Texas Health Sciences Center in San Antonio, editor of the *Journal of Musculoskeletal Pain*, and emeritus founding president of the International MYOPAIN Society.

Disclosures: Dr. Russell is a consultant to and on the advisory boards of Eli Lilly, Jazz, and Pfizer; is on the speaker's bureaus of Ortho-McNeil and Pfizer; and receives research contract support from Eli Lilly, Jazz, Ortho-McNeil, and Pfizer. He is supported, in part, by the RGK Foundation of Austin Texas. This article references unlabeled or unapproved uses of duloxetine, pregabalin, and sodium oxybate.

Acknowledgments: Dr. Russell would like to thank the RGK Foundation of Austin Texas.

Submitted for publication: December 31, 2007. Accepted for publication: February 18, 2008.

Please direct all correspondence to: I. Jon Russell, MD, PhD, Department of Medicine, Mail Code 7868, University of Texas Health Center, 7703 Floyd Curl Dr, San Antonio, TX 78229-3900; Tel: 201-567-4661; E-mail: russell@uthscsa.dcci.com.

is balanced and multimodal. Patients should be guided through a combination of social support, education, physical modalities, and medication.[1,2] Periodic follow-up allows the clinician to assess over time the benefit derived. A simple acronym, "ADEPT Living," is provided to help the practitioner remember these six main categories of intervention (Table 1).

THE "ADEPT LIVING" ACRONYM

Attitude

Attitude refers to the preparation, or frame of mind, that each participant brings to the therapeutic interaction. Clinicians must be prepared to accept FMS as a real condition that exerts a tremendous impact on the patient's life. Empathy will be more therapeutic than baseless recriminations. It is similarly important for the patient to understand that FMS is just one of thousands of conditions that the healthcare provider must face and that the physician's time with each patient is limited. The attitudes of family members, employers, policy makers, and politicians all can impact importantly on the patient's condition.

Diagnosis

Clinical diagnoses should not only identify FMS, but should also disclose any comorbid medical conditions. If the patient has concomitant hypothyroidism, diabetes mellitus, or renal insufficiency, the approach to management will need to accommodate the other conditions as well. For example, when rheumatoid arthritis and FMS are evident in the same patient, treatment is more successful when both conditions are treated as if the other were not present.

TABLE 1.
Fibromyalgia Management Acronym

Six Steps to ADEPT Living
• **A**ttitude – patient, healthcare professional, family, society
• **D**iagnosis – diagnosis and differential diagnosis
• **E**ducation – didactic, group, reading, psychosocial, biomedical
• **P**hysical – home (pacing, exercise, heat) and/or formal physical therapy
• **T**reatments – medications, surgical interventions
• **Living** – interval objective assessment, adjustment, support

Russell IJ. *CNS Spectr.* Vol 13, No 3 (Suppl 5). 2008.

Education

Education is crucial to the management of FMS. Patient understanding is power, when it comes to adapting to limitations and to the patients' taking an active role in the therapeutic program. Cognitive-behavioral therapy is a specific form of education that requires a guide and active participation. It has been shown to improve pain scores, pain coping, pain behavior, depression, and physical functioning.[3] The benefits are often maintained for 6 months to a year or more. Support groups have been viewed negatively by some clinicians and patients for their tendency to be counterproductive, but patients who join a resource-oriented group can benefit from the supportive and educational aspects.

Physical Therapies

Useful physical modalities can be segregated into two categories: those that the patients can accomplish independently at home and those that require active participation by a trained therapist. At home, the patient can pace activities by setting a clock to time necessary work activity and then balance the work time with an equal period of rest. Progressive exercise, heat applied as shower or bath, and Jacobsonian relaxation techniques can all be self-directed therapies at minimal cost.[3]

Aerobic exercise was among the first nonpharmacologic strategies to evidence benefit for FMS.[3] Besides improvement of cardiovascular fitness, it is believed to improve aerobic capacity, reduce pain, improve sleep, balance mood, improve stamina, instill new perspectives, restore cognition, and facilitate a sense of well-being.[4] Patients who are able to exercise sustain less negative impact of FMS in their lives.

On the other hand, imprudent bursts of exertion by a patient who is chronically deconditioned can temporarily worsen pain. When prescribing exercise for FMS patients, the clinician should begin with low intensity exercise, (such as walking in place in a swimming pool) and minimize eccentric muscle contractions.[5] A potential role for pyridostigmine in this process has been proposed.[6]

Most patients report benefit from heat in the form of a hot bath, hot-water bottles, electric heat pads, or a sauna. A hot bath or shower can be more effective than an analgesic for

headache, body pain, and stiffness. The application of heat can relax muscles, facilitate exercise, and improve a sense of well-being. Cold applications are preferred by some. Light massage that gradually progress to deep sedative palpation of large body surfaces can reduce muscle tension, but its influence on the body pain is transient.

Treatments

In the ADEPT acronym, treatments refer to therapies advised and/or prescribed by healthcare professionals (Table 2).

TREATMENT OF FIBROMYALGIA SYNDROME

Surgery

Surgery will be addressed first because there is no surgical therapy specific for FMS. It has been argued that surgical therapy for Chiari malformation results in improvement of FMS symptoms but it seems likely that FMS-like symptoms benefited are actually manifestations of the Chiari syndrome.

Other kinds of surgery have been applied to FMS patients. Many patients undergo marginally beneficial surgical procedures (eg, carpal tunnel release or cervical spine procedures)[7] because they have pain and are insistent that something be done about it. This can be a trap for surgeons who are poorly informed about FMS. Patients with FMS should not be promised that surgery will cure their pain.

Medications

The most exciting new developments regarding FMS therapy relate to new medications. The theoretical basis for application of these agents to FMS has been a variety of documented biochemical or physiological abnormalities in FMS.[8-10]

Analgesics

It seems logical that analgesics should be an important component of a multimodal treatment program, but non-steroidal anti-inflammatory drugs are not effective as monotherapy. While opioids have not been formally tested in large placebo-controlled trials, most experts believe them to lack benefit in FMS. Synergy may be an important concept for medicinal therapy of FMS. For example, acetaminophen enhances the benefit achieved from tramadol therapy.[11]

Precursors

The synthesis of serotonin (5-HT) can be augmented by administration of 5-hydroxytryptophan (5HTP) which benefits from one-way

TABLE 2.
Therapeutic Agents for Fibromyalgia Syndrome

Analgesics

- NSAIDs – not adequate as monotherapy for FMS on the basis of any clinical study
- Tramadol, tramadol + acetaminophen (the combination is more effective than either tramadol or acetaminophen alone)
- Acetaminophen
- Opioids (controversial, inadequately studied, appear ineffective in FMS, probably because endogenous opioids are high in spinal fluid and receptors for opioid ligands are low)

Precursor

- 5-hydroxytryptophan (mandatory conversion to serotonin, known to be benefical in FMS for pain and other manifestations)

Biogenic Amine Reuptake Inhibitors

- With weak opioid activity, tramadol, or tramadol + acetaminophen (see above)
- SSRIs – many are helpful for depression but none for pain in usual dosages
- SNRIs – duloxetine (FMS pain and depression but not insomnia)
- NSRIs – milnacipran (await follow-up studies)

Serotonin Receptor Blockade

- Tropisetron, a 5-HT_3 antagonist (effective dosage is narrow, higher dosage less effective than lower dosage)

NMDA Receptor Blockade

- Ketamine (only ~50% of FMS patients respond)
- Dextromethorphan (reported marginally effective in FMS)

Anticonvulsant

- Pregabalin (FMS pain and insomnia but not depression)

Sedative

- Sodium oxybate (FMS pain and insomnia but not depression)

NSAIDs=nonsteroidal anti-inflammatory drugs; FMS=fibromyalgia syndrome; SSRIs=selective serotonin reuptake inhibitors; SNRIs=serotonin norepinephrine reuptake inhibitors; NSRIs=norepinephrine serotonin reuptake inhibitors; 5-HT=serotonin.

Russell IJ. *CNS Spectr.* Vol 13, No 3 (Suppl 5). 2008.

kinetics in conversion to 5-HT. It has been shown to be effective in the treatment of FMS at dosages of 100 mg three times daily[12] and is available over-the-counter in the United States.

Inhibition of Biogenic Amine Transport

The tricyclic antidepressants (TCAs) were traditionally used in low dosage to improve sleep and to enhance the effects of analgesics. For example, amitriptyline in low doses (10–25 mg) or cyclobenzaprine at 5–10 mg would be given at night to improve sleep. One study showed that a combination of fluoxetine and amitriptyline can be more effective than either agent alone.[13]

Tramadol was a drug designer's improvement on the TCAs. Reuptake inhibition was combined with weak μ-opioid agonism. As monotherapy, especially in combination with acetaminophen, it significantly reduced the severity of experienced pain, but did not help with insomnia or depression.[14] Nausea and dizziness can be limiting at first in ~20% of patients but can be avoided by initiating therapy at a very low dosage, and gradually increasing to full dosage at two tablets three to four times daily.

Selective serotonin reuptake inhibitor (SSRI) drugs were developed for the treatment of depression. In usual antidepressant dosages, these agents were effective as monotherapy for depression in ~50% of depressed patients but did not attenuate FMS body pain. In very high dosages (fluoxetine 80 mg/day), they may exhibit analgesic effects, probably because it is no longer "selective."[15]

The analgesic effects of the TCAs, in comparison with the SSRIs, suggested that inhibition of the norepinephrine transporter might be critical to their pain relieving effect. A new class of agents called serotonin and norepinephrine reuptake inhibitors were developed to achieve better balance between serotonin and the norepinephrine effects. Duloxetine exhibits nearly equal activities on these two biogenic amines, while milnacipran exhibits marginal greater norepinephrine reuptake inhibition than serotonin.

In dosages of 60–120 mg once daily, duloxetine can be effective in controlling FMS body pain whether or not the patient is depressed.[16,17] It is well-tolerated by most FMS patients, but nausea, dry mouth, constipation, diarrhea, and anorexia were reported adverse events. Duloxetine is available in the US for neuropathic pain and depression indications, but has been submitted to the Food and Drug Administration for FMS indication. Milnacipran is available in Europe for depression, but is not yet available in the US.

Serotonin Receptor Antagonists

Tropisetron is a 5-HT_3 antagonist that has been subjected to controlled study in Europe for the treatment of FMS.[18] A responder group (39%) exhibiting a rapid and steady decrease in pain intensity was distinguished from a nonresponder group. Treatment with tropisetron was well-tolerated and limited mainly by gastrointestinal side effects.

Dopaminergic Agents

The level homovanilic acid, a metabolite of dopamine, is low in the CSF of people with FMS,[10] so there is a theoretical basis for believing that dopaminergic agents could be beneficial in FMS.

Neurokinin-1 Receptor Antagonists

Since substance P seems to play a role in the pathogenesis of FMS, the discovery and characterization of the substance P receptor (neurokinin-1 [NK1] receptors) gave rise to hopes that developing potent NK1 receptor blockade drugs would provide new treatment options. Unfortunately, the potent agents that were developed failed to exhibit much analgesic activity in FMS.[19] It is still possible that they will be synergistic with other agents under study.

NMDA Receptor Agonists

Central sensitization can be inhibited or attenuated by *N*-methyl-D-aspartate (NMDA) receptor antagonists. Two NMDA receptor antagonists, ketamine and dextromethorphan, have been studied in FMS and were both found to exhibit beneficial effects on pain and allodynia.[20] In the case of ketamine, ~50% of FMS patients benefited. Ketamine's utility was further limited by frequent adverse effects, such as psychic disturbances such as feeling of unreality, altered body image perception, modulation of hearing and vision, dizziness, anxiety, aggression, and nausea.

Dextromethorphan exhibited a better side-effects profile than ketamine, so it was administered orally to FMS patients in combination with tramadol.[21] A favorable response was achieved in 58% of FMS subjects. The investigators concluded that this combination might have promise for a subgroup of FMS patients, perhaps pre-selected by a parenteral ketamine response test.

Anticonvulsants

Drugs with anticonvulsant activity have the potential to raise the threshold for pain fiber depolarization, as they do for central neurons to reduce seizure activity. Pregabalin is a ligand for the newly discovered $\alpha 2\delta$ subunit of voltage gated calcium channels.[22,23] It has analgesic, anxiolytic, and anticonvulsant activity in animal models. It reduces the release of several neurochemicals, including glutamate, norepinephrine, and substance P. It was found to be effective in reducing the severity of body pain, improving quality sleep, and reducing fatigue in FMS.[24] Pregabalin is the only drug specifically approved with an indication for treatment of fibromyalgia in the US. It is scheduled because of its mild anxiolytic activity. In therapeutic dosages (300–450 mg/day in two divided doses), it is generally well tolerated, with adverse effects such as dose-related dizziness and somnolence resolving within a few days of continuous therapy. This observation suggests value in starting low in dosage and gradually increasing it. Weight gain and peripheral edema occur in 10% to 15% of patients.

Sedatives

Sodium oxybate, a metabolite of γ-aminobutyric acid (GABA), exhibits sedative hypnotic activity. It influences both pre- and postsynaptic $GABA_B$ receptors[25] through a G-protein-coupled complex receptor for which intracellular cyclic adenosine monophosphate is the second messenger.[26] An allosteric effect on calcium channels is also reported.[27] This scheduled drug is approved by the US FDA for the treatment of narcolepsy with cataplexy, and excessive daytime sleepiness. It is available from only one pharmacy in the US, which delivers the properly prescribed medication directly to the home of the intended patient. In several studies, it was found to be beneficial in the management of FMS insomnia and pain.[28-30] Nausea and dizziness were the most common adverse events.

Strategic Polypharmacy

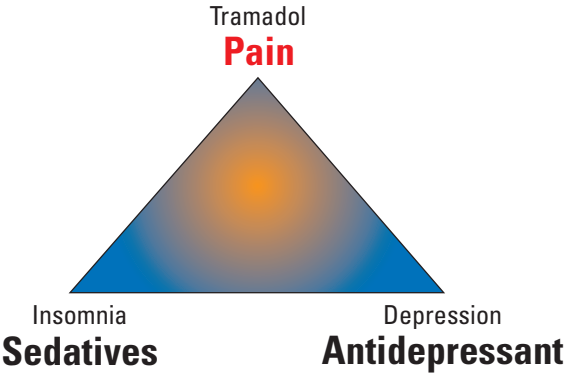
There are very little data on the effects of combining effective drugs to achieve increased benefit or to allow lower dosages that would spare adverse effects. The critical principle of this concept is that complementary medications would address the same symptomatic domain with different mechanisms of action or address different domains in the same affected individual. Figure 1A illustrates this concept on a theoretical basis using three important symptomatic domains (pain, insomnia, depression) as the therapeutic targets. While this figure illustrates the use of tramadol to treat the pain, other medications would be needed for the other domains if they were active. Addition of an SSRI as the antidepressant or a TCA as the sedative in this setting would be relatively contraindicated on the basis of mechanism of action and risk of toxicity.

In an FMS patient with two prominent domains, both pain and depression, the use of duloxetine would be logical (Figure 1B). Duloxetine could be used to treat the pain even if depression were not present, because it was equally effective for pain whether or not depression was present.[17]

In an FMS patient with two prominent domains, both pain and insomnia, the use of pregabalin is first-line therapy but the use of oxybate would be logical as well (Figure 1C). Of course, either of these drugs could be used to treat the pain even if insomnia were not present.

In an FMS patient with three prominent domains (pain, insomnia, and depression), the combined use of either pregabalin or oxybate along with duloxetine could be considered because their mechanisms of action and elimination are quite different (Figure 1D). Since there is very little experience with such a regimen, it must be tailored to the individual patient and carefully monitored.

FIGURE 1A.
Strategic polypharmacy for fibromyalgia syndrome with pain and minor insomnia and depression



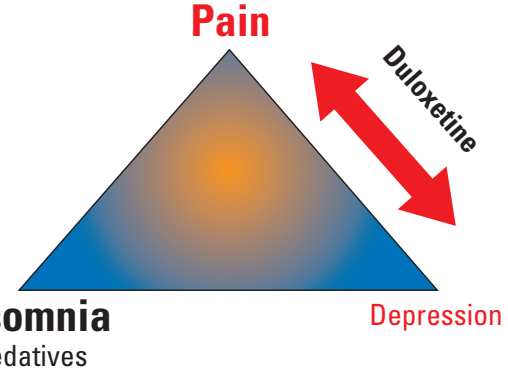
The use of tramadol for treatment of pain when it is the predominant manifestation in a patient with fibromyalgia syndrome. Minor insomnia and depression can be addressed with available sedative and antidepressant medications, such as bupropion, but it may be best to avoid selective serotonin reuptake inhibitors to avoid the hyperserotonin syndrome.

Russell IJ. *CNS Spectr.* Vol 13, No 3 (Suppl 5). 2008.

CONCLUSION

Treatment of FMS is still multidimensional but dramatic improvements have occurred, particularly in medications that target two or more of the symptomatic domains of the disorder. A simple acronym like "ADEPT" Living can help the clinician recall the elements of effective therapy. It is predicted that strategic polypharmacy will be the favored approach to FMS therapy for the next 5–10 years. ***CNS***

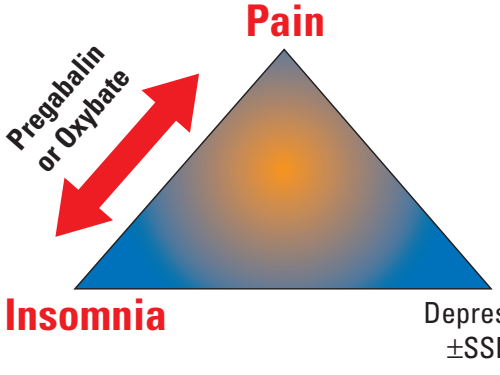
FIGURE 1B.
Strategic polypharmacy for fibromyalgia syndrome with pain and depression



The use of duloxetine for treatment of pain and depression when they are the predominant manifestations in a patient with fibromyalgia syndrome. Minor Insomnia can be addressed with an available sedative medication.

Russell IJ. *CNS Spectr.* Vol 13, No 3 (Suppl 5). 2008.

FIGURE 1C.
Strategic polypharmacy for fibromyalgia syndrome with pain and insomnia



The use of pregabalin or oxybate for the treatment of pain and insomnia when they are the predominant manifestations in a patient with fibromyalgia syndrome. Minor depression can be addressed with an available antidepressant medication.

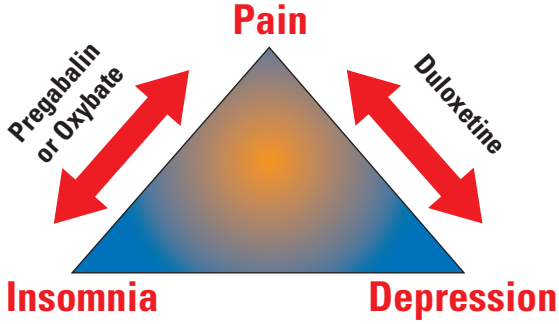
SSRIs=selective serotonin reuptake inhibitors.

Russell IJ. *CNS Spectr.* Vol 13, No 3 (Suppl 5). 2008.

REFERENCES

1. Russell IJ, Bieber C. Muscle and fibromyalgia Ssyndrome. In: McMahon SB, Koltzenburg M, ed. *Wall and Melzack's Textbook of Pain.* London, England: Elsevier: 2005.
2. Russell IJ. Fibromyalgia syndrome: approaches to management. *Bull Rheum Dis.* 1996;45(3):1-4.
3. Burckhardt CS. Nonpharmacologic management strategies in fibromyalgia. *Rheum Dis Clin North Am.* 2002;28(2):291-304.
4. Jones KD, Clark SR. Individualizing the exercise prescription for persons with fibromyalgia. *Rheum Dis Clin North Am.* 2002;28(2):419-436.
5. Jones KD, Clark SR, Bennett RM. Prescribing exercise for people with fibromyalgia. *AACN Clin Issues.* 2002;13(2):277-293.
6. Paiva ES, Deodhar A, Jones KD, Bennett R. Impaired growth hormone secretion in fibromyalgia patients: evidence for augmented hypothalamic somatostatin tone. *Arthritis Rheum.* 2002;46(5):1344-1350.
7. Meyer HP, Van der Westhuizen FD. Impact of spinal surgery in patients with fibromyalgia syndrome and back pain. *J Musculoske Pain.* 2004;12(suppl 9):61.
8. Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain.* 2001;91(1-2):165-175.
9. Staud R. Evidence of involvement of central neural mechanisms in generating fibromyalgia pain. *Curr Rheumatol Rep.* 2002;4(4):299-305.
10. Russell IJ. Advances in fibromyalgia: possible role for central neurochemicals. *Am J Med Sci.* 1998;315(6):377-384.
11. 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(7):537-545.
12. Caruso I, Sarzi Puttini P, Cazzola M, Azzolini V. Double-blind study of 5-hydroxytryptophan versus placebo in the treatment of primary fibromyalgia syndrome. *J Internat Med Res.* 1990;18(3):201-209.
13. Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. *Arthritis Rheum.*1996;39(11):1852-1859.
14. Russell IJ, Kamin M, Bennett RM, Schnitzer TJ, Green JA, Katz WA. Efficacy of tramadol in treatment of pain in fibromyalgia. *J Clin Rheumatol.* 2000; 6:250-257.
15. Arnold LM, Hess EV, Hudson JI, Welge JA, Berno SE, Keck PE, Jr. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. *Am J Med.* 2002;112(3):191-197.
16. Arnold LM, Lu Y, Crofford LJ, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum.* 2004;50(9):2974-2984.

FIGURE 1D.
Strategic polypharmacy for fibromyalgia syndrome with predominant pain, insomnia, and depression



Use of pregabalin or oxybate for the treatment of pain and insomnia and concomitant use of duloxetine for the treatment of pain and depression when all three domains are prominent manifestations in a patient with fibromyalgia syndrome.

Russell IJ. *CNS Spectr.* Vol 13, No 3 (Suppl 5). 2008.

17. Arnold LM, Rosen A, Pritchett YL, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain.* 2005;119(1-3):5-15.
18. Stratz T, Farber L, Varga B, Baumgartner C, Haus U, Muller W. Fibromyalgia treatment with intravenous tropisetron administration. *Drugs Exp Clin Res.* 2001;27(3):113-118.
19. Russell IJ. The promise of substance P inhibitors in fibromyalgia. *Rheum Diss Clin North Am.* 2002;28(2):329-342.
20. Henriksson KG, Sorensen J. The promise of N-methyl-D-aspartate receptor antagonists in fibromyalgia. *Rheum Dis Clin North Am.* 2002;28(2):343-351.
21. Clark SR, Bennett RM. Supplemental dextromethorphan in the treatment of fibromyalgia. A double blind, placebo controlled study of efficacy and side-effects. *Arthritis Rheum.* 2000;43:333.
22. Dooley DJ, Donovan CM, Meder WP, Whetzel SZ. Preferential action of gabapentin and pregabalin at P/Q-type voltage-sensitive calcium channels: inhibition of K+-evoked [3H]-norepinephrine release from rat neocortical slices. *Synapse.* 2002;45(3):171-190.
23. Taylor CP. Meeting report: the biology and pharmacology of calcium channel proteins Pfizer Satellite Symposium to the 2003 Society for Neuroscience Meeting. Sheraton New Orleans Hotel, New Orleans, LA November 10, 2003. *CNS Drug Rev.* 2004;10(2):159-164.
24. 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.* 2006;52(4):1264-1273.
25. Carter LP, Flores LR, Wu H, et al. The role of GABAB receptors in the discriminative stimulus effects of gamma-hydroxybutyrate in rats: time course and antagonism studies. *J Pharmacol Exp Therap.* 2003;305(2):668-674.
26. Snead OC. Evidence for a G protein-coupled gamma-hydroxybutyric acid receptor. *J Neurochem.* 2000;75:1986-1996.
27. Malawska B, Kulig K, Antkiewicz-Michaluk L, Porter R, Misra A, Cliffe IA. Synthesis, physicochemical properties, anticonvulsant activities, and GABA-ergic and voltage-sensitive calcium channel receptor affinities of alpha-substituted N-benzylamides of gamma-hydroxybutyric acid. Part 4: Search for new anticonvulsant compounds. *Arch Pharm.* 1999;332(5):167-174.
28. Scharf MB, Hauck M, Stover R, McDannold M, Berkowitz D. Effect of gamma-hydroxybutyrate on pain, fatigue, and the alpha sleep anomaly in patients with fibromyalgia. Preliminary report. *J Rheumatol.* 1998;25(10):1986-1990.
29. Scharf MB, Baumann M, Berkowitz DV. The effects of sodium oxybate on clinical symptoms and sleep patterns in patients with fibromyalgia. *J Rheumatol.* 2003; 30(5):1070-1074.
30. Russell IJ, Bennett RM, Michalek JE, Oxybate for FMS Study Group. Sodium oxybate relieves pain and improves sleep in fibromyalgia syndrome [FMS]: a randomized, double-blind, placebo-controlled, multi-center clinical trial. Presented at: The 69th Annual Meeting of the American College of Rheumatology; November 12-17, 2005; San Diego, Ca. Abstract 80.