FIBROMYALGIA MANAGEMENT

A FRAMEWORK FOR FIBROMYALGIA MANAGEMENT FOR PRIMARY CARE PHYSICIANS

CONTENTS

PREFACE

This monograph, *Fibromyalgia Management: A Framework for Fibromyalgia Management for Primary Care Physicians*, is a product of the FibroCollaborative, an educational initiative supported by Pfizer Inc. In 2010 the FibroCollaborative brought together a faculty of 23 leading experts in fibromyalgia (FM) management—including primary care practitioners and specialists from the fields of rheumatology, pain management, neurology, and psychiatry—to identify core principles and practical strategies for managing FM in the primary care setting, where many FM patients first present and seek ongoing care.

Fibromyalgia Management: A Framework for Fibromyalgia Management for Primary Care Physicians was developed by Pfizer in 2010 based on in-depth faculty interviews, a series of faculty meetings, and reviews of the medical literature. The faculty also reviewed and provided editorial comment to the draft manuscript.

Pfizer Inc is grateful to the FibroCollaborative Faculty for contributing their valuable perspective and insight to this project:

Co-Chairs

Lesley M. Arnold, MD

Daniel J. Clauw, MD

Faculty

Kenneth Barrow, PA-C, MHS

Lucinda Bateman, MD

Larry Culpepper, MD, MPH

Cassandra Curtis, MD

Yvonne D'Arcy, MS, CRNP, CNS

L. Jean Dunegan, MD, JD, FCLM

Kevin B. Gebke, MD

Robert Gerwin, MD

Don L. Goldenberg, MD

James I. Hudson, MD, ScD

Rakesh Jain, MD, MPH

Arnold L. Katz, MD

Andrew Kowal, MD

Charles Lapp, MD

Michael McNett, MD

Philip J. Mease, MD

Irwin Jon Russell, MD, PhD

Stephen M. Stahl, MD, PhD

Roland Staud, MD

Dennis C. Turk, PhD

Alvin F. Wells, MD, PhD

INTRODUCTION

Fibromyalgia (FM) is one of the most common, chronic widespread pain conditions in the United States, estimated to affect more than 5 million Americans, or 2 to 5 percent of the adult population in the US[1,2]

As such, FM is a common clinical problem seen in the primary care setting.

FM can impair a person's ability to work and engage in everyday activities, and their relationships with family, friends and employers.[3] It can also cause significant emotional distress and disability, and imposes economic burdens on affected individuals, their significant others, and on society.[4,5]

Understanding of FM pathophysiology has grown substantially in recent years. Chronic widespread pain, the hallmark symptom, is now thought to be the result of neurochemical dysfunction in the central nervous system that leads to a "central amplification" in pain processing.[6] This improved understanding helps explain many of the symptoms people with FM experience and the efficacy of various treatment approaches, including several pharmacotherapies recently approved for FM.

Despite these improvements, FM remains underdiagnosed and undertreated. An estimated two-thirds of people with FM remain undiagnosed (based on unpublished data, the only type currently available on the rate of FM diagnosis).[7] Men, in particular, are underdiagnosed (prevalence in women vs men: 3.4% vs 0.5%),[1] possibly because they are less likely than women to meet FM critieria on the American College of Rheumatology tender point examination.[8]

Many people with FM first present and seek ongoing care in the primary care setting. However, for many practitioners strategies for managing FM remain unclear. The perception persists that managing FM patients is difficult and time-consuming, and the absence of objective diagnostic criteria lead many to think it is a psychological problem. There are diverse treatments purporting to be effective, and practical strategies and tools to streamline care are lacking.

In reality, managing FM is in many ways similar to managing other complex chronic conditions such as hypertension, diabetes and asthma – conditions that primary care practitioners deal with on a daily basis. As is the case with the aforementioned conditions, there is no cure for FM; it affects many aspects of patients' lives, and requires patient self-management. Disease management strategies similar to those utilized in other chronic conditions can help FM patients feel better and improve their physical and emotional quality of life. Among other things, this means that non-pharmacologic therapies (eg, education, exercise) and patient self-management strategies and behaviors need to be critical components of the treatment plan in addition to pharmacologic therapy.

FM management is consistent with key elements of the Chronic Care Model (CCM), which was first developed by Wagner and colleagues in the mid-1990s, and that has since become a widely adopted approach to improving the care of chronic illness in ambulatory care settings in the United States and around the world.[9] In this model, improved outcomes are achieved when patients are informed and activated, providers are prepared and proactive, care is patient-centric and collaborative, and community and other resources are appropriately accessed.[10] There is a need to take a similar disease management approach rather than a solely pharmacological approach to the management of FM and other chronic pain conditions.[11]

With this in mind, the FibroCollaborative, an initiative supported by Pfizer, brought together a diverse group of leading experts to identify core principles and practical strategies for more effectively and efficiently managing FM in the primary care setting. The result was the creation of a chronic care framework for FM management derived in part from key elements of the CCM. The 4 Core Principles that serve as the pillars for this framework are:

1) Explain the condition

2) Set treatment goals in collaboration with the patient

3) Implement a comprehensive, multimodal treatment approach

4) Track progress (symptoms and physical, emotional, cognitive, and social functioning)

Effective implementation of these Core Principles requires that primary care practitioners know their individual FM patient's priorities and preferences, and individualize treatment approaches accordingly; be familiar with and utilize, as appropriate, other members of the health care team within and outside the primary care practice; and be familiar with local resources (eg, exercise programs, support groups) that the patient can employ as part of their therapy. In short, as a primary care practitioner, you need to know your patient, know your team, and know your community.

The following sections of this monograph review each of the Core Principles in a step-wise fashion. A clinical vignette, based on actual events, extends across each of the Core Principle sections to illustrate key challenges and strategies for effective FM patient management. An introduction to the case is provided below.

VIGNETTE

Mrs. C is a 42-year-old wife and mother of 3 children (daughters ages 11 and 9, and a 7-year-old son) who works 5 days a week in a day care center with 3- to 5-year-olds. Her reason for coming to the office today is severe pain in the neck and shoulder region that she has been experiencing for several weeks. You have been her primary care provider for approximately 2 years, and in her chart you quickly peruse a number of chief complaints for which you have seen and treated her, including migraine headaches, chronic interstitial cystitis, and low back pain. Currently she is only taking a prescription NSAID as needed for pain.

When you see her this morning she states she hasn't been injured but says that just touching or gently massaging her neck or shoulders, as her husband has tried to do, causes much pain and tenderness. In addition to shoulder pain and the low back pain she's had previously, Mrs. C reports that at times she feels the pain is "all over" in her muscles and joints. You ask her how she's sleeping, and she reports frequent insomnia and fatigue. Her sleep is unrefreshing and she struggles with daytime sleepiness. She wakes up frequently and also snores loudly, according to her husband. As she relates her symptoms she begins to get emotional and tears come to her eyes as she apologizes to you, saying she knows it is "always something" and that she is sorry for taking up so much of your time.

Continued in next section

1 EXPLAIN THE CONDITION

VIGNETTE (cont'd)

There is tenderness on palpation at multiple sites (15 out of 18 on the manual tender point exam).[12] Otherwise Mrs. C's physical exam findings are unremarkable (including evaluation of her presenting neck and shoulder complaints). Additionally, lab results obtained in the last 6 months were normal. Given this and reflecting on Mrs. C's chronic pain history and current symptoms, you diagnose Mrs. C with fibromyalgia (FM). When you ask if she has heard of or knows anything about FM, she says she's familiar with the term from television and magazine ads, but has also heard it's "all in your head." You briefly describe (in layman's terms) FM as a central nervous system disorder that causes people to have a lower threshold for sensing stimuli as painful. Then you review her symptoms and previous symptom complaints, the physical exam and other findings that lead you to believe she has FM. You talk with Mrs. C about FM as a chronic condition similar to others like diabetes, asthma and hypertension. Similar to these you note that while there is currently no cure for FM, a combination of non-pharmacologic and pharmacologic treatment can markedly improve quality of life by lessening pain and restoring function. You explain that if you and she embark together on a comprehensive, multimodal treatment plan, in a step-wise fashion, you believe she will once again enjoy a much more active life.

Continued in next section

EDUCATION AT DIAGNOSIS SETS THE STAGE FOR EFFECTIVE MANAGEMENT

Similar to other chronic conditions such as diabetes, hypertension and asthma, patient education plays an essential role in managing FM and should be integrated with the diagnosis and continue throughout management.[13]

Simply confirming the diagnosis can have a positive impact on people with FM. (A detailed discussion of FM recognition and diagnosis is beyond the scope of this paper. For additional information, including background on the American College of Rheumatology [ACR] diagnostic criteria for FM and the manual tender point exam referenced in the vignette above, please visit ACR at www.rheumatology.org, or www.fibroknowledge.com, sponsored by Pfizer.) When diagnosis is delivered by a health care professional who can explain FM – its pathophysiology, symptoms, treatment and prognosis – as well as confidently answer questions about the condition, patients often feel validated that their symptoms have a medical explanation, relieved they are not due to a more serious or life-threatening illness, and reassured that improvement is achievable.[14] Some data suggest that receiving a diagnostic label of FM is associated with improvements in certain outcomes (eg, greater patient health satisfaction and a decreased number of symptoms).[15] Education also begins the journey of empowerment for patients, as it equips them with the knowledge and understanding they will need to self-manage and gain the upper hand over FM going forward.

Primary care providers should be prepared to provide all newly diagnosed patients with a core set of information about FM diagnosis, pathophysiology, treatment and prognosis, and be prepared to address common questions and concerns.[16] [Table 1.] It can be very helpful to involve family members or significant others in the discussion, particularly in those cases where the patient's FM has strained important relationships.

Table 1. After the Diagnosis: What Patients and Families Need to Know

What is FM?	• Growing evidence suggests that FM is a specific medical condition in which there are changes in how the central nervous system (CNS) processes pain signals – To feel pain, the body sends signals to the spinal cord, which then sends these signals to the brain (the spinal cord and brain are known as the central nervous system, or CNS) – Research shows that in FM, changes in the CNS cause the brain to process pain signals abnormally, thus amplifying pain • People with FM have a heightened sensitivity to things that are painful (called "hyperalgesia"). Even things that are not normally painful (eg, a handshake or hug, wearing a bra or tight-fitting clothing) can be painful to a person with FM ("allodynia"). This is known as a "central amplification of pain processing" – It is as if the "volume control setting" for pain is abnormally high in people with FM – Another way of explaining it is to say that a person with FM has a low pain "threshold" for processing pain (ie, experiences pain with lower stimulus) • In addition, FM can be thought of as a "sensory processing disorder," because some people with FM also experience a more intense response to other stimuli like bright lights and loud noises • Many of the CNS changes in patients with FM also influence sleep, mood and energy – This helps to explain, at least in part, some of the other FM symptoms patients commonly experience (eg, sleep disturbances, fatigue, tenderness, stiffness, mood disturbances and thinking difficulties or "fibro fog") • Often patients with FM also have other pain conditions like irritable bowel syndrome, tension-type headache/migraine, temporomandibular joint pain, etc • FM is not a problem with a person's muscles or joints, although muscle pain (eg, from injury) or in joints (eg, from OA) can prolong the pain of FM. So if you have OA (or another pain condition) that condition needs to be treated as well
What causes FM?	• The exact causes of FM are not fully understood • Evidence suggests that environmental, genetic and other factors may predispose an individual to developing FM[17]
Can FM be cured?	• FM is similar to a lot of chronic conditions such as diabetes and asthma in that it can't be completely cured, but it can be controlled • New treatments are available and there is much that can be done to improve symptoms and function over time, so that you can get back to doing more of the things that you enjoy and are important to you
How is FM treated?	• No single treatment works for every symptom • FM is usually treated using a combination of approaches: – FDA-approved medications that act on central pain pathways (and other medications that are sometimes used) to minimize symptoms and improve function – Non-pharmacologic approaches (eg, sleep hygiene, physical activity/exercise, CBT) to further improve symptoms and function – Requires patients to be active participants in their care

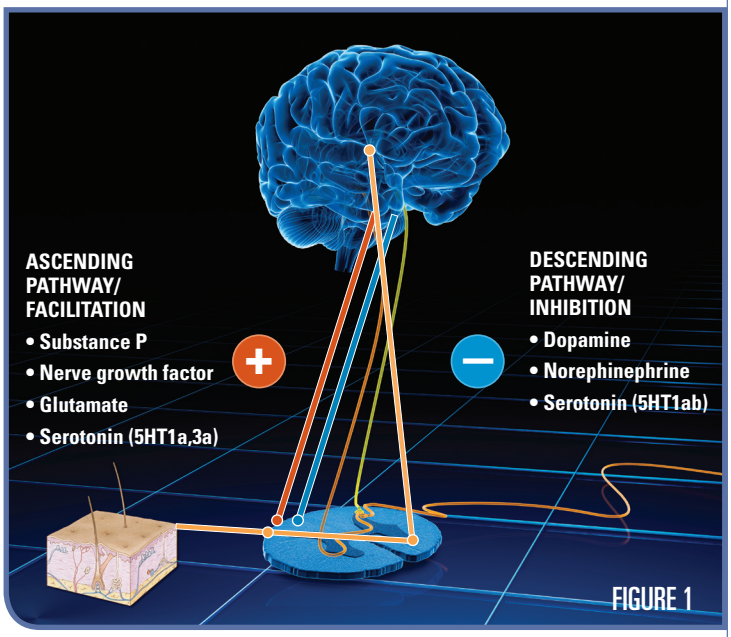
The Science Behind the Explanation

The pain of FM and, to at least some degree, many of its other symptoms are believed to result from dysfunctional sensory processing in the central nervous system (CNS).[18] Pain perception involves both ascending and descending neural pathways. Normally, peripheral nerves transmit sensory signals, including pain (nociceptive) signals, to the spinal cord, where they are transmitted via the ascending pathway to the brain for processing. Descending pain pathways send both excitatory and inhibitory (antinociceptive) signals from the brain to the spinal cord and periphery, increasing or decreasing, respectively, incoming pain signals. Various neurotransmitters and neurochemicals propagate and modulate the signals in these pathways. [Figure 1.]

Studies show these 2 main pathways operate abnormally in FM, resulting in "central amplification" of pain signals.[6] It is as if the "volume control setting" for pain is abnormally high – the result of both increased excitability of central neurons and reduced pain inhibitory mechanisms.[6,19] Though other mechanisms may be involved in FM pathogenesis, an extensive and growing body of evidence supports the concept of central amplification and the lowered threshold for perceiving painful sensory information. For example, studies show that, compared to healthy individuals, FM patients:

- Show (in neuroimaging studies) greater activation and regional cerebral blood flow in areas of the brain associated with pain processing.[20]
- Report perceiving pain at a lower threshold.[21]
- Exhibit changes in levels of neurochemicals (eg, in cerebrospinal fluid) and receptors associated with increased signaling in ascending pathways and decreased signaling in descending pathways.[6,19] Many of these neurotransmitters and neuroprocessing mechanisms also influence mood, energy, and sleep, which may help to explain, at least in part, the mood disorders, sleep dysfunction, and fatigue frequently associated with FM. However, research continues to examine the degree to which these other cardinal symptoms of FM can be explained by central amplification, are secondary to pain, and/or are caused by some other pathophysiological process.

Figure 1. Neural Pathways and Some Key Neurotransmitters that Influence Pain Sensitivity



Elevated levels of neurotransmitters that tend to be pronociceptive (ie, on the left side of the figure), or reduced levels of neurotransmitters that inhibit pain transmission (ie, on the right side of the figure) have a tendency to increase the "volume control" on pain and sensory processing.

Adapted from: Ablin K, Clauw DJ. From fibrositis to functional somatic syndromes to a bell-shaped curve of pain and sensory sensitivity: evolution of a clinical construct. *Rheum Dis Clinics N Am.* 2009;233-251.[6]

MANAGE EXPECTATIONS UP FRONT

It is also useful at this early stage to help patients set appropriate expectations for what the long-term management of FM will entail and what it can achieve. FM is a chronic condition and, as with many other chronic conditions, patients should understand the aim of treatment is symptom and function improvement over time rather than cure. Emphasis should be placed on the fact that much has been learned in recent years about FM and the ways it can be effectively treated. While flares and exacerbations may occur, optimism (on the part of both patient and clinician) is important and fully warranted because with appropriate management most people with FM can, and do, improve. Inform patients about the dynamic course of FM – the fact that flare-ups and setbacks are not unexpected and there are strategies that patients can use to deal with them – to help prevent discouragement, giving up and feelings of helplessness.

Clinicians should discuss with patients the critical role that the patient must play in FM management. As with other chronic conditions, treatment success in FM depends greatly on patients adhering to a treatment plan, including both pharmacologic and non-pharmacologic therapies, and making necessary lifestyle changes. At the same time, there needs to be a collaborative, team effort between clinician, patient and significant others.

A challenging issue between clinician and patient can sometimes arise when a patient is considering or requests assessment for work disability due to FM. Clinicians may consider the issues of disability, and some are more willing to be involved in the disability claims process than others. Whatever your position is regarding disability issues, it may be helpful to make your perspective on them clear with your patients at the outset.

Setting basic expectations for how you and your patient will work together can help establish a productive, more efficient partnership. It can be helpful to discuss:

- How frequent office visits will be. Although it may seem counterintuitive, experts suggest that seeing FM patients more frequently, and working on non-pharmacologic therapies at interval visits (rather than seeing them less often and solely focusing on modifying drug therapies) may be very helpful to both patient and provider
- How much time is available at each visit
- The need to prioritize treatment goals and take a step-by-step approach rather than trying to solve everything all at once

INTEGRATING PATIENT EDUCATION IN PRACTICE

Time for patient education is often in short supply in busy primary care practices and inadequately reimbursed, making it important to plan and make optimal use of existing resources.[16] Depending on your practice philosophy and structure, consider:

- Providing patients with informational brochures or handouts, question and answer sheets, or packets with selected journal articles
- Directing patients to credible, evidence-based educational sources on the Internet or in the community; many FM patients will explore themselves and find a great deal of misleading or erroneous information[22] [Table 2.]
- Suggesting that patients do their own research and then bring specific questions to the next follow-up visit. (This approach may have the advantage of encouraging patients to begin taking some ownership in the process and, based on the direction the patient's research takes, can provide you with helpful clues about the patient's concerns and treatment preferences)
- Utilizing clinical support staff to provide supplemental education, or perhaps organizing a small group educational session for newly diagnosed patients and patient's spouse or other family members

Table 2. FM Education and Self-Management Resources for Patients*

*Note: These Web sites are neither owned nor controlled by Pfizer nor the FibroCollaborative. Neither Pfizer nor the FibroCollaborative are responsible for the content or services of these sites.

Patient Advocacy Organizations	• American Chronic Pain Association (www.theacpa.org) • American Pain Foundation (www.painfoundation.org) • HealthyWomen (www.healthywomen.org) • Helping Our Pain and Exhaustion, Inc. (H.O.P.E.) (www.hffcf.org) • National Fibromyalgia Association (www.fmaware.org) • National Fibromyalgia Research Association (www.nfra.net)
Group Education Programs	• Arthritis Foundation Self Help Program† (www.arthritis.org/self-help-program.php) †FM Self-Help course no longer available; however, Web site directs FM patients to AF Self-Help Program.
Web-Based CBT Programs	• CFIDS and Fibromyalgia Self-Help (www.cfidsselfhelp.org and www.treatcfsfm.org) – Online self-help courses, tools, books, and CDs • Fibro Guide: A Self-Management Program for People Living with Fibromyalgia (www.knowfibro.com) Sponsored by Eli Lilly & Co.
Professional CBT Association	• National Association of Cognitive-Behavioral Therapists (www.nacbt.org) – CBT therapist referral directory
Other Educational/ Self-Management Resources	• FibroCenter (www.fibrocenter.com) Sponsored by Pfizer Inc • FibroKnowledge (www.FibroKnowledge.com) Sponsored by Pfizer Inc • FibroTogether (www.fibrotogether.com) Sponsored by Forest Labs, Inc
Suggested Reading	• *Managing Pain Before It Manages You* (3rd edition) By Margaret A. Caudill. New York: Guilford Press, 2009 • *The Fibromyalgia Help Book: Practical Guide to Living Better With Fibromyalgia* By Jenny Fransen, RN, and I. Jon Russell, MD, PhD. Saint Paul, MN: Smith House Press, 1996 • *Managing Chronic Pain: A Cognitive-Behavioral Approach Workbook* By John D. Otis. New York: Oxford University Press, 2007 • *The Pain Survival Guide: How to Reclaim Your Life* By Dennis C. Turk and Frits Winter. Washington, DC: APA Press, 2006

2 SET TREATMENT GOALS

VIGNETTE (cont'd)

While reviewing Mrs. C's history you ask her to rate her recent levels of pain, sleep quality, and fatigue on a 0-10 (best-worst) scale. She rates pain and fatigue at 8, and sleep quality at 7. You also ask her, "What bothers you most about the effect FM has had on your life?" Becoming emotional again, she says the worst thing is the impact that pain and fatigue has on her ability to care for her children. She states that she still functions reasonably well at work but "drops out at home." Her husband has had to take over many family chores, especially in the evenings to meet the children's needs. Recently, her oldest daughter planned a sleepover with several friends to celebrate her birthday. The day before the party Mrs. C cancelled it because "I just didn't have the energy to straighten up the house." She felt guilty and very upset about her behavior.

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PATIENT-CENTERED PRIORITIZATION OF TREATMENT GOALS

FM can have a substantial impact on a patient's life across multiple domains, affecting a person's ability to work and engage in everyday activities, their emotional and cognitive functioning, and relationships with family/significant others, friends and employers.[3] [Table 3.] To manage FM optimally and efficiently within the time constraints of primary care medicine, it is important to assess the impact of FM across multiple domains of a patient's life and then work collaboratively to focus treatment on those areas of most concern to the patient. This kind of patient-centered prioritization is particularly important when managing a condition like FM. Patients frequently have multiple issues they are contending with and will often come in with long lists of problems, making prioritization and goal-setting critical.[23] Selecting the wrong target, too many targets or some targets too soon runs the risk of lowering adherence and reducing the chances for success.

Setting goals and developing a treatment plan should reflect the dual aims of FM patient management – to improve both symptoms and function. Important symptom domains for the patient and their severity should be identified. Patients will often present with 1 or 2 of FM's hallmark symptoms (ie, chronic pain, sleep disturbance, fatigue) as their predominant concern. Cognitive impairment, depression and anxiety symptoms are also common and their presence and severity should be assessed. Then it is important to assess the impact of FM on daily functioning:

- What has the impact been on the patient's social relationships with family, friends?
- How has it affected the patient's ability to function at work or participate in activities at home?

Table 3. Key FM Domains and Impact Identified by People With FM

Not ranked by order of importance

DOMAIN	IMPACT		
Physical	• Pain	• Fatigue	• Disturbed sleep
Social	• Disrupted family relationships	• Social isolation	• Disrupted relationships with friends
Emotional/ cognitive	• Depression, anxiety	• Cognitive impairment (decreased concentration, disorganization)	• Memory problems
Work/activity	• Reduced activities of daily living	• Reduced leisure activities/ avoidance of physical activity	• Loss of career/inability to advance in career or education

Adapted from: Arnold LM, et al. *Patient Educ Couns.* 2008;73(1):114-120.[3]

Hallmark Symptoms of FM

FM is characterized by chronic (at least 3 months) widespread pain and tenderness, including both allodynia (perception of pain due to stimuli that normally are not painful) and hyperalgesia (amplified response to painful stimuli). Pain is considered widespread when it occurs on the left and right sides of the body, and above and below the waist; in addition axial skeletal pain must be present.[12] Many FM patients also experience fatigue that is not relieved by rest, and sleep disturbances (ie, a lack of deep sleep, frequent awakenings, and waking up feeling tired). Other clinical aspects frequently seen with FM include cognitive difficulties, mood disturbances (eg, depression or anxiety), and stiffness. [Figure 2.] FM also is frequently accompanied by a history of overlapping pain conditions like irritable bowel syndrome, tension-type headache/migraine, temporomandibular joint pain, etc.[6,24] [Table 4.]

Figure 2. Hallmark Symptoms of FM

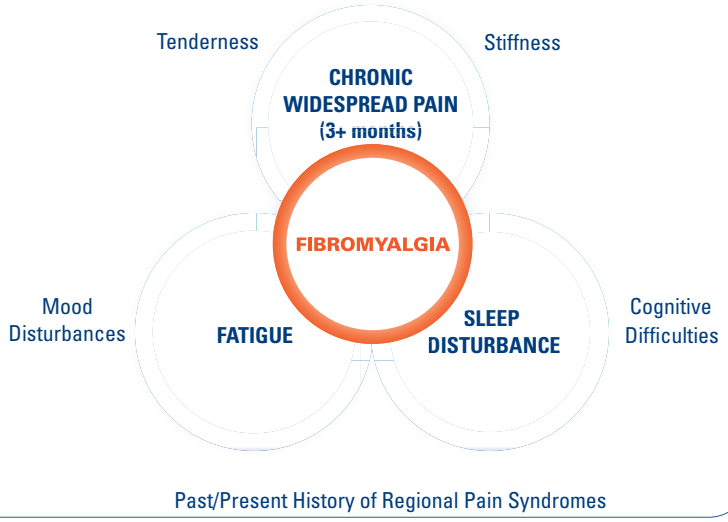

Table 4. Pain Conditions That Are Associated/Frequently Overlap With FM

- Irritable bowel syndrome and other functional gastrointestinal disorders
- Tension-type headache/migraine
- Interstitial cystitis/painful bladder syndrome/chronic prostatitis/prostadynia
- Temporomandibular joint disorder
- Idiopathic low back pain
- Chronic pelvic pain
- Vulvodynia
- Myofascial pain

SIMPLE, TIME-SAVING TOOLS AVAILABLE TO ASSESS PATIENTS

The initial evaluation can be aided by the use of various assessment tools that are available to measure FM pain, function (physical, emotional, cognitive, social) and quality of life. Several that are multidimensional but easy to use are described in Table 5 and included in the Appendix. These can also be used to establish a baseline and track progress over time. The most practical of these are simple to use and interpret, can be completed by the patient and can be used to assess key symptom and functional domains. Some clinicians prefer to utilize more comprehensive and validated instruments like the Revised Fibromyalgia Impact Questionnaire[25] (FIQR), or the questionnaire based on new provisional criteria being considered by the American College of Rheumatology,[26] particularly for the initial evaluation. These instruments are also useful to assess progress on an ongoing basis, especially if ancillary staff are available to help administer and score (although none of the tools described in Table 5 are particularly time-consuming or complex, and can be completed by the patient in the waiting room). Other clinicians prefer simple 0-10 scales to assess key symptom domains like pain, sleep and fatigue as well as specific functional areas of concern, and have found it practical to record these in the chart or embed in the electronic medical record for easy comparison from visit to visit. Regardless of the specific approach, some measurement of symptomatic and functional burden is important at the outset to help guide goal-setting and development of a treatment plan, and will be helpful in documenting patient progress over time or areas in need of attention.

Measurement tools tailored to the primary care setting also may be time efficient in the managing of common comorbidities such as daytime sleepiness (for which the Epworth Sleepiness Scale [ESS] is an excellent tool) and major depression (for which the PHQ-9, or QIDS, are excellent diagnostic and long-term management tools).

Table 5. Tools for Patient Assessment and Tracking Progress

TOOL	DESCRIPTION	COMMENTS
Revised FM Impact Questionnaire (FIQR)	• Multidimensional • Consists of 21 questions that assess symptoms and functional status over previous 7 days, with responses graded 0-10 and then scored to obtain a total FIQR score • Shown valid and reliable in FM patients[25]	• Sensitive. Can measure even small degrees of progress across the major aspects of FM over time • Requires PCP or office staff time to score (scoring is not complicated, takes less than 2 minutes) • Can be used at each visit, or for initial comprehensive assessment and then every 3 months, using simpler measures (eg, 0-10 scale) to track specific symptom/ function domains from visit to visit
Modified Visual Analogue Scale of the Fibromyalgia Impact Questionnaire (mVASFIQ)	• Multidimensional • Modifies the VAS of the FIQ to quantify the severity of individual FM symptoms[27]	• Designed for ease of use in clinical practice • Can provide the basis for initial treatment plan and can also be used to monitor therapeutic response over time • The FIBRO mnemonic (Fatigue, Insomnia, Blues, Rigidity, Ow!) can be used to remember the items on this questionnaire
American College of Rheumatology (ACR) Provisional Criteria (2010)	• Multidimensional • Consists of widespread pain index (WPI) to assess pain, symptom severity score (SS) to assess other symptom domains (fatigue, waking unrefreshed, cognitive symptoms) • Shown valid and reliable in FM patients,[26] and a form for patient use has been developed[28]	• Initially developed to provide alternative diagnostic criteria for FM that does not require manual tender point exam, but SS score portion of questionnaire may also be used to track progress over time • Validated as a diagnostic tool against the 1990 ACR criteria • Its use to track progress has not been validated
Numeric Rating Scales (0-10)	• Unidimensional or multidimensional • Can be used to assess symptom severity/ functional impact on 0-10 rating scales (eg,"How severe has your pain been over the last week, on a scale of 0 to 10, with 0 being "no pain" and 10 being "extremely severe"?)	• Easy to use on each visit • Adaptable for specific symptom/functional domains being tracked • Values can be directly entered into patient's chart or EMR; no scoring required

GOAL-SETTING HELPS FOCUS AND STREAMLINE FOLLOW-UP VISITS

VIGNETTE (cont'd)

You ask Mrs. C what she'd like to do most that she can't do right now and she describes simple things – rescheduling the sleepover for her daughter, cooking, going to the movies with her husband. The most important thing to her is the sleepover for her daughter. You suggest that for now, a play date instead of a sleepover might be more realistic. She agrees to focus on this as a goal to accomplish over the next several weeks as she begins to improve with treatment. At subsequent visits you'll assess her progress toward this goal, identify any barriers, and suggest ways she might overcome them (eg, scheduling the play date for the time during the day when she usually feels best), and modify the treatment plan as needed.

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Appropriate goals for FM management are specific, realistic and measureable, reflect the patient's priorities and have a target date for completion. Thus, a patient who states her goal is to feel better needs to be guided to a more a more appropriate set – ie, "what will you be doing so that you and I will both know that you are feeling better?" Once identified, this becomes the goal, as opposed to "feel better."

In addition, goal-setting should aim for improved functionality in key domains, eg:

- Home (eg, as a spouse, or a parent)
- Work
- Recreation (eg, social and/or physical activities)

Meaningful improvement for someone like Mrs. C (in our vignette example) might start with managing her symptoms enough to pick one task to accomplish each evening and follow through in completing it (eg, cooking a meal for her family or getting the kids ready for bed), pacing herself at work so she is not exhausted at the end of the day, or committing to some form of regular physical activity each week. For someone else, success might mean being able to sit through a child's baseball game, getting a part-time job, or sharing a favorite activity with a friend or spouse. The point is not to accomplish all these in all areas all at once, but to recognize that over time the objective of FM patient management is improved functionality in these key areas of a person's life.

Identify appropriate goals by asking patients simple questions:

- What did you most enjoy or value doing before that you can't do now?
- What specifically is most troubling or frustrating to you about your current situation?
- What do you like doing on good days that you can't on bad days?[29]

To help ensure that specific goals are realistic, assess potential barriers and help the patient problem-solve to minimize them.

- Once you and the patient agree on a particular goal, you can ask the patient if she can imagine anything that might interfere with working toward, and accomplishing, that goal
- If barriers are identified, you can ask the patient what she would do should problems arise, and then brainstorm about possibilities that might reduce the problem and make it more likely that she will attain a particular goal

A main benefit of goal-setting in FM management is that it helps provide a starting point for the treatment plan and focuses the patient on targeted functional outcomes. It also provides structure for follow-up visits. For instance, if the patient wants and agrees to walk 10 minutes a day or participate in an aquatic therapy class, either of these activities might serve as a goal to track at each visit. Visits become more streamlined as patients begin to anticipate the questions you may ask and know what is expected of them.[30] It is useful to have patients record their goals and use a chart to graph progress toward their goals. Documented progress can help show a patient they are making progress and increase their confidence that they can do what it takes to continue to improve. Coaching like this is a critical component of long-term FM patient management, and depending on the size of your practice can also be done by a nurse or nurse practitioner, or physician assistant.

3 APPLY A MULTIMODAL TREATMENT APPROACH

VIGNETTE (cont'd)

You discuss with Mrs. C some treatment options for FM, explaining that what's been learned about the science and biology of FM, especially over the last decade, has led to the approval of several medications for FM. These drugs act on the pathways that influence pain processing, and 3 of these have been approved by the FDA in recent years. Also, because of her interrupted sleep, frequent awakenings and snoring, you suggest she see a sleep specialist for evaluation of possible sleep apnea. You explain that in addition to medications, there are other treatments that have been shown to improve FM, including education about the condition and physical activity. You tell Mrs. C that you understand that becoming more active may sound impossible right now given her current level of pain and fatigue, but you stress that gradually increasing physical activity is an important part of FM treatment, and that you and she can work together to find the right type and pace to start with. You emphasize that with FM it is important to take things one step at a time.

Continued in next section

There is no single treatment for FM that targets every symptom. Therefore, optimal management of FM requires a comprehensive, multimodal approach that includes both pharmacologic and non-pharmacologic therapies, potentially involving specialists and other extended members of the health care team. In addition, as with any chronic medical condition, it also requires patients to develop self-help and problem-solving skills, and may involve other sources of support beyond you and your office staff.

BEING PROACTIVE AND PREPARED

While this may seem daunting, effectively managing FM in a primary care setting is very similar to the management of other chronic conditions.

Know your patient. Because FM is not an acute illness but rather a chronic condition that often involves multiple domains, it is important to address symptoms from a holistic perspective – to treat the patient, not just the pain.[18] An optimal treatment plan needs to be individualized and reflect the patient's own particular mix of symptoms, priorities and preferences while taking into account other factors that can affect adherence (eg, cognitive/emotional and social supports, financial circumstances).

Know your team. As a primary care practitioner, you are used to being the medical "home" for many patients. But the health care team for any particular FM patient can vary. Many people with FM have seen multiple health care providers for various aspects of their condition. Work with your patient to learn who they are, clarify roles and responsibilities and make sure changes to medication or the overall treatment plan are coordinated. If you are managing your patients' FM then they should know you need to be informed if changes to medication or the treatment plan are being considered or recommended by other health care providers.

In addition, there may be health care providers within your practice or outside of it who can be available as needed to help implement a multimodal treatment approach. Some to consider are listed in Table 6. You may want to refer patients with complex comorbid conditions, or those not responding well to therapy, to appropriate specialists or interdisciplinary pain rehabilitation programs or facilities. Be mindful that some health care professionals are more knowledgeable about FM and other chronic pain conditions, and more willing to work with these patients or provide consultation than others. Identify where there are gaps in available resources and consider strategies to fill them.

Know your community. While it is relatively easy to describe the ideal in terms of resources for optimal management of FM and similar chronic pain conditions, the reality is often quite different. Practice settings vary dramatically, as do communities. Much in FM management depends on what patients do or don't do – and what resources are available for them to tap into – outside of your office.

Community resources outside of the health care team as they relate to self-management are important to consider as well. Some patients will benefit from additional psychosocial support in the form of support groups available through national patient advocacy organizations and their local chapters, or educational programs about FM or chronic pain and/or counseling services organized by local hospitals, community and religious organizations.

Table 6. Know Your Team to Implement a Multimodal Treatment Plan

Most people with FM will benefit from a multidisciplinary approach to management that may involve extended members of the health care team to provide education and support, or assistance with management of more complex comorbidities or pain management regimens. Not all practitioners are experienced working with FM patients, so it is helpful to identify health care providers in your own practice or outside of it who are familiar with FM and who can be available as needed to help implement a multimodal treatment approach. You may not need all of the suggestions below for every patient, but health care professionals to proactively identify as part of your team include:

Specialists	• Rheumatologists – To identify and/or management comorbid rheumatologic disorders (eg, rheumatoid arthritis) • Neurologists – To identify and/or manage comorbid neurologic disorders (eg, multiple sclerosis) • Physical medicine and rehabilitation specialists – To help with physical therapy and exercise components of management, as well as improving occupational functioning • Sleep specialists – To help diagnose primary sleep disturbances (eg, sleep apnea, RLS, delta sleep deficiency) • Cognitive behavioral therapists – To help patients manage their condition through coping strategies, behavior modification • Clinical psychologists, psychiatrists – To evaluate and treat comorbid mood or anxiety disorders, if present • Pain specialists – To help, if needed, in determining optimal pain management strategies
Mid-Level Professionals	• Nurse practitioners and physician assistants can provide patients with valuable emotional support, guidance on physical aspects of management, and help monitor progress
Allied Health Professionals	• Physical therapists (conditioning vs rehab) – Help with conditioning, myofascial release, and exercise components of management • Occupational therapists • Social workers – Psychological and emotional support, financial concerns • Nutritionists – Can help treat overweight and obesity, commonly seen in FM patients, and advise about other dietary aspects of FM management, eg, reduction of caffeine and alcohol intake, meal planning • Pharmacists – Can help flag potential drug interactions in patients prescribed polypharmacy, reinforce physician advice re drug side effects

Know Your Patient, Team and Community: An Example

Considerations When Prescribing Physical Conditioning

- Are there pool facilities that offer aquatic therapy, especially in warm water? (This is a particularly good way to start for more seriously deconditioned patients.)
- Is the patient motivated and financially able to join the local Y or health club, or sign up for exercise, tai chi or yoga classes? Whatever is recommended needs to be realistic and doable for the patient
- If finances are an issue or if the patient prefers, does the patient live in a pedestrian-friendly community that makes walking easy, or would walking around the local mall or large super-store (especially when the weather's bad), a certain number of times a week, be more doable?
- Is there a local physical therapist who can help initiate a conditioning program that insurance may cover?

STEP-BY-STEP TO A TREATMENT PLAN

As described above, the treatment plan for FM[31] is developed based on the patient's unique characteristics and should take into account:

- Severity of pain and other FM symptoms
- Level of patient function
- Presence and severity of any comorbidities
- Psychosocial stressors, fitness, and barriers to treatment

With these factors in mind the treatment plan can then focus in a step-wise fashion on:

- Medical management (eg, pharmacotherapy) to minimize the pain of FM and other symptoms
- Management of any comorbidities
- Implementation of non-pharmacologic interventions to further improve symptom and function

STRATEGIES FOR INITIATING PHARMACOTHERAPY

VIGNETTE (cont'd)

After reviewing treatment options with Mrs. C, she elects to try medication. She has no previous experience with medications shown to be efficacious for FM. You select one based on her symptom profile and review the risks and benefits. You:

- Discuss expectations, explaining that medications used in FM management are not a cure, but they can help alleviate symptoms so that Mrs. C can do other things that will help her improve
- Explain that every person is different and that it may take some time and trial and error to determine if the chosen medication works and at which dose
- Describe the possible side effects and explain that at first she may feel the side effects before she experiences benefit, which may take several weeks
- Encourage her to stick with it through this initial period because she needs to give it time to work and side effects may resolve as her body gets used to the drug
- Start at a low dose to minimize side effects with a plan to slowly titrate upward as needed to achieve therapeutic efficacy
- Ask her to schedule a follow-up visit with you in 2 weeks

Continued in next section

Medications in FM treatment are used to alleviate FM symptoms, thereby helping patients engage in and benefit from other non-pharmacologic disease management strategies including exercise, education and cognitive-behavioral therapy (CBT).[32] Patient expectations need to be set accordingly. Available treatments can improve some symptoms, but are not a cure. About 30-50 percent improvement is realistic, although some patients will have better results and others less improvement or none at all.[33]

It is important to keep in mind – and explain to your patient – that multiple pathophysiological abnormalities are involved in FM and everybody is different. Similar to hypertension, for instance, individuals will respond differently to different medications used in FM management, and different therapies may need to be tried before the optimal approach is found.

Three medications that act via central pain processing pathways have been FDA approved for FM management in recent years. Their classification and dosing are described in Table 7. Some physicians use other, non-FDA approved medications to manage FM. Those supported by some evidence from randomized controlled clinical trials are listed in Table 8.[34]

FM Science Provides Insights for Pharmacologic Treatment

Because it is thought that the primary problem in FM involves amplified central processing of pain, pain medications that act primarily through peripheral mechanisms, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, are often less effective than other modalities and have not been shown to reduce pain in FM patients in clinical trials. However, these medications may be appropriate for FM patients under certain circumstances; for instance, if there is a concurrent peripheral pain condition (eg, osteoarthritis or rheumatoid arthritis).[16,24,35,36] And, while endogenous opioid levels are increased in FM patients,[37] opioid receptor binding is diminished,[38] which may be one reason opioid treatments are often less effective in the long term than other treatment modalities in FM.

On the other hand, pharmacologic agents that act centrally in ascending and/or descending pain processing pathways, such as medications currently approved for FM, can be effective for many FM patients.[19]

The complexity of the pathways and neurochemical abnormalities involved in FM may vary from person to person, which could explain why not all medications for FM work for all patients.[6] In this way, FM can be thought of as similar to hypertension, in which various root causes can result in elevated blood pressure, and various drug classes targeting different points in blood pressure regulation (eg, diuresis, renin-angiotensin system, etc) may need to be used to treat it.[6]

Table 7. FDA-Approved Medications for FM Management*

FDA-APPROVED MED	DRUG CLASS	DOSING
Pregabalin† (Lyrica) (approved for FM in 2007)	Alpha$_2$-delta ligand[38]	• Dosing for FM: 300 to 450 mg/day. It is recommended dosing begin at 75 mg 2 times a day (150 mg/day). The dose may be increased to 150 mg 2 times a day (300 mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg two times a day (450 mg/day). In view of the dose-dependent adverse reactions, treatment with doses above 450 mg is not recommended[38]
Duloxetine‡ (Cymbalta) (approved for FM in 2008)	Serotonin and norepinephrine reuptake inhibitor[39]	• Dosing for FM: 60 mg once daily. Treatment should begin at 30 mg once daily for 1 week before increasing to 60 mg once daily. Some patients may respond to the starting dose. There is no evidence that doses greater than 60 mg/day confer additional benefit, even in patients who do not respond to a 60 mg dose, and higher doses are associated with a higher rate of adverse reactions[39]
Milnacipran‡ (Savella) (approved for FM in 2009)	Serotonin and norepinephrine reuptake inhibitor[40]	• Dosing for FM: 50 mg twice daily, titrated over 1 week from a starting dose of 12.5 mg/day. Based on patient response, the dose may be increased to 100 mg twice daily. Doses above 200 mg/day have not been studied[40]

*Note: No published clinical studies have compared the efficacy and safety of these medications to one another.

†Please see Full Prescribing Information and Medication Guide for LYRICA on the inside back cover of this document.

‡For safety and prescribing information for Cymbalta and Savella, please refer to their respective Prescribing Information and Medication Guide documents.

LYRICA is approved for the management of Fibromyalgia. Although Fibromyalgia patients may present with a number of symptoms, clinical data support the use of LYRICA for Fibromyalgia pain but not for any other ancillary symptoms.

LYRICA is contraindicated in patients with known hypersensitivity to pregabalin or any of its other components. Hypersensitivity reactions (eg, hives, dyspnea, and wheezing) can occur. Discontinue LYRICA immediately in these patients.

Angioedema (eg, swelling of the throat, head, and neck) can occur and may be associated with life-threatening respiratory compromise requiring emergency treatment. Discontinue LYRICA immediately in these cases.

Antiepileptic drugs (AEDs) including LYRICA increase the risk of suicidal thoughts or behavior in patients taking AEDs for any indication. Monitor patients treated with any AED for any indication for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

The most common adverse reactions across all LYRICA clinical trials are dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, constipation, euphoric mood, balance disorder, increased appetite, and thinking abnormal (primarily difficulty with concentration/attention).

LYRICA may cause dizziness and somnolence, and impair patients' ability to drive or operate machinery.

LYRICA may cause peripheral edema. Exercise caution when coadministering LYRICA and thiazolidinedione antidiabetic agents.

LYRICA may exacerbate the effects of oxycodone, lorazepam, or ethanol on cognitive and gross motor functioning.

Patients with a history of drug or alcohol abuse may have a higher chance of misuse or abuse of LYRICA.

Withdraw LYRICA gradually over a minimum of 1 week. Discontinue LYRICA immediately in patients with symptoms of hypersensitivity or angioedema.

Patients with a creatinine clearance of 30 to 60 mL/min had a greater incidence of discontinuation due to adverse reactions than patients with normal creatinine clearance. Adjust the daily dose of LYRICA for patients with reduced renal function (creatinine clearance <60 mL/min) and in those undergoing hemodialysis. Administer a supplemental dose of LYRICA immediately following every 4-hour hemodialysis treatment.

Table 8. Medications Not FDA Approved for FM Management for Which There Is Some Evidence From Randomized Clinical Trials

- Tricyclics (eg, amitriptyline and cyclobenzaprine)[34]
- Analgesics* (eg, tramadol)[34]
- Other CNS-active drugs (eg, gabapentin[31] and sodium oxybate[34])
- Selective serotonin reuptake inhibitors (eg, fluoxetine, paroxetine)[34]
- Serotonin-norepinephrine reuptake inhibitors (other than duloxetine and milnacipran, which are approved for FM management; eg, venlafaxine)[34]

*Note: Although FM patients often use other analgesics, such as acetaminphen and NSAIDs,[41] efficacy has not been demonstrated in RCTs, though they may be helpful in FM when peripheral pain disorders are involved (eg, osteoarthritis).[16,24,28,36]
Abbreviations: CNS=central nervous system.

General strategies to keep in mind when initiating pharmacotherapy for FM [Table 9.] include:

Evaluate treatment history. When starting a patient on medication for FM, evaluate what other medications the patient is taking or has taken in the past, and what non-pharmacologic approaches have been tried, and consider potential drug interactions. If the patient has taken a medication appropriate for FM previously but reports "it didn't work," explore what the dosing was and any adherence issues. Perhaps dosing stopped short of therapeutic efficacy, or the patient did not give it an adequate trial due to side effects that might have resolved with time. In any event another trial might be warranted.

A special circumstance presents when a patient has been taking opiates in an effort to manage FM pain. There have been no randomized controlled clinical trials of opiates in FM, and in open label studies opiate use did not reduce pain symptoms or pain intensity.[16] While opioids may be appropriate in certain circumstances, they may be less effective than other treatments for FM.[42] The significant adverse effects associated with opioid use are well-known and include habituation, respiratory depression, sexual dysfunction, constipation, reduced testosterone levels and risk of dependence and abuse.[43] There is also emerging evidence supporting the theory of opioid-induced hyperalgesia[44] (ie, an increase in pain perception resulting from opioid use). Consequently, published FM management guidelines recommend that opioids be considered only after other pharmacologic and non-pharmacologic therapies have been attempted,[32,45] and then only intermittently for flare-ups.

Despite the lack of data supporting the use of opiates in FM, a recent survey of US academic medical centers found that about 14 percent of FM patients were being treated with them.[16] When a patient has been taking opioids for FM pain, discuss the issue:

- Ask, "Do you feel you've improved since taking opioids?" Often, the answer will be "no," and this realization may heighten the patient's willingness to consider alternatives
- Point out the potential for adverse effects from opioids
- Explain that newer medications for FM management, targeted to the known pathophysiology of the condition, are available to help manage (although not cure) FM pain and other symptoms and have been shown to effectively treat FM symptoms in randomized clinical trials
- Consider whether, with cooperation from the patient and with something else in its place, it would be beneficial attempt to wean the patient from opioids (eg, if the patient has clinically worsened since being placed on opioids) and whether referral or comanagement with a pain specialist might be in order

Start low and go slow. Treatment-emergent adverse effects are a common reason patients prematurely discontinue medication therapy for FM. To minimize the risk for adverse events early in treatment and improve persistence:

- Select a drug and begin at the lower end of the dosing range and plan to titrate gradually upward to a dose that is effective
- Manage expectations by explaining this strategy to your patients so they know that it may take several weeks to begin experiencing benefit from the medication
- Discuss potential side effects of the selected drug and suggest strategies patients can take to help reduce side effects
- Schedule more frequent visits in the first months of treatment to help assess therapeutic efficacy and tolerability, manage drug titration and facilitate the prompt identification and management of any barriers to adherence with the treatment plan

Studies of combination therapy in FM management are limited, and no drugs are approved by the FDA for combination use in FM. As a result, it is not possible to give guidance on combining specific drugs as a way to improve therapeutic response. For those clinicians who choose to combine pharmacological treatments, for safety reasons it is important to assess for potential drug interactions, monitor patients closely for potential adverse effects, and it has been suggested that clinicians combine drugs with different mechanisms of action.[27,31,46]

Table 9. General Strategies When Initiating Medication Therapy

Evaluate previous or existing pharmacological/nonpharmacological therapies • Determine if previous drug treatment trials were adequate (duration and dose) • Consider potential drug interactions, opioid use
Educate patients regarding rationale for medication therapy
To help manage medication intolerance: • Start with one drug at a time • Initiate at lower dose and titrate up • Discuss strategies for managing side effects
To help improve persistence: • Manage expectations regarding efficacy/side effects, dosing, and time needed for adequate trial. If more than one medication is needed: • Be aware of potential drug interactions • Add medications with different mechanisms of action
Avoid prescribing opioids routinely for FM • As a last resort, and then only sparingly for breakthrough pain

IDENTIFY AND ADDRESS COMORBIDITIES

At this stage, it also is important to identify and plan to address comorbidities and associated conditions that frequently "travel" with FM and that can exacerbate FM symptoms or make it difficult for patients to adhere to a treatment plan. Priorities include:

- Peripheral pain generators (eg, osteoarthritis, rheumatoid arthritis, neuropathies)
- Mood disorders (eg, depression, anxiety)
- Regional pain syndromes (eg, irritable bowel syndrome, headache)
- Sleep disorders. Up to 45 percent of people with FM have primary sleep disorders[47] so a high level of suspicion about these is warranted, along with early referral for evaluation, as indicated
- Fatigue. When fatigue is a significant problem, be aware that fatigue may be multi-factorial (ie, due to pain, poor sleep, deconditioning, depression) and is best initially treated by improving these aspects of FM or carefully treating comorbidities (eg, obstructive or central sleep apnea, restless legs syndrome). A sleep consultation and sleep study may be useful

NON-PHARMACOLOGIC THERAPIES IN FM MANAGEMENT

VIGNETTE (cont'd)

Two weeks later as scheduled, Mrs. C has returned to see you. She reports good tolerability to the medication so far. Her pain and sleep have improved somewhat (decreased to 7 from 8 on a 0-10 scale), and you continue upward titration. Her fatigue is the same at 7 (0-10). She has not yet scheduled the sleep study, and you encourage her to do so, explaining that if she has sleep apnea it is something that can be treated and may help a lot with her sleep and fatigue, which are major problems for her. Meanwhile you discuss sleep hygiene and provide a handout with tips to take home. She has not increased her physical activity; barriers are continued pain and fatigue. You assess her fitness level, ask what physical activities she prefers, and together you come up with a plan for her to walk 10 or 15 minutes a day for the next week (doing so at the mall if the weather is bad), and to gradually increase this as she feels able. You write all of this clearly on a prescription pad to emphasize its importance as part of the treatment plan to reach the first goal she has set (hosting a play date), and you ask that she schedule an appointment to see you in 4 weeks.

Continued in next section

There is strong evidence that multidisciplinary therapy, including significant non-pharmacologic and patient self-management components, is effective in FM management. It is best to integrate non-pharmacologic approaches early in the treatment plan, which helps reinforce the importance of the patient's role in his or her own care.[48]

The non-pharmacologic approaches to FM management that have been most efficacious in randomized controlled clinical trials are exercise, CBT, and patient education.[16] Other approaches have been evaluated in FM patients including (but not limited to) strength training, movement-based therapy (eg, tai-chi), balneotherapy (medicinal bathing), acupuncture, and various complementary and alternative therapies. A list of these and the evidence for them is provided in Table 10. People with FM also report that interventions such as resting, heat modalities (warm water, hot packs), distraction (reading, watching TV, etc), relaxation/meditation, massage, and chiropractic can be effective management strategies.[49]

Provide Advice Regarding Sleep Hygiene

Sleep hygiene is another area that merits discussion with FM patients. Individuals with FM have a number of problems related to getting a good night's sleep, including difficulty falling asleep; being awakened by pain or discomfort; or, if able to fall asleep, awakening unrefreshed and unrestored.[50] Behavioral strategies aimed at improving sleep hygiene, if used regularly, can help individuals get more restorative sleep with additional benefits in improved mood, better management of pain, less fatigue, and improved mental clarity.[50,51] Sleep hygiene recommendations to share with FM patients are provided in Table 11. (Again, this is not meant to be an exhaustive list but to include those modalities for which there is the best published evidence.)

When simple measures don't improve sleep and the unrefreshing nature of sleep, particularly if daytime somnolence is present (which is different from fatigue), consider obtaining a consultation from a sleep specialist to exclude primary sleep disorders such as sleep apnea, periodic limb movements, restless legs syndrome, and other treatable disorders.

Table 10. Non-Pharmacologic Therapies for FM Management

THERAPY	EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS (RCTs) AND META-ANALYSES
Physical activity	• At least 35 RCTs and 4 meta-analyses collectively showed positive findings with mild-to-moderate intensity land- or water-based aerobic exercise[52-55] • Improvements usually not maintained if exercise stops[56] • Strength training also appears beneficial,[57] though fewer studies have evaluated it and more research is recommended[53] • An RCT recently showed tai chi may also be beneficial[58]
Cognitive-behavioral therapy (CBT)	• Favorable findings shown in at least 12 RCTs[59-70] and 2 meta-analyses[71,72] • Improvements often sustained for months after CBT stopped[56]
Patient education	• At least 6 RCTs suggest patient education can help improve symptoms and/or functioning to some degree.[68,69,73-76] (Note: definitions of CBT and education vary across studies and often overlap, so some studies supporting CBT apply to education and vice versa)
Combination therapy (physical activity, CBT, education, and/or social support)	• At least 9 RCTs show combination therapy with physical activity, education, CBT, and/or social support provides greater benefits than the individual therapies alone[62,73-80]
Balneotherapy (medicinal bathing)	• Favorable findings in at least 11 RCTs[77,84-93] • A meta-analysis[94] and 2 systematic reviews[95,96] showed at least short-term beneficial effects
Acupuncture	• Some RCTs have shown benefits[97-100] but others have not[101,102] • Two meta-analyses[103,104] and 2 systematic reviews[96,105] of RCTs found insufficient evidence of benefits in FM
Complementary and alternative medicine (CAM)	• A meta-analysis[106] identified a total of only 7 RCTs of CAM therapies in FM (homeopathy, anthocyanidins, capsaicin, S-adenosylmethionine and soy), and found that while some improvements on single outcomes were shown, there was insufficient evidence overall • A systematic review[106] of various CAMs found at least somewhat positive results for homeopathy, mild infrared hyperthermia (1 RCT for each), mindfulness meditation (2 RCTs), connective tissue massage, osteopathy and magnet therapy; and no positive evidence for Qi Gong, biofeedback, or body-awareness therapy • Favorable results in 3 of 4 RCTs with transcranial electrical or magnetic stimulation[107-110] • Favorable results in 1 RCT of hypnotherapy[111]

Table 11. Sleep Hygiene Advice for FM Patients

Routines	• Make sleep a priority • Go to bed and get up at the same time everyday – even on weekends • Avoid taking naps during the day • Do something relaxing before bed – Listen to music, practice relaxation techniques (meditation, guided imagery), read
Sleep Environment	• Make your sleep environment conducive to sleep – Cool, dark, quiet and comfortable • Reserve your bedroom for sleep and sex – No TV, video games, laptop, stressful activities
Diet and Exercise	• Avoid stimulants (eg, caffeinated drinks, sugar, alcohol, smoking) before bed – Alcohol may make you feel tired initially, but it also fragments sleep and makes it less restful • Do some type of exercise during the day, but not within 4-6 hours of bedtime (to allow core body temperature to return to normal)
Additional Tips	• Hide the clock from view, don't look at it during the night • Keep a notepad/pencil by your bed, write down thoughts that wake you so you can put them to rest • If you are unable to fall asleep within 15-20 minutes, get up and go to another room and do something quietly; avoid watching television or playing video games

*Adapted from: National Sleep Foundation. Ask the Sleep Expert: Sleep Hygiene. Available at http://www.sleepfoundation.org/article/ask-the-expert/sleep-hygiene.org. Accessed: October 27, 2010.[112]

Explain Rationale for Exercise in FM

Physical activity can worsen the pain of FM, therefore many patients are sedentary. What this often results in, however, is a negative downward spiral in which inactivity leads to physical deconditioning, which then causes FM symptoms to become worse with minimal effort or at rest.[16] Increasing physical activity can help to interrupt this cycle and in fact, aerobic exercise has been shown to be helpful in a number of studies of FM, resulting in improved function and symptoms.[113]

Making Exercise Work in FM Management

The use of low-intensity, low-impact programs and the ability to individually tailor the regimens are key factors in patient adherence.[114] In addition, supervised, group exercise interventions may be preferable to home-based regimens, especially at initiation.[31] Additional strategies to improve exercise adherence in FM are discussed below and summarized in Table 12.

Educate. Educate patients about the role of physical activity in FM patient management. It can help to avoid the word "exercise" and talk instead about the benefits of physical conditioning in general. In fact, a recent study has shown that simply increasing the amount of "lifestyle physical activity" (ie, integrating an accumulated 30 minutes of short bouts of moderate-intensity activity such as walking, performing more yard work, using the stairs more, etc, throughout the day, most days of the week) produces clinically relevant changes in perceived physical function and pain in previously minimally active adults with FM.[115] Discuss physical conditioning as an overall goal at the start of treatment and talk about it at each visit to stress its importance.

Personalize the plan. Tailor physical activity recommendations to fitness level and endurance, what is comfortable for the patient, what the patient likes to do, and what resources (YMCAs, pools, gyms, walkable neighborhoods, etc) are available in the community. Discuss any barriers to physical activity

and develop plans to address them (eg, if the patient cannot swim and no pool is available, walk instead; if the neighborhood offers no place to walk, head for the mall or local super-store; if no babysitter is available, bring the child along). Write a clear "prescription" for increasing physical activity, with specific goals and instructions for how to progress, and follow-up on these goals at each visit. Use charts or graphs to plot progress over time.

Start low, go slow. For sedentary and seriously deconditioned patients, it can be helpful to start with breathing/relaxation and stretching, then add light strengthening, and gradually move to more cardiovascular exercise. "Water before land" is also a good approach, starting with warm water pool exercise (if available) and progressing to low impact activity (eg, bicycling, then walking) as tolerated. Initially, help patients aim to do less than they think they can and slowly build endurance. High levels of activity are not required to obtain benefits – mild aerobic exercise done regularly is usually adequate. Emphasize that consistency of effort is important, and create a program that makes this practical for the patient.

Like anyone starting a physical fitness regimen, patients can expect to experience some soreness at first. Encourage patients to work through any tolerable but short-term increases in post-exercise pain and fatigue, letting them know that this should improve within a few weeks.[113]

For most patients, aim for a gradual increase, as tolerated, in exercise to reach a goal of 30 to 60 minutes of low-moderate intensity exercise (eg, walking, pool exercises, stationary bike) or physical activity (house chores, gardening, shopping, etc) at least 2-3 times a week.[31]

Discuss pacing. People with FM will frequently compensate for the days when their activities are limited by overdoing things on days they feel better. The end result is often another debilitating symptom flare. Counsel patients to strike a balance between too much and too little activity, reinforcing that too little activity will lead to stiffness, fatigue and deconditioning; too much can lead to relapse of pain and other symptoms. Short periods of activity can be balanced with rest. Explain that many people with FM have limited "energy dollars" each day and it's important to spend them wisely and prioritize. Provide patients with advice on coping with symptom flares to help feel in control. Advise patients to learn what works for them and plan in advance for difficult days, so that they are able to slow down if needed, get adequate rest, practice relaxation techniques, find distractions (eg, funny movies, talking with a good friend).

Provide support and reinforcement. Ask patients to track their physical activity on a simple calendar to share with you at each visit. This will reinforce progress and demonstrate that you consider physical activity a priority. Encourage patients to wear an inexpensive pedometer or heart rate monitoring watch (or provide them yourself) to make physical activity levels tangible and progress measureable. For patients who have a smart phone, free apps are available for tracking exercise and diet. There are also many websites that offer tracking programs.

Supervised or group exercise programs result in better adherence to an exercise regimen and improved functional outcomes, especially at the initiation of an exercise program.[73] In addition, some patients may benefit from working with a physical therapist on reconditioning. However, it is important to identify physical therapists in the community who understand FM and the special needs of FM patients. Techniques that are appropriate for rehabilitation following injury are usually inappropriate for FM patients and in fact can make things worse.

What to Look for in a Physical Therapist

Some approaches to physical therapy (such as those that might be used to speed recovery from an acute injury, for example) can be too aggressive for most FM patients and may make matters worse. Moreover, although a supervised exercise/rehabilitation program (ie, where the therapist is present during exercise) may be practical for acute injuries, it is not when the exercise is being used to treat a chronic condition. Thus, patients with FM are more likely to benefit from a gentler approach to reconditioning involving slow stretching, strength training and other appropriate modalities, and the teaching of self-management skills to relieve pain and stiffness in everyday life. Build referral resources by networking with local physical therapy practices to explain the need and, if necessary, educate interested practitioners.

Table 12. Strategies to Improve Exercise Adherence in FM

Educate	• Educate patients about the role of physical activity in fibromyalgia management at the start, discuss at each visit to stress its importance • Discuss in terms of physical activity or physical conditioning, avoiding the word "exercise," which may be off-putting to some patients • Raise this as an overall goal at the start of treatment and discuss at each visit
Personalize the plan	• Tailor physical activity recommendations to fitness level,[31] patient preferences and community resources • Identify barriers and ways to address them • Write an individual "prescription" for exercise, with specific goals/instructions, and follow-up at each visit
Start low, go slow	• Plan to do less than is possible, and slowly build endurance • For seriously deconditioned patients start with breathing/relaxation and stretching, add light strengthening, gradually incorporate cardiovascular exercise – Alternatively, start with "water before land" – warm water pool exercise (if available), progressing to low impact activity as tolerated • Emphasize consistency of effort, develop plan to make this practical for the patient • Aim for gradual increase, as tolerated, in physical activity to reach a goal of 30 to 60 minutes of low-moderate intensity exercise, or daily physical activity at least 2-3 times a week[31]
Discuss pacing	• Strike a balance between too much and too little activity • Balance short periods of activity with rest • Prioritize to spend each day's "energy dollars" wisely
Build in support	• Use simple calendar to track physical activity and bring to each visit • Wear an inexpensive pedometer or heart rate monitoring watch to see results, track progress • Utilize free smart phone apps or Web sites to track exercise and diet • Encourage participation in supervised or group exercise programs, especially at the initiation of an exercise program. • Consider referral to a physical therapist who understands FM and the special needs of FM patients to help with reconditioning

VIGNETTE (cont'd)

It's 4 weeks later (8 weeks postdiagnosis) and Mrs. C is in the office for her scheduled follow-up visit. She has had the sleep study and the results showed significant sleep apnea. She completed a trial of CPAP (Continuous Positive Airway Pressure) and has begun to feel some improvement. She reports improved sleep (now at 4 on 0-10 scale). Pain is also improved (4), but fatigue is only slightly better. You remark on all the good progress and ask how she's doing with increasing her physical activity and caring for her children. She seems overwhelmed when she says that not much has changed. She does more than she should on "good" days resulting in symptom flares, and she is still avoiding scheduling any favorite activities for herself or with her family. You consider whether she is depressed, but she says "no" when you ask about symptoms of major depression. You talk with her about the importance of activity pacing. You stress that a key to living with any chronic condition is to learn ways that you can control it, and not the other way around, and suggest that she visit a website that offers a self-management program for people with fibromyalgia, which she agrees to do. You remind her of the other goals she has agreed to and ask her to schedule another follow-up visit in 4 weeks.

Continued in next section

Build Patient Self-Management Skills

The self-management component of any FM treatment plan is particularly critical because certain lifestyle and behavioral changes (eg, physical activity according to fitness level, activity pacing, stress management and sleep hygiene) may be needed to restore function, and this is something that patients have to do for themselves. At the same time, patients differ in their readiness to change and will benefit over time from the clinician maintaining a positive, supportive and non-judgmental attitude. FM is appropriate for the same type of holistic disease management approach that is employed in primary care to address other complex chronic conditions like diabetes, asthma, and hypertension where lifestyle and behavioral change are also integral to their management. Key elements of a patient-centered approach include:

- Providing information clearly and at an appropriate level for the patient
- Refocusing office visits from making treatment recommendations to supporting the patient's self-care
- Fostering increased patient control of decision-making and responsibility for self-care[30]
- Reinforcing efforts and not just accomplishments

Strategies for Facilitating Behavioral Change

An important long-term goal for patients with FM is for them to become experts in understanding their own symptoms and treatment responses, thus improving their self-management skills.[116] Self-help topics that often need to be addressed at various points in the management of FM include activity pacing, sleep hygiene, active coping skills, dealing with symptom flares, stress management and relaxation techniques, and pleasant activity scheduling. Depending on practice size and other resources, this education can be provided by the clinician, by nurse educators or social workers during planned visits, in community-based education programs and support groups, and via Web-based self-management programs.

In addition, what a patient believes about his or her condition can have a significant impact on their motivation to change and ability to self-manage the condition. Be alert to patients' attitudes and beliefs about FM and its impact on their lives, and listen for misconceptions about FM or dysfunctional attitudes that you might be able to address.

In general, if you can offer your FM patients validation (by legitimizing their experience and treatment), education, enthusiasm and therapeutic optimism that the patient can cope and can

improve, if not fully remit, you will provide them with beneficial support that, according to numerous surveys, FM patients sincerely value but do not often find in their relationships with health care providers.

The strategies described above reflect approaches to educating patients, setting goals, and building self-management capacity have much in common with CBT techniques. There is evidence supporting the role of CBT in helping patients with FM and other chronic conditions (eg, coronary disease, cancer survival, osteoarthritis and rheumatoid arthritis) make the necessary lifestyle adaptations for dealing with their illness, improving pain and functional status in the process.[50,71] Other reviews have found less evidence supporting CBT's efficacy in reducing specific symptoms (eg, pain, fatigue, sleep disturbance), while still finding that CBT can improve pain coping skills and reduce depressed mood and the number of physician visits at follow-up.[72]

CBT may be particularly helpful for patients who do not respond fully to medication alone or in cases where FM has had a prominent impact on psychosocial functioning.[31] There are many forms of CBT and different ways it can be provided (eg, by trained psychotherapists or other health care providers, in groups or individually). What they all have in common is the teaching of skills to help patients regain a sense of control and power over their condition. A key ingredient of CBT is helping patients identify self-defeating and maladaptive thoughts about their condition and their ability to exert any control over it, and to replace these with more hopeful, active and resourceful ways to regain control. This is sometimes referred to as "cognitive restructuring."

CBT focuses on teaching patients techniques to reduce their symptoms, improve coping strategies, and identify and eliminate maladaptive illness behaviors. CBT is short term and goal-oriented. In contrast to traditional psychotherapy, CBT aims for changes in thought patterns and behaviors rather than achieving deep insight, with the overall goal of helping patients see the relationship between treatment success and their own personal actions. In contrast to education alone, CBT requires patients to take action within a defined timeframe and demonstrate changed behavior. CBT goals and methods are summarized in Table 13.

Access to CBT can be problematic. Therapists trained in CBT – especially those with knowledge about FM and who are skilled in working with FM patients – are in short supply in many communities. To fill this gap:

- Consider forming a "strategic alliance" with CBT practitioners (doctoral level or allied health professionals) or psychotherapists who are more "practically" oriented in your community, or finding those willing to deliver coping skills training to patients over the phone if they do not practice in your community.[50,117] With patient consent, regular communication between the primary care provider and CBT practitioners is helpful to both in monitoring progress and coordinating non-pharmacologic and pharmacologic therapies
- Identify skilled social workers and nurse educators to provide coaching about physical activity, pacing, sleep hygiene, etc, and counseling, or other community resources for education and support
- Web-based CBT and self-management programs are another option. In one recent study, patients randomized to standard care plus access to an Internet-enhanced behavioral self-management program designed for use in routine clinical care reported significantly greater improvement in pain, physical functioning, and overall global improvement that patients receiving standard care alone.[118] Some suggested resources for patients are provided in Table 2

If you feel that a patient with FM might benefit from some form of psychological counseling, whether CBT provided by a trained therapist or some other type of psychotherapy, keep in mind that people with chronic pain problems are often not receptive to a referral to a psychologist. It may be interpreted as implying that the individual is weak or incompetent, emotionally disturbed, that the symptoms are psychologically induced, or that he or she is exaggerating (if not faking) symptoms. When preparing a patient for referral for counseling you may want to consider:

- Reinforcing that you believe the symptoms are real and not caused by psychological problems
- Acknowledging that living with a chronic disease like FM can affect many domains of a person's life, including their physical, social, and emotional functioning. Patients are usually willing to acknowledge this, too, providing additional rationale for consultation
- Reinforcing that the reason for consulting a professional specialized in helping people with chronic pain is to help a person learn effective methods to reduce the suffering caused by the disease or physical limitations
- Making clear that any information provided to the mental health professional will be confidential, but that you consider him or her to be part of the health care team, and that you'll be sharing some information so that each will be aware of the other's treatment[119]

Complementary and Alternative Medicine Treatments

Patients frequently seek out complementary and alternative medicine (CAM) approaches to FM management, some of which are included in Table 10. A number of CAMs have been studied although many not rigorously, and therefore robust evidence for the efficacy of many approaches is lacking.[13,120] Providing evidence-based care in this regard will often involve a compromise between available clinical evidence, patient preference, and your own clinical experience.[120] When discussing CAM use with patients:

- Hear the patient out with respect
- Educate regarding the evidence base
- Appreciate that if a patient is already using a CAM therapy that has not been shown to be efficacious, and they feel that they are benefiting from this therapy (even if it may be working via a placebo effect) that it may be a very reasonable therapy for that patient
- Be aware of potential interactions or side effects

TABLE 13. Goals and Methods of Cognitive-Behavioral Therapy in FM

Goals	• Help patients view FM as a manageable illness • Educate patients that through treatment they will learn skills to deal with symptoms more adaptively • Realize that success is largely due to their own efforts • Recognize that they are not helpless and passive • Monitor thoughts, feelings and behavior • Anticipate problems and barriers, discover ways to deal with them
Methods	• Relaxation techniques • Goal-setting and accountability for achieving those goals • Problem solving • Self-reinforcement • Substituting maladaptive thoughts with positive cognitions

Adapted from: Goldenberg DL. *Clinical Management of Fibromyalgia.* New York: Professional Communications, Inc. 2009.[16]

4 TRACK PROGRESS

VIGNETTE (cont'd)

It's been 6 months since you began treating Mrs. C for FM, and she has gradually improved. In that time you have adjusted the dosing of the medication you prescribed to manage her symptoms. There have been some setbacks. Her symptoms flared with the onset of winter and this affected her mood. At one point you invited her husband to accompany her to an appointment to reinforce to both of them how important it was for Mrs. C to increase her physical activity levels, and you helped them problem-solve together about ways of doing so. Mrs. C has made use of the self-management information she found on the Internet, and your follow-up visits have tracked progress in the specific areas she has worked on. She hosted her daughter's play date during the third month post-diagnosis and several since, and makes efforts in other ways to avoid disappointing her children. She still has good and bad days, but with pacing and scheduling she does more with her family and is now focused on ensuring that she and her husband have a "date night" every 2 or 3 weeks. At her most recent visit she showed marked improvement in pain, sleep, fatigue and overall well-being, which you reinforced by reviewing her 0-10 scores over time and the progress she has made toward her goals. You'll see her now only every 3 to 6 months unless issues arise.

The course of FM is often not a straightforward one. Coping with medication side effects and adherence issues, symptoms that wax and wane, and the varying impact of FM on multiple spheres of life all make FM management a dynamic process for both clinician and patient. Nevertheless, with appropriate management most patients do make progress especially if patients can be encouraged to maintain a focus on achieving functional improvements over time, rather than on their daily ups and downs – which are natural. Let them know that, so they will not become discouraged and give up.

MONITOR SYMPTOM AND FUNCTIONAL STATUS WHILE IMPLEMENTING A MULTIMODAL PLAN

To help accomplish this, make consistent use of assessment measures that are easy for your patients to use and for you to incorporate into your practice, such as those described in Table 5. This is particularly valuable when a patient comes to see you after a bad week and you can show that despite the current symptom flare, she has actually made measurable progress over time. Helping patients to see the big picture this way, in terms of what they themselves have already been able to accomplish, can help to sustain their motivation to work toward further improvement. Assessment scores that are not heading in a positive direction can help guide treatment adjustments or may signal the need for specialist referral and evaluation.

For diabetes and some other chronic conditions, well-established and accepted protocols provide clear guidance as to what variables should be tracked and what problems should be followed from visit to visit. This has not always been the case for FM.[27] However, there is much good work that can be accomplished with FM patients from visit to visit, beyond medication management and consistent with a chronic care framework. To facilitate FM follow-up within the constraints of a busy primary care practice:

- Structure office visits to focus on monitoring symptoms and desired functional outcomes in key domains (eg, home, work, recreation) and the specific goals the patient has agreed to – eg, walking 10 minutes or a certain number of steps a day, pacing during the work day so as to conserve energy for evening tasks, scheduling dinner out with a friend or spouse, attending an exercise class or support group meeting, making time for favorite hobbies

- At each visit ask patients how much physical activity they are doing, and how much they are using self-management techniques, to emphasize that you feel that these are important. Patients will become accustomed to this and the visits will become more streamlined.[30] Use each visit to work through the patient's priority list in a step-by-step fashion, or to cover important educational and self-help topics (exercise and pacing, sleep hygiene, etc)
- Encourage patients to take ownership for managing FM by giving simple "homework." For instance, ask the patient to look up information on specific topics and report back. Note it in the chart when you do, and ask about it on the next visit

As the patient's situation improves or changes, the patient's priorities and goals will change, too. Goal-setting and follow-up thus becomes a dynamic process that can be motivating and drive ongoing success.

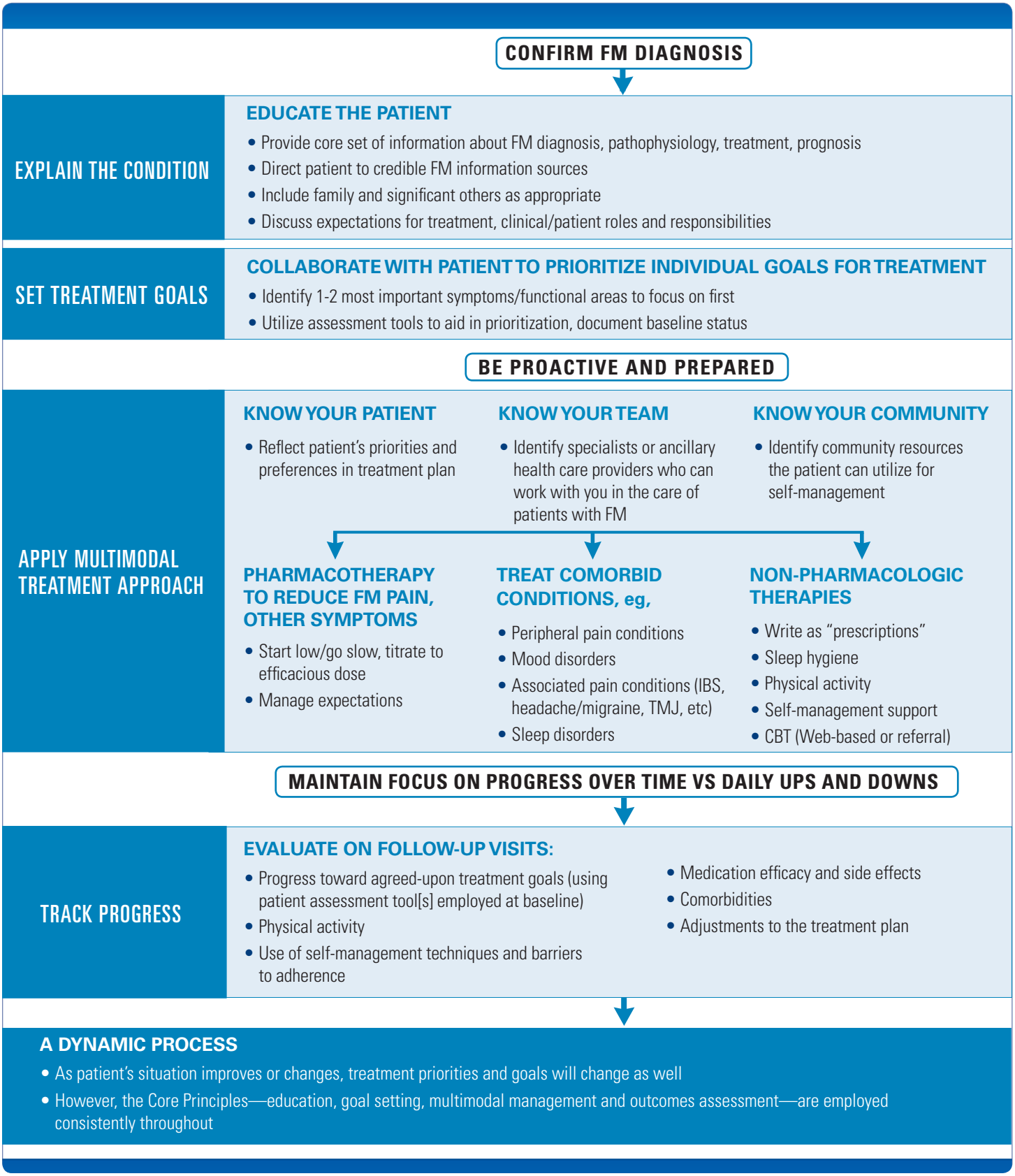
CONCLUSION

FM is a chronic, widespread pain condition that until recently was poorly understood. As a result, timely diagnosis and appropriate management has often been difficult to achieve, with often devastating consequences for many patients suffering from the condition. Fortunately, FM cannot be described as "poorly understood" today and with recent research and treatment advances, the prognosis for people with FM is continuing to improve.

Many complex and chronic diseases are now effectively managed in primary care. This is being facilitated by the increasing adoption of a chronic care model for disease management that reflects the need to change daily care for people with chronic illnesses from acute and reactive to proactive and planned.[9] Primary care practitioners can effectively manage FM by following a similar approach, as described in this monograph and summarized in Figure 3 on the following page.

Further development and dissemination of diagnostic and treatment guidelines would be helpful to clarify evidence-based approaches to FM management but in the meantime, there is much that is known about treatment strategies that can enable people with FM to regain function and quality of life. The management of FM in the primary care setting can be optimized by implementing a chronic care framework for FM that is patient-centric and based on the core principles of patient education, goal setting, multidisciplinary management (including a significant patient self-management component), and outcomes assessment.

Figure 3. Core Principles of Fibromyalgia Management



APPENDIX: TOOLS FOR FM ASSESSMENT AND TRACKING PROGRESS

Revised Fibromyalgia Impact Questionnaire (FIQR)

From Bennett et al. *Arthritis Res Therap.* 2009;11(4):1-14.[25]

REVISED FIBROMYALGIA IMPACT QUESTIONNAIRE (FIQR)

Last Name: _____ **Duration of FM symptoms (years):** _____

First Name: _____ **Time since FM was first diagnosed (years):** _____

Age: _____

DOMAIN 1: FUNCTION

Directions: For each of the following 9 questions, check the box that best indicates how much your Fibromyalgia made it difficult to perform each of the following activities during the past 7 days. If you did not perform a particular activity in the last 7 days, rate the difficulty for the last time you performed the activity. If you can't perform an activity, check the last box.

BRUSH OR COMB YOUR HAIR

No difficulty ❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ 9 ❑ 10 Very difficult

WALK CONTINUOUSLY FOR 20 MINUTES

No difficulty ❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ 9 ❑ 10 Very difficult

PREPARE A HOMEMADE MEAL

No difficulty ❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ 9 ❑ 10 Very difficult

VACUUM, SCRUB, OR SWEEP FLOORS

No difficulty ❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ 9 ❑ 10 Very difficult

LIFT AND CARRY A BAG FULL OF GROCERIES

No difficulty ❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ 9 ❑ 10 Very difficult

CLIMB ONE FLIGHT OF STAIRS

No difficulty ❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ 9 ❑ 10 Very difficult

CHANGE BEDSHEETS

No difficulty ❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ 9 ❑ 10 Very difficult

SIT IN A CHAIR FOR 45 MINUTES

No difficulty ❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ 9 ❑ 10 Very difficult

SHOP FOR GROCERIES

No difficulty ❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ 9 ❑ 10 Very difficult

DOMAIN 1 SUBTOTAL: _____

Revised Fibromyalgia Impact Questionnaire (FIQR) *cont'd*

From Bennett et al. *Arthritis Res Therap.* 2009;11(4):1-14.[25]

DOMAIN 2: OVERALL

Directions: For each of the following 2 questions, check the box that best describes the overall impact of your Fibromyalgia over the last 7 days.

FIBROMYALGIA PREVENTED ME FROM ACCOMPLISHING GOALS FOR THE WEEK

Never	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8	❑ 9	❑ 10	**Always**

I WAS COMPLETELY OVERWHELMED BY MY FIBROMYALGIA SYMPTOMS

Never	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8	❑ 9	❑ 10	**Always**

DOMAIN 2 SUBTOTAL: _____

DOMAIN 3: SYMPTOMS

Directions: For each of the following 10 questions, select the box that best indicates your intensity level of these common Fibromyalgia symptoms over the past 7 days.

PLEASE RATE THE LEVEL OF PAIN

No pain	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8	❑ 9	❑ 10	**Unbearable pain**

PLEASE RATE YOUR LEVEL OF ENERGY

Lots of energy	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8	❑ 9	❑ 10	**No energy**

PLEASE RATE YOUR LEVEL OF STIFFNESS

No stiffness	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8	❑ 9	❑ 10	**Severe stiffness**

PLEASE RATE THE QUALITY OF YOUR SLEEP

Awoke well rested	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8	❑ 9	❑ 10	**Awoke very tired**

PLEASE RATE YOUR LEVEL OF DEPRESSION

No depression	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8	❑ 9	❑ 10	**Very depressed**

PLEASE RATE YOUR LEVEL OF MEMORY PROBLEMS

Good memory	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8	❑ 9	❑ 10	**Very poor memory**

PLEASE RATE YOUR LEVEL OF ANXIETY

Not anxious	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8	❑ 9	❑ 10	**Very anxious**

Revised Fibromyalgia Impact Questionnaire (FIQR)

From Bennett et al. *Arthritis Res Therap.* 2009;11(4):1-14.[25]

PLEASE RATE YOUR LEVEL OF TENDERNESS TO TOUCH

No tenderness	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8	❑ 9	❑ 10	Very tender

PLEASE RATE YOUR LEVEL OF BALANCE PROBLEMS

No imbalance	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8	❑ 9	❑ 10	Severe imbalance

PLEASE RATE YOUR LEVEL OF SENSITIVITY TO LOUD NOISES, BRIGHT LIGHTS, ODORS, AND COLD

No sensitivity	❑ 0	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8	❑ 9	❑ 10	Extreme sensitivity

DOMAIN 3 SUBTOTAL: _____

SCORING:

1) Sum the scores for each of the 3 domains (function, overall, and symptoms).

2) Divide domain 1 score by 3, leave domain 2 score unchanged, and divide domain 3 score by 2.

3) Add the 3 resulting domain scores to obtain the total FIQR score.

DOMAIN 1 SUBTOTAL _____ ÷ 3 = _____

DOMAIN 2 SUBTOTAL _____ CARRY OVER SUBTOTAL = _____

DOMAIN 3 SUBTOTAL _____ ÷ 2 = _____

TOTAL FIQR SCORE

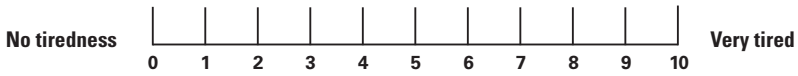
Modified Visual Analogue Scale of the FIQ (mVASFIQ)

From Boomershine C, Crofford L. *Nat Rev Rheum.* 2009;5:191-199.[27]

MODIFIED VISUAL ANALOGUE SCALE OF THE FIBROMYALGIA IMPACT QUESTIONNAIRE (mVASFIQ)

Directions: Please indicate by marking a "/" through the line at a point that best indicates how you've felt overall for the past week.

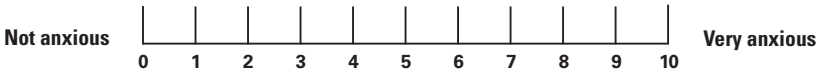
FATIGUE: How tired have you been?



INSOMNIA: How have you felt when you got up in the morning?

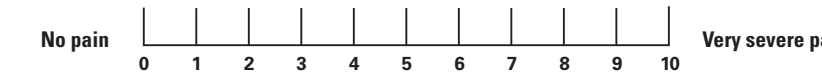
BLUES: How depressed or blue have you felt?

How nervous or anxious have you felt?

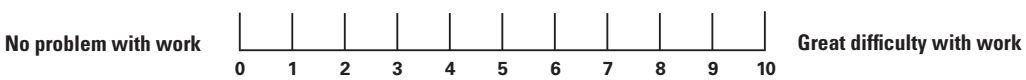


RIGIDITY: How bad has your stiffness been?

OW!: How bad has your pain been?



When you worked, how much did pain or other symptoms interfere with your ability to do your work, including housework?



The FIBRO mnemonic can be used to remember the items on this questionnaire (mVASFIQ). VASFIQ modified with permission from RM Bennett. Adapted with permission from *The Journal of Rheumatology* © Burckhardt, C. S., Clark, S. R. & Bennett, R. M. The fibromyalgia impact questionnaire: development and validation. *J Rheumatol.* 18, 728-734 (1991).

ACR Provisional Criteria

Based on Wolfe et al. *Arthritis Care Res.* 2010;62(5):600-610.[26]

AMERICAN COLLEGE OF RHEUMATOLOGY (ACR) PRELIMINARY DIAGNOSTIC CRITERIA FOR FIBROMYALGIA[1]

The information contained on this form was derived from Wolfe F, Clauw DJ, Fitzcharles M-A, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res.* 2010;62(5):600-610.

PART 1: WIDESPREAD PAIN INDEX

HOW TO CALCULATE THE PATIENT'S WIDESPREAD PAIN INDEX (WPI)

1. Using the list of 19 body areas, identify the areas where the patient felt pain over the past week. As a visual aid, front/back body diagrams are included.

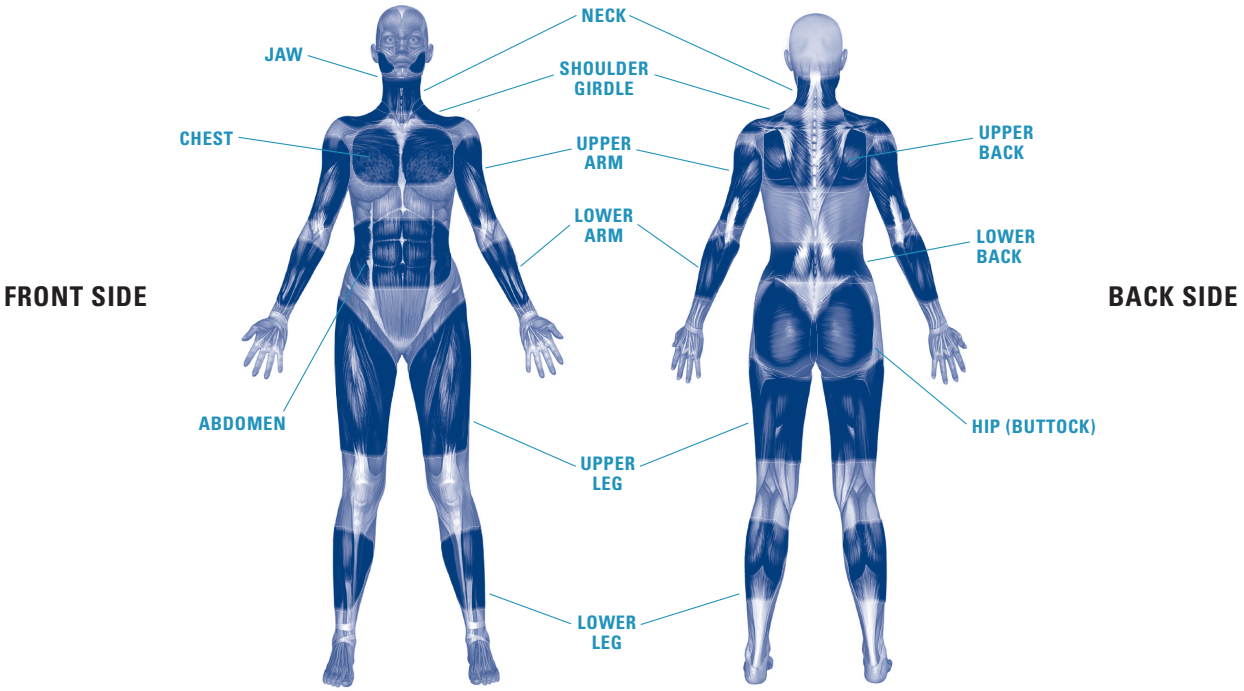
   — Each area identified on the list counts as 1

2. Total the number of body areas (the WPI score can range from 0 to 19).

Write the patient's WPI score here: _____.

Identify the areas where the patient felt pain over the past week

❑ Shoulder girdle, left	❑ Lower arm, right	❑ Lower leg, left	❑ Abdomen
❑ Shoulder girdle, right	❑ Hip (buttock), left	❑ Lower leg, right	❑ Neck
❑ Upper arm, left	❑ Hip (buttock), right	❑ Jaw, left	❑ Upper back
❑ Upper arm, right	❑ Upper leg, left	❑ Jaw, right	❑ Lower back
❑ Lower arm, left	❑ Upper leg, right	❑ Chest	



ACR Provisional Criteria *cont'd*

Based on Wolfe et al. *Arthritis Care Res.* 2010;62(5):600-610.[26]

PART 2A: SYMPTOM SEVERITY SCALE (LEVELS OF SEVERITY)

HOW TO MEASURE THE PATIENT'S LEVEL OF SYMPTOM SEVERITY

1. Using a scale of 0 to 3, indicate the patient's level of symptom severity over the past week in each of the 3 symptom categories. Choose only 1 level of severity for each category.

   — The score is the sum of the numbers that correspond to the severity levels identified in all 3 categories

2. Total the scale numbers for all the 3 categories and write the number here: _____.

Fatigue

- ❑ 0 = No problem
- ❑ 1 = Slight or mild problems; generally mild or intermittent
- ❑ 2 = Moderate; considerable problems; often present and/or at a moderate level
- ❑ 3 = Severe; pervasive, continuous, life-disturbing problems

Waking unrefreshed

- ❑ 0 = No problem
- ❑ 1 = Slight or mild problems; generally mild or intermittent
- ❑ 2 = Moderate; considerable problems; often present and/or at a moderate level
- ❑ 3 = Severe; pervasive, continuous, life-disturbing problems

Cognitive symptoms

- ❑ 0 = No problem
- ❑ 1 = Slight or mild problems; generally mild or intermittent
- ❑ 2 = Moderate; considerable problems; often present and/or at a moderate level
- ❑ 3 = Severe; pervasive, continuous, life-disturbing problems

PART 2B: SYMPTOM SEVERITY SCALE (OTHER SOMATIC SYMPTOMS)

HOW TO DETERMINE THE EXTENT OF THE PATIENT'S OTHER SOMATIC SYMPTOMS

Using the symptoms list on the following page, determine the extent of other somatic symptoms the patient may have experienced over the past week.

1. Determine the quantity of somatic symptoms using the list on the following page.
2. Using your best judgment, calculate the score that matches the quantity of those somatic symptoms and write the number here: _____.

Add the scores from Parts 2a and 2b (the Symptom Severity score, or SS score, can range from 0 to 12).
Write the patient's SS score here: _____.

ACR Provisional Criteria *cont'd*

Based on Wolfe et al. *Arthritis Care Res.* 2010;62(5):600-610.[26]

OTHER SYMPTOMS

❑ Muscle pain	❑ Depression	❑ Itching	❑ Dry eyes
❑ Irritable bowel syndrome	❑ Constipation	❑ Wheezing	❑ Shortness of breath
❑ Fatigue/tiredness	❑ Pain in upper abdomen	❑ Raynaud's	❑ Loss of appetite
❑ Thinking or memory problem	❑ Nausea	❑ Hives/welts	❑ Rash
❑ Muscle weakness	❑ Nervousness	❑ Ringing in ears	❑ Sun sensitivity
❑ Headache	❑ Chest pain	❑ Vomiting	❑ Hearing difficulties
❑ Pain/cramps in abdomen	❑ Blurred vision	❑ Heartburn	❑ Easy bruising
❑ Numbness/tingling	❑ Fever	❑ Oral ulcers	❑ Hair loss
❑ Dizziness	❑ Diarrhea	❑ Loss/change in taste	❑ Frequent urination
❑ Insomnia	❑ Dry mouth	❑ Seizures	❑ Bladder spasms

Based on the quantity of symptoms, the patient's score is:

❑ 0 = No symptoms
❑ 1 = Few symptoms
❑ 2 = A moderate number of symptoms
❑ 3 = A great deal of symptoms

WHAT THE PATIENT'S SCORE MEANS

The patient's WPI score (Part 1): _____. **The patient's SS score (Parts 2a and 2b):** _____.

A PATIENT MEETS THE DIAGNOSTIC CRITERIA FOR FIBROMYALGIA IF THE FOLLOWING 3 CONDITIONS ARE MET:

1a. The WPI score (Part 1) is greater than or equal to 7 and the SS score (Parts 2a and 2b) is greater than or equal to 5.

OR

1b. The WPI score (Part 1) is from 3 to 6 and the SS score (Parts 2a and 2b) is greater than or equal to 9.

2. Symptoms have been present at a similar level for at least 3 months.

3. The patient does not have a disorder that would otherwise explain the pain.

Numeric Rating Scales (NRS) for Symptoms and Function in FM

NUMERIC RATING SCALES (NRS) FOR SYMPTOMS AND FUNCTION IN FIBROMYALGIA

PAIN

What number would you give your pain in the **past week**?

No pain 0 1 2 3 4 5 6 7 8 9 10 **Most severe pain you can possibly imagine**

SLEEP

What number would you give your sleep in the **past week**?

No sleep problems 0 1 2 3 4 5 6 7 8 9 10 **Worst sleep problems you can possibly imagine**

FATIGUE

What number would you give your fatigue in the **past week**?

No fatigue 0 1 2 3 4 5 6 7 8 9 10 **Most severe fatigue you can possibly imagine**

EFFECT ON ABILITY TO WORK

What number would you give for the amount of impairment your Fibromyalgia has had on work in the **past week**?

No effect 0 1 2 3 4 5 6 7 8 9 10 **Most severe effect you can possibly imagine**

EFFECT ON FAMILY CARE

What number would you give for the amount of impairment your Fibromyalgia has had on family care in the **past week**?

No effect 0 1 2 3 4 5 6 7 8 9 10 **Most severe effect on family care you can possibly imagine**

EFFECT ON COGNITION ("FIBRO FOG")

What number would you give for the amount of impairment your Fibromyalgia has had on your ability to think clearly in the **past week**?

No effect on your ability to think clearly 0 1 2 3 4 5 6 7 8 9 10 **Most severe effect on thinking you can possibly imagine**

REFERENCES

1. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum*. 1995;38:19-28.

2. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, Hirsch R, Hochberg MC, Hunder GG, Jordan JM, Katz JN, Kremers HM, Wolfe F; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum*. 2008 Jan;58(1):26-35.

3. Arnold LM, Crofford LJ, Mease PJ, Burgess SM, Palmer SC, Abetz L, Martin SA. Patient perspectives on the impact of fibromyalgia. *Patient Educ Couns*. 2008;73(1):114-120.

4. Goldenberg D, Schaefer C, Ryan K, Chandran A, Slateva G. What is the true cost of fibromyalgia to our society: results from a cross-sectional survey in the United States. Abstract presented at: American College of Rheumatology; October 18, 2009; Philadelphia, PA.

5. Berger A, Dukes E, Martin S, Edelsberg J, Oster G. Characteristics and healthcare costs of patients with fibromyalgia syndrome. *Int J Clin Pract*. 2007;61:1498-1508.

6. Ablin K, Clauw DJ. From fibrositis to functional somatic syndromes to a bell -shaped curve of pain and sensory sensitivity: evolution of a clinical construct. *Rheum Dis Clin N Am*. 2009;35:233-251.

7. Data on file. Decision Resources Report 2009. Pfizer Inc, New York, NY.

8. Clauw DJ. Fibromyalgia: update on mechanisms and management. *J Clin Rheumatol*. 2007;13(2):102-109.

9. Coleman K, Austin BT, Branch C, Wagner EH. Evidence on the chronic care model in the new millennium. *Health Affairs*. 2009;28(1):75-85.

10. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. *JAMA*. 2002;288(14):1775-1779.

11. Clauw DJ. Alpha-2-delta ligands for fibromyalgia: is the glass half empty or half full? *Pain*. 2009;145:8-9.

12. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of a multicenter criteria committee. *Arthritis Rheum*. 1990;33(2):160-172.

13. Hassett AL, Givertz RN. Nonpharmacological treatment for fibromyalgia: patient education, cognitive-behavioral therapy, relaxation techniques, and complementary and alternative medicine. *Rheum Dis Clin N Am*. 2009;35(2):393-408.

14. Sim J, Madden S. Illness experience in fibromyalgia syndrome: a metasynthesis of qualitative studies. *Soc Sci Med*. 2008 Jul;67(1):57-67.

15. White KP, Nielson WR, Harth M, Ostbye T, Speechley M. Does the label "fibromyalgia" alter health status, function, and health service utilization? A prospective, within-group comparison in a community cohort of adults with chronic widespread pain. *Arthritis Rheum*. 2002 Jun 15;47(3):260-265.

16. Goldenberg D. Clinical management of fibromyalgia. New York: Professional Communications, Inc. 2009.

17. Arnold LJ, Hudson JI, Hess EV, Ware AE, Fritz DA, Auchenbach MB, Starck LO, Keck PE Jr. Family study of fibromyalgia. *Arthritis Rheum*. 2004;50:944-952.

18. Stahl SM. Stahl's illustrated chronic pain and fibromyalgia. New York: Cambridge University Press, 2009.

19. Russell IJ, Larson AA. Neurophysiopathogenesis of fibromyalgia syndrome: a unified hypothesis. *Rheum Dis Clin N Am*. 2009;35: 421-435.

20. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum*. 2002;46 (5):1333-1343.

21. Marques AP, Ferreira EA, Matsutani LA, Pereira CA, Assumpção A. Quantifying pain threshold and quality of life of fibromyalgia patients. *Clin Rheumatol*. 2005 Jun;24(3):266-271.

22. D'Arcy Y, McCarberg BH. New fibromyalgia pain management recommendations. *J Nurse Pract*. 2005;218-225.

23. Bayliss EA, Bosworth PH, Noel PH, Wolff JL, Damush TM, Mciver L. Supporting self-management for patients with complex medical needs: recommendations of a working group. *Chronic Illn*. 2007;3:167-175.

24. Williams DA, Clauw DJ. Understanding fibromyalgia: lessons from the broader pain research community. *J Pain*. 2009;10(8): 777-791.

25. Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL. The revised fibromyalgia impact questionnaire (FIQR): validation and psychometric properties. *Arthritis Res Ther*. 2009;11(4):R120.

26. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB, Yunus MB. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res*. 2010;62(5):800-810.

27. Boomershine CS, Crofford LJ. A symptom-based approach to pharmacologic management of fibromyalgia. *Nat Rev Rheum*. 2009;5:191-199.

28. Mease P, Clauw D, Fitzcharles M, Goldenberg D, Hauser W, Katz R, Russell A, Russell IJ, Winfield J, Wolfe F. Development of the Fibromyalgia Survey Diagnostic Criteria, a modification of the ACR (2010) preliminary diagnostic criteria for fibromyalgia. Presented at MYOPAIN 2010, 8th International Congress of Myofascial Pain Syndrome and Fibromyalgia Syndrome. Toledo, Spain, October 3-7, 2010.

29. Filoramo MA. Improving goal setting and goal attainment in patients with chronic noncancer pain. *Pain Man Nurs*. 2007;8(2): 96-101.

30. McCarberg BH. Fibromyalgia management for the primary care provider. In: McCarberg BH, Clauw DJ, eds. *Fibromyalgia*. New York, NY: Informa Healthcare USA, Inc; 2009:152-158.

31. Arnold LM. Biology and therapy of fibromyalgia: new therapies in fibromyalgia. *Arthritis Res Ther*. 2006;8(4):212.

32. Carville SF, Arendt-Nielsen S, Bliddal J, et al. EULAR evidence based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis* published online 20 Jul 2007; doi:10.1136/ard.2007.071522.

33. Paiva ES, Jones KD. Rational treatment of fibromyalgia for a solo practitioner. *Best Pract Res Clin Rheum*. 2010;24:341-352.

34. Arnold LM The pharmacological treatment of fibromyalgia. In: McCarberg BH, Clauw DJ, eds. *Fibromyalgia*. New York, NY: Informa Healthcare USA, Inc; 2009:56-80.

35. Mease PJ. Pharmacotherapy of fibromyalgia. *Rheum Dis Clin Am*. 2009;35:359-372.

36. Goldenberg DL. Pharmacological treatment of fibromyalgia and other chronic musculoskeletal pain. *Best Pract Res Clin Rheumatol*. 2007 Jun;21(3):499-511.

37. Baraniuk JN, Whalen G, Cunningham J, Clauw DJ. Cerebrospinal fluid levels of opioid peptides in fibromyalgia and chronic low back pain. *BMC Musculoskelet Disord*. 2004 Dec 9;5:48.

38. Lyrica (pregabalin) full prescribing information. December 2009, Pfizer Inc.

39. Cymbalta (duloxetine hydrochloride) full prescribing information. January 13, 2010, Eli Lilly and Company.

40. Savella (milnacipran HCl) full prescribing information. January 2009, Forest Pharmaceuticals, Inc.

41. Wolfe F, Zhao S, Lane N. Preference for nonsteroidal antiinflammatory drugs over acetaminophen by rheumatic disease patients: a survey of 1,799 patients with osteoarthritis, rheumatoid arthritis, and fibromyalgia. *Arthritis Rheum*. 2000 Feb;43(2):378-385.

42. Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta JK. Decreased central mu-opioid receptor availability in fibromyalgia. *J Neurosci*. 2007 Sep 12;27(37):10000-10006.

43. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, Glaser SE, Vallejo R. Opioid complications and side effects. *Pain Physician*. 2008;11:S105-S120.

44. Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. *J Pain*. 2006;7:43-48.

45. Burckhardt CS, Goldenberg D, Crofford L, et al. *Guidelines for the Management of Fibromyalgia Syndrome Pain in Adults and Children*, APS Clinical Guidelines Series, No. 4 (2005). Glenview, IL: American Pain Society.

46. Mease PJ, Seymour K. Fibromyalgia: should the treatment paradigm be monotherapy or combination therapy? *Curr Pain Headache Rep*. 2008:12:399-405.

47. Staud R. Nonrestorative sleep in fibromyalgia: from assessment to therapy—focus on diagnosis CME/CE. *Medscape Rheum*. 2010 April; 1-6.

48. Burckhardt CS. Educating patients: self-management approaches. *Dis Rehab*. 2005;27(12):703-709.

49. Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L. An internet survey of 2,596 people with fibromyalgia. *BMC Musculoskel Dis*. 2007;8:27; doi10.1186/1471-2474/8/27.

50. Williams DA, Marshak ML. Motivating behavioral change in fibromyalgia. In: McCarberg BH, Clauw DJ, eds. *Fibromyalgia*. New York, NY: Informa Healthcare USA, Inc; 2009:152-158.

51. Morin CM, Culbert JP, Schwartz SM. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. *Am J Psychiatry*. 1994;151(8):1172-1180.

52. Häuser W, Klose P, Langhorst J, Moradi B, Steinbach M, Schiltenwolf M, Busch A. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. *Arthritis Res Ther*. 2010;12(3):R79. Epub 2010 May 10.

53. Busch AJ, Barber KA, Overend TJ, Peloso PM, Schachter CL. Exercise for treating fibromyalgia syndrome. *Cochrane Database Syst Rev*. 2007 Oct 17;(4):CD003786.

54. Kelley GA, Kelley KS, Hootman JM, Jones DL. Exercise and global well-being in community-dwelling adults with fibromyalgia: a systematic review with meta-analysis. *BMC Public Health*. 2010 Apr 20;10:198.

55. Brosseau L, Wells GA, Tugwell P, Egan M, Wilson KG, Dubouloz CJ, Casimiro L, Robinson VA, McGowan J, Busch A, Poitras S, Moldofsky H, Harth M, Finestone HM, Nielson W, Haines-Wangda A, Russell-Doreleyers M, Lambert K, Marshall AD, Veilleux L; Ottawa Panel Members. Ottawa Panel evidence-based clinical practice guidelines for aerobic fitness exercises in the management of fibromyalgia: part 1. *Phys Ther*. 2008 Jul;88(7):857-871.

56. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA*. 2004;292(19):2388-2395.

57. Brosseau L, Wells GA, Tugwell P, Egan M, Wilson KG, Dubouloz CJ, Casimiro L, Robinson VA, McGowan J, Busch A, Poitras S, Moldofsky H, Harth M, Finestone HM, Nielson W, Haines-Wangda A, Russell-Doreleyers M, Lambert K, Marshall AD, Veilleux L; Ottawa Panel Members. Ottawa Panel evidence-based clinical practice guidelines for strengthening exercises in the management of fibromyalgia: part 2. *Phys Ther*. 2008 Jul;88(7):873-886.

58. Wang C, Schmid CH, Rones R, Kalish R, Yinh J, Goldenberg DL, Lee Y, McAlindon T. A randomized trial of tai chi for fibromyalgia. *N Engl J Med*. 2010 Aug 19;363(8):743-754.

59. van Koulil S, van Lankveld W, Kraaimaat FW, van Helmond T, Vedder A, van Hoorn H, Donders R, de Jong AJ, Haverman JF, Korff KJ, van Riel PL, Cats HA, Evers AW. Tailored cognitive-behavioral therapy and exercise training for high-risk patients with fibromyalgia. *Arthritis Care Res* (Hoboken). 2010 Oct;62(10):1377-1385.

60. Redondo JR, Justo CM, Moraleda FV, Velayos YG, Puche JJ, Zubero JR, Hernández TG, Ortells LC, Pareja MA. Long-term efficacy of therapy in patients with fibromyalgia: a physical exercise-based program and a cognitive-behavioral approach. *Arthritis Rheum*. 2004 Apr 15;51(2):184-192.

61. Williams DA, Cary MA, Groner KH, Chaplin W, Glazer LJ, Rodriguez AM, Clauw DJ. Improving physical functional status in patients with fibromyalgia: a brief cognitive behavioral intervention. *J Rheumatol*. 2002 Jun;29(6):1280-1286.

62. Hammond A, Freeman K. Community patient education and exercise for people with fibromyalgia: a parallel group randomized controlled trial. *Clin Rehabil*. 2006; 20(10):835-846.

63. Nielson WR, Walker C, Mccain GA. Cognitive behavioral treatment of fibromyalgia syndrome: preliminary findings. *J Rheumatol*. 1992;19:98-103.

64. White KP, Nielson WR. Cognitive behavioral treatment of fibromyalgia syndrome: a follow-up assessement. *J Rheumatol*. 1995;22:717-721.

65. Creamer P, Singh BB, Hochberg MC, Berman BM. Sustained improvement produced by nonpharmacologic intervention in fibromyalgia: results of a pilot study. *Arthritis Care Res*. 2000;13:198-204.

66. Singh BB, Berman BM, Creamer P. A pilot study of cognitive behavioral therapy in fibromyalgia. *Altern Ther Health Med*. 1998;4:67-70.

67. Goldenberg DL, Kaplan KH, Nadeau MG, Brodeur C, Smith S, Schmid CH. A controlled study of a stress reduction, cognitive-behavioral treatment program in fibromyalgia. *J Muscoskel Pain*. 1994;2(2):53-66.

68. Nicassio PM, Radojevic V, Weisman MH, Schuman C, Kim J, Schoenfeld-Smith K, Krall T. A comparison of behavioral and educational interventions for fibromyalgia. *J Rheumatol*. 1997 Oct;24(10):2000-2007.

69. Vlaeyen JW, Teeken-Gruben NJ, Goossens ME, Rutten-van Mölken MP, Pelt RA, van Eek H, Heuts PH. Cognitive-educational treatment of fibromyalgia: a randomized clinical trial. I. Clinical effects. *J Rheumatol*. 1996 Jul;23(7):1237-1245.

70. Thieme K, Flor H, Turk D. Psychological pain treatment in fibromyalgia syndrome: efficacy of operant behavioural and cognitive behavioural treatments. *Arthritis Res Ther*. 2006;8:121-132.

71. Glombiewski JA, Sawyer At, Guterman J, Koenig K, Rief W, Hofman SG. Psychological treatments for fibromyalgia: a meta-analysis. *Pain*. 2010;151:280-295.

72. Bernardy K, Fuber N, Kollner V, Hauser W. Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome: a systematic review and mataanalysis of randomized controlled trials. *J Rheum*. 2010;37:10;doi:10.3889/jrheum.100104.

73. Rooks DS, Gautam S, Romeling M, Cross ML, Stratigakis D, Evans B, Goldenberg DL, Iversen MD, Katz JN. Group exercise, education, and combination self-management in women with fibromyalgia: a randomized trial. *Arch Intern Med*. 2007;167: 2192-2200.

74. Burckhardt CS, Mannerkorpi K, Hedenberg L, Bjelle A. A randomized, controlled clinical trial of education and physical training for women with fibromyalgia. *J Rheumatol*. 1994;21(4): 714-720.

75. Alamo M, Moral RR, Perula de Torres LA. Evaluation of a patient-centered approach in generalized musculoskeletal chronic pain/fibromyalgia patients in primary care. *Patient Educ Couns*. 2002;48:23-31.

76. Pfeiffer A, Thompson JM, Nelson A, Tucker S, Luedtke C, Finnie S, Sletten C, Postier J. Effects of a 1.5-day multidiscplinary outpatient treatment program for fibromyalgia: a pilot study. *Am J Phys Med Rehabil*. 2003;82:186-191.

77. Zijlstra TR, van de Laar MA, Bernelot Moens HJ, Taal E, Zakraoui L, Rasker JJ. Spa treatment for primary fibromyalgia syndrome: a combination of thalassotherapy, exercise and patient education improves symptoms and quality of life. *Rheumatology* (Oxford). 2005 Apr;44(4):539-546.

78. Keel PJ, Bodoky C, Gerhard U, Muller W. Comparison of integrated group therapy and group relaxation training for fibromyalgia. *Clin J Pain*. 1998;14: 232-238.

79. King SJ, Wessel J, Bhambhani Y, Sholter D, Maksymowych W. The effects of exercise and education, individually or combined, in women with fibromyalgia. *J Rheumatol*. 2002 Dec;29(12):2620-2627.

80. Mannerkorpi K, Nyberg B, Ahlmén M, Ekdahl C. Pool exercise combined with an education program for patients with fibromyalgia syndrome. A prospective, randomized study. *J Rheumatol*. 2000 Oct;27(10):2473-2481.

81. Mannerkorpi K, Ahlmén M, Ekdahl C. Six- and 24-month follow-up of pool exercise therapy and education for patients with fibromyalgia. *Scand J Rheumatol*. 2002;31(5):306-310.

82. Oliver K, Cronan TA, Walen HR, Tomita M. Effects of social support and education on health care costs for patients with fibromyalgia. *J Rheumatol*. 2001 Dec;28(12):2711-2719.

83. Gowans SE, deHueck A, Voss S, Richardson M. A randomized, controlled trial of exercise and education for individuals with fibromyalgia. *Arthritis Care Res*. 1999 Apr;12(2):120-128.

84. Ammer K, Melnizky P. [Medicinal baths for treatment of generalized fibromyalgia] [in German]. *Forsch Komplementarmed*. 1999;6:80-85.

85. Ardiç F, Ozgen M, Aybek H, Rota S, Cubukçu D, Gökgöz A. Effects of balneotherapy on serum IL-1, PGE2 and LTB4 levels in fibromyalgia patients. *Rheumatol Int*. 2007;27:441-446.

86. Donmez A, Karagulle MZ, Tercan N, Dinler M, Işsever H, Karagülle M, Turan M. SPA therapy in fibromyalgia: a randomized controlled clinic study. *Rheumatol Int*. 2005;26:168-172.

87. Evcik D, Kizilay B, Gokcen E. The effects of balneotherapy on fibromyalgia patients. *Rheumatol Int*. 2002;22:56-59.

88. Eksioglu E, Yazar D, Bal A, Usan HD, Cakci A. Effects of Stanger bath therapy on fibromyalgia. *Clin Rheumatol*. 2007;26:691-694.

89. Fioravanti A, Perpignano G, Tirri G, Cardinale G, Gianniti C, Lanza CE, Loi A, Tirri E, Sfriso P, Cozzi F. Effects of mud-bath treatment on fibromyalgia patients: a randomized clinical trial. *Rheumatol Int*. 2007;27:1157-1161.

90. Gunther V, Mur E, Kinigadner U, Miller C. Fibromyalgia—the effect of relaxation and hydrogalvanic bath therapy on the subjective pain experience. *Clin Rheumatol*. 1994;13:573-578.

91. Kurzeja R, Gutenbrunner C, Krohn-Grimberghe B. Fibromyalgia: comparison of whole-body-cryotherapy with two classical thermotherapy methods. *Akt Rheumatol*. 2003;28:158-163.

92. Yurtkuran M, Celiktas M. A randomized, controlled trial of balneotherapy in the treatment of patients with primary fibromyalgia syndrome. *Phys Rehab Kur Med*. 1996;6:109-112.

93. Neumann L, Sukenik S, Bolotin A, Abu-Shakra M, Amir M, Flusser D, Buskila D. The effects of balneotherapy at the dead sea on the quality of life of patients with fibromyalgia syndrome. *Clin Rheumatol*. 2001; 20:15-19.

94. Langhorst J, Musial F, Klose P, Häuser W. Efficacy of hydrotherapy in fibromyalgia syndrome--a meta-analysis of randomized controlled clinical trials. *Rheumatology* (Oxford). 2009 Sep;48(9):1155-1159.

95. McVeigh JG, McGaughey H, Hall M, Kane P. The effectiveness of hydrotherapy in the management of fibromyalgia syndrome: a systematic review. *Rheumatol Int*. 2008 Dec;29(2):119-130.

96. Baranowsky J, Klose P, Musial F, Hauser W, Dobos G, Langhorst J. Qualitative systemic review of randomized controlled trials on complementary and alternative medicine treatments in fibromyalgia. *Rheumatol Int*. 2009 Nov;30(1):1-21.

97. Itoh K, Kitakoji H. Effects of acupuncture to treat fibromyalgia: a preliminary randomised controlled trial. *Chin Med*. 2010 Mar 23;5:11.

98. Targino RA, Imamura M, Kaziyama HH, Souza LP, Hsing WT, Furlan AD, Imamura ST, Azevedo Neto RS. A randomized controlled trial of acupuncture added to usual treatment for fibromyalgia. *J Rehabil Med*. 2008 Jul;40(7):582-588.

99. Martin DP, Sletten CD, Williams BA, Berger IH. Improvement in fibromyalgia symptoms with acupuncture: results of a randomized controlled trial. *Mayo Clin Proc*. 2006 Jun;81(6):749-757.

100. Deluze C, Bosia L, Zirbs A, Chantraine A, Vischer TL. Electroacupuncture in fibromyalgia: results of a controlled trial. *BMJ*. 1992 Nov 21;305(6864):1249-1252.

101. Assefi NP, Sherman KJ, Jacobsen C, Goldberg J, Smith WR, Buchwald D. A randomized clinical trial of acupuncture compared with sham acupuncture in fibromyalgia. *Ann Intern Med*. 2005 Jul 5;143(1):10-19.

102. Harris RE, Tian X, Williams DA, Cupps TR, Petzke F, Groner KH, Biswas P, Gracely RH, Clauw DJ. Treatment of fibromyalgia with formula acupuncture: investigation of needle placement, needle stimulation, and treatment frequency. *J Altern Complement Med*. 2005;11(4):663-671.

103. Langhorst J, Klose P, Musial F, Irnich D, Häuser W. Efficacy of acupuncture in fibromyalgia syndrome--a systematic review with a meta-analysis of controlled clinical trials *Rheumatology* (Oxford). 2010 Apr;49(4):778-788.

104. Martin-Sanchez E, Torralba E, Díaz-Domínguez E, Barriga A, Martin JL. Efficacy of acupuncture for the treatment of fibromyalgia: systematic review and meta-analysis of randomized trials. *Open Rheumatol J*. 2009 Jun 16;3:25-29.

105. Mayhew E, Ernst E. Acupuncture for fibromyalgia--a systematic review of randomized clinical trials. *Rheumatology* (Oxford). 2007 May;46(5):801-804.

106. De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ; Arthritis Research Campaign working group on complementary and alternative medicines. Evidence for the efficacy of complementary and alternative medicines in the management of fibromyalgia: a systematic review. *Rheumatology* (Oxford). 2010 Jun;49(6):1063-1068.

107. Roizenblatt S, Fregni F, Gimenez R, Wetzel T, Rigonatti SP, Tufik S, Boggio PS, Valle AC. Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: a randomized, sham-controlled study. *Pain Pract*. 2007 Dec;7(4):297-306.

108. Passard A, Attal N, Benadhira R, Brasseur L, Saba G, Sichere P, Perrot S, Januel D, Bouhassira D. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. *Brain*. 2007 Oct;130(Pt 10):2661-2670.

109. Fregni F, Gimenes R, Valle AC, Ferreira MJ, Rocha RR, Natalle L, Bravo R, Rigonatti SP, Freedman SD, Nitsche MA, Pascual-Leone A, Boggio PS. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. *Arthritis Rheum*. 2006 Dec;54(12):3988-3998.

110. Carretero B, Martín MJ, Juan A, Pradana ML, Martín B, Carral M, Jimeno T, Pareja A, Montoya P, Aguirre I, Salva J, Roca M, Gili M, Garcia-Toro M. Low-frequency transcranial magnetic stimulation in patients with fibromyalgia and major depression. *Pain Med*. 2009 May-Jun;10(4):748-753.

111. Haanen HC, Hoenderdos HT, van Romunde LK, Hop WC, Mallee C, Terwiel JP, Hekster GB. Controlled trial of hypnotherapy in the treatment of refractory fibromyalgia. *J Rheumatol*. 1991 Jan;18(1):72-75.

112. National Sleep Foundation. Ask the Sleep Expert: Sleep Hygiene. Available at http://www.sleepfoundation.org/article/ask-the-expert/sleep-hygiene.org. Accessed: October 27, 2010.

113. Gowans SE, deHueck A. Exercise as an intervention for individuals with fibromyalgia. In: McCarberg BH, Clauw DJ, eds. *Fibromyalgia*. New York, NY: Informa Healthcare USA, Inc; 2009:128-135.

114. Jones KD, Liptan GL. Exercise interventions: clinical applications from the evidence. *Rheum Dis Clin N Am*. 2009; 373-391.

115. Fontaine KR, Conn L, Clauw DJ. Effects of lifestyle physical activity on perceived symptoms and physical function in adults with fibromyalgia: results of a randomized trial. *Arthritis Res Ther*. 2010;12:R55.

116. Culpepper L. Nonpharmacologic care of patients with fibromyalgia. *J Clin Psychiatry*. 2010;71(8):e20.

117. Naylor MR, Keefe FJ, Brigidi B, Naud S, Helzer JE. Therapeutic interactive voice response for chronic pain reduction and relapse prevention. *Pain*. 2008;134(3):335-345.

118. Williams DA, Kuper D, Segar M, Mohan N, Sheth M, Clauw DJ. Internet-enhanced management of fibromyalgia: a randomized controlled clinical trial. *Pain*. 2010;151:694-702.

119. Turk DC. Psychological aspects of pain. In: Bakule P, ed. *Expert Guide to Pain Management*. Springhouse, PA: Springhouse Corporation. 1997;124-178.

120. Bonakdar RA. Nonpharmacological, complementary and alternative treatments for fibromyalgia. In: McCarberg BH, Clauw DJ, eds. *Fibromyalgia*. New York, NY: Informa Healthcare USA, Inc; 2009:35-55.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LYRICA safely and effectively. See full prescribing information for LYRICA.

LYRICA (pregabalin) Capsules, CV
LYRICA (pregabalin) Oral Solution, CV
Initial U.S. Approval: 2004

------ INDICATIONS AND USAGE ------

LYRICA is indicated for:

- Neuropathic pain associated with diabetic peripheral neuropathy (DPN) (1.1)
- Post herpetic neuralgia (PHN) (1.2)
- Adjunctive therapy for adult patients with partial onset seizures (1.3)
- Fibromyalgia (1.4)

------ DOSAGE AND ADMINISTRATION ------

DPN Pain (2.1):

- Administer in 3 divided doses per day
- Begin dosing at 150 mg/day
- May be increased to a maximum of 300 mg/day within 1 week.

PHN (2.2):

- Administer in 2 or 3 divided doses per day
- Begin dosing at 150 mg/day
- May be increased to 300 mg/day within 1 week
- Maximum dose of 600 mg/day.

Adjunctive Therapy for Adult Patients with Partial Onset Seizures (2.3):

- Administer in 2 or 3 divided doses per day
- Begin dosing at 150 mg/day
- Maximum dose of 600 mg/day.

Fibromyalgia (2.4):

- Administer in 2 divided doses per day
- Begin dosing at 150 mg/day
- May be increased to 300 mg/day within 1 week
- Maximum dose of 450 mg/day.

Dose should be adjusted in patients with reduced renal function. (2.5)
Oral Solution Concentration and Dispensing (2.6)

------ DOSAGE FORMS AND STRENGTHS ------

- Capsules: 25mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg. (3)
- Oral Solution: 20 mg/ mL. (3)

------ CONTRAINDICATIONS ------

- Known hypersensitivity to pregabalin or any of its components. (4)

----- WARNINGS AND PRECAUTIONS ---

- Angioedema (e.g. swelling of the throat, head and neck) can occur, and may be associated with life-threatening respiratory compromise requiring emergency treatment. Discontinue LYRICA immediately in these cases. (5.1)
- Hypersensitivity reactions (e.g. hives, dyspnea, and wheezing) can occur. Discontinue LYRICA immediately in these patients. (5.2)
- Increased seizure frequency may occur in patients with seizure disorders if LYRICA is rapidly discontinued. Withdraw LYRICA gradually over a minimum of 1 week. (5.3)
- Antiepileptic drugs, including LYRICA, increase the risk of suicidal thoughts or behavior. (5.4)
- LYRICA may cause peripheral edema. Exercise caution when co-administering LYRICA and thiazolidinedione antidiabetic agents. (5.5)
- LYRICA may cause dizziness and somnolence and impair patients' ability to drive or operate machinery.(5.6)

------ ADVERSE REACTIONS ------

Most common adverse reactions (≥ 5% and twice placebo) are dizziness, somnolence, dry mouth, edema, blurred vision, weight gain and thinking abnormal (primarily difficulty with concentration/attention). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at (800) 438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------USE IN SPECIFIC POPULATIONS----------

To enroll in the North American Antiepileptic Drug Pregnancy Registry call 1-888-233-2334 (toll free). (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

Revised: 6/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LYRICA is indicated for:

1.1 Management of neuropathic pain associated with diabetic peripheral neuropathy

1.2 Management of postherpetic neuralgia

1.3 Adjunctive therapy for adult patients with partial onset seizures

1.4 Management of fibromyalgia

2 DOSAGE AND ADMINISTRATION

LYRICA is given orally with or without food.

When discontinuing LYRICA, taper gradually over a minimum of 1 week.

2.1 Neuropathic pain associated with diabetic peripheral neuropathy

The maximum recommended dose of LYRICA is 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Begin dosing at 50 mg three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because LYRICA is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function *[see Dosage and Administration (2.5)]*.

Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended *[see Adverse Reactions (6.1)]*.

2.2 Postherpetic neuralgia

The recommended dose of LYRICA is 75 to 150 mg two times a day, or 50 to 100 mg three times a day (150 to 300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Begin dosing at 75 mg two times a day, or 50 mg three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because LYRICA is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function *[see Dosage and Administration (2.5)]*.

Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 300 mg/day, and who are able to tolerate LYRICA, may be treated with up to 300 mg two times

a day, or 200 mg three times a day (600 mg/day). In view of the dose-dependent adverse reactions and the higher rate of treatment discontinuation due to adverse reactions, reserve dosing above 300 mg/day for those patients who have on-going pain and are tolerating 300 mg daily *[see Adverse Reactions (6.1)]*.

2.3 Adjunctive therapy for adult patients with partial onset seizures

LYRICA at doses of 150 to 600 mg/day has been shown to be effective as adjunctive therapy in the treatment of partial onset seizures in adults. Both the efficacy and adverse event profiles of LYRICA have been shown to be dose-related. Administer the total daily dose in two or three divided doses. In general, it is recommended that patients be started on a total daily dose no greater than 150 mg/day (75 mg two times a day, or 50 mg three times a day). Based on individual patient response and tolerability, the dose may be increased to a maximum dose of 600 mg/day.

Because LYRICA is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function *[see Dosage and Administration (2.5)]*.

The effect of dose escalation rate on the tolerability of LYRICA has not been formally studied.

The efficacy of add-on LYRICA in patients taking gabapentin has not been evaluated in controlled trials. Consequently, dosing recommendations for the use of LYRICA with gabapentin cannot be offered.

2.4 Management of Fibromyalgia

The recommended dose of LYRICA for fibromyalgia is 300 to 450 mg/day. Begin dosing at 75 mg two times a day (150 mg/day). The dose may be increased to 150 mg two times a day (300 mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg two times a day (450 mg/day). Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended *[see Adverse Reactions (6.1)]*. Because LYRICA is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function *[see Dosage and Administration (2.5)]*.

2.5 Patients with Renal Impairment

In view of dose-dependent adverse reactions and since LYRICA is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function. Base the dose adjustment in patients with renal impairment on creatinine clearance (CLcr), as indicated in Table 1. To use this dosing table, an estimate of the patient's CLcr in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

$$CLCr = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \; (\times \; 0.85 \text{ for female patients})$$

Next, refer to the Dosage and Administration section to determine the recommended total daily dose based on indication, for a patient with normal renal function (CLcr ≥60 mL/min). Then refer to Table 1 to determine the corresponding renal adjusted dose.

(For example: A patient initiating LYRICA therapy for postherpetic neuralgia with normal renal function (CLcr ≥60 mL/min), receives a total daily dose of 150 mg/day pregabalin. Therefore, a renal impaired patient with a CLcr of 50 mL/min would receive a total daily dose of 75 mg/day pregabalin administered in two or three divided doses.)

For patients undergoing hemodialysis, adjust the pregabalin daily dose based on renal function. In addition to the daily dose adjustment, administer a supplemental dose immediately following every 4-hour hemodialysis treatment (see Table 1).

Table 1. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	**Total Pregabalin Daily Dose (mg/day)***				**Dose Regimen**
≥60	150	300	450	600	BID or TID
30–60	75	150	225	300	BID or TID
15–30	25–50	75	100–150	150	QD or BID
<15	25	25–50	50–75	75	QD
Supplementary dosage following hemodialysis (mg)†					
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg Patients on the 25–50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg Patients on the 50–75 mg QD regimen: take one supplemental dose of 75 mg or 100 mg Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg					

TID= Three divided doses; BID = Two divided doses; QD = Single daily dose.

* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

† Supplementary dose is a single additional dose.

2.6 Oral Solution Concentration and Dispensing

The oral solution is 20 mg pregabalin per milliliter (mL) and prescriptions should be written in milligrams (mg). The pharmacist will calculate the applicable dose in mL for dispensing (e.g., 150 mg equals 7.5 mL oral solution).

3 DOSAGE FORMS AND STRENGTHS

Capsules: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg
Oral Solution: 20 mg/mL
[see Description (11) and How Supplied/Storage and Handling (16)].

4 CONTRAINDICATIONS

LYRICA is contraindicated in patients with known hypersensitivity to pregabalin or any of its components. Angioedema and hypersensitivity reactions have occurred in patients receiving pregabalin therapy.

5 WARNINGS AND PRECAUTIONS

5.1 Angioedema

There have been postmarketing reports of angioedema in patients during initial and chronic treatment with LYRICA. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Discontinue LYRICA immediately in patients with these symptoms.

Exercise caution when prescribing LYRICA to patients who have had a previous episode of angioedema. In addition, patients who are taking other drugs associated with angioedema (e.g., angiotensin converting enzyme inhibitors [ACE-inhibitors]) may be at increased risk of developing angioedema.

5.2 Hypersensitivity

There have been postmarketing reports of hypersensitivity in patients shortly after initiation of treatment with LYRICA. Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. Discontinue LYRICA immediately in patients with these symptoms.

5.3 Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, withdraw LYRICA gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If LYRICA is discontinued, taper the drug gradually over a minimum of 1 week.

5.4 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including LYRICA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Monitor patients treated with any AED for any indication for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated

patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.
Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2 Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing LYRICA or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Inform patients, their caregivers, and families that LYRICA and other AEDs increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Report behaviors of concern immediately to healthcare providers.

5.5 Peripheral Edema

LYRICA treatment may cause peripheral edema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

In controlled clinical trials the incidence of peripheral edema was 6% in the LYRICA group compared with 2% in the placebo group. In controlled clinical trials, 0.5% of LYRICA patients and 0.2% placebo patients withdrew due to peripheral edema.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with LYRICA only, and 19% (23/120) of patients who were on both LYRICA and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on LYRICA only; and 7.5% (9/120) of patients on both drugs.

As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, exercise caution when co-administering LYRICA and these agents.

Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, exercise caution when using LYRICA in these patients.

5.6 Dizziness and Somnolence

LYRICA may cause dizziness and somnolence. Inform patients that LYRICA-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery *[see Patient Counseling Information (17.5)]*.

In the LYRICA controlled trials, dizziness was experienced by 31% of LYRICA-treated patients compared to 9% of placebo-treated patients; somnolence was experienced by 22% of LYRICA-treated patients compared to 7% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of LYRICA therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse reactions most frequently leading to withdrawal (4% each) from controlled studies. In LYRICA-treated patients reporting these adverse reactions in short-term, controlled studies, dizziness persisted until the last dose in 30% and somnolence persisted until the last dose in 42% of patients.

5.7 Weight Gain

LYRICA treatment may cause weight gain. In LYRICA controlled clinical trials of up to 14 weeks, a gain of 7% or more over baseline weight was observed in 9% of LYRICA-treated patients and 2% of placebo-treated patients. Few patients treated with LYRICA (0.3%) withdrew from controlled trials due to weight gain. LYRICA associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema *[see Warnings and Precautions (5.5)]*.

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of LYRICA-associated weight gain are unknown.

Among diabetic patients, LYRICA-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received LYRICA for at least 2 years, the average weight gain was 5.2 kg.

While the effects of LYRICA-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, LYRICA treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1C}).

5.8 Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache, and diarrhea. Taper LYRICA gradually over a minimum of 1 week rather than discontinuing the drug abruptly.

5.9 Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies of LYRICA, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice *[see Nonclinical Toxicology (13.1)]*. The clinical significance of this finding is unknown. Clinical experience during LYRICA's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients >12 years of age, new or worsening-preexisting tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with LYRICA, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

5.10 Ophthalmological Effects

In controlled studies, a higher proportion of patients treated with LYRICA reported blurred vision (7%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued LYRICA treatment due to vision-related events (primarily blurred vision).

Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with LYRICA, and 5% of placebo-treated patients. Visual field changes were detected in 13% of LYRICA-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of LYRICA-treated and 2% of placebo-treated patients.

Although the clinical significance of the ophthalmologic findings is unknown, inform patients to notify their physician if changes in vision occur. If visual disturbance persists, consider further assessment. Consider more frequent assessment for patients who are already routinely monitored for ocular conditions *[see Patient Counseling Information (17.8)]*.

5.11 Creatine Kinase Elevations

LYRICA treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for LYRICA-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 1.5% of patients on LYRICA and 0.7% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three LYRICA treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and LYRICA is not completely understood because the cases had documented factors that may have caused or contributed to these events. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Discontinue treatment with LYRICA if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

5.12 Decreased Platelet Count

LYRICA treatment was associated with a decrease in platelet count. LYRICA-treated subjects experienced a mean maximal decrease in platelet count of $20 \times 10^3/\mu L$, compared to $11 \times 10^3/\mu L$ in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of LYRICA patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and $<150 \times 10^3/\mu L$. A single LYRICA treated subject developed severe thrombocytopenia with a platelet count less than $20 \times 10^3/\mu L$. In randomized controlled trials, LYRICA was not associated with an increase in bleeding-related adverse reactions.

5.13 PR Interval Prolongation

LYRICA treatment was associated with PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3–6 msec at LYRICA doses ≥300 mg/day. This mean change difference was not associated with an increased risk of PR increase ≥25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse reactions of second or third degree AV block.

Subgroup analyses did not identify an increased risk of PR prolongation in patients with baseline PR prolongation or in patients taking other PR prolonging medications. However, these analyses cannot be considered definitive because of the limited number of patients in these categories.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In all controlled and uncontrolled trials across various patient populations during the premarketing development of LYRICA, more than 10,000 patients have received LYRICA. Approximately 5000 patients were treated for 6 months or more, over 3100 patients were treated for 1 year or longer, and over 1400 patients were treated for at least 2 years.

Adverse Reactions Most Commonly Leading to Discontinuation in All Premarketing Controlled Clinical Studies

In premarketing controlled trials of all populations combined, 14% of patients treated with LYRICA and 7% of patients treated with placebo discontinued prematurely due to adverse reactions. In the LYRICA treatment group, the adverse reactions most frequently leading to discontinuation were dizziness (4%) and somnolence (3%). In the placebo group, 1% of patients withdrew due to dizziness and <1% withdrew due to somnolence. Other adverse reactions that led to discontinuation from controlled trials more frequently in the LYRICA group compared to the placebo group were ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, and peripheral edema (1% each).

Most Common Adverse Reactions in All Premarketing Controlled Clinical Studies

In premarketing controlled trials of all patient populations combined, dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and "thinking abnormal" (primarily difficulty with concentration/attention) were more commonly reported by subjects treated with LYRICA than by subjects treated with placebo (≥5% and twice the rate of that seen in placebo).

Controlled Studies with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Adverse Reactions Leading to Discontinuation

In clinical trials in patients with neuropathic pain associated with diabetic peripheral neuropathy, 9% of patients treated with LYRICA and 4% of patients treated with placebo discontinued prematurely due to adverse reactions. In the LYRICA treatment group, the most common reasons for discontinuation due to adverse reactions were dizziness (3%) and somnolence (2%). In comparison, <1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the LYRICA group than in the placebo group, were asthenia, confusion, and peripheral edema. Each of these events led to withdrawal in approximately 1% of patients.

Most Common Adverse Reactions

Table 3 lists all adverse reactions, regardless of causality, occurring in ≥1% of patients with neuropathic pain associated with diabetic neuropathy in the combined LYRICA group for which the incidence was greater in this combined LYRICA group than in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse reactions with a maximum intensity of "mild" or "moderate".

Table 3 Treatment-emergent adverse reaction incidence in controlled trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all LYRICA than in the placebo group)

Body system - Preferred term	75 mg/day [N=77] %	150 mg/day [N=212] %	300 mg/day [N=321] %	600 mg/day [N=369] %	All PGB* [N=979] %	Placebo [N=459] %
Body as a whole						
Asthenia	4	2	4	7	5	2
Accidental injury	5	2	2	6	4	3
Back pain	0	2	1	2	2	0
Chest pain	4	1	1	2	2	1
Face edema	0	1	1	2	1	0
Digestive system						
Dry mouth	3	2	5	7	5	1
Constipation	0	2	4	6	4	2
Flatulence	3	0	2	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	4	6	9	12	9	2
Weight gain	0	4	4	6	4	0
Edema	0	2	4	2	2	0
Hypoglycemia	1	3	2	1	2	1
Nervous system						

Dizziness	8	9	23	29	21	5
Somnolence	4	6	13	16	12	3
Neuropathy	9	2	2	5	4	3
Ataxia	6	1	2	4	3	1
Vertigo	1	2	2	4	3	1
Confusion	0	1	2	3	2	1
Euphoria	0	0	3	2	2	0
Incoordination	1	0	2	2	2	0
Thinking abnormal[†]	1	0	1	3	2	0
Tremor	1	1	1	2	1	0
Abnormal gait	1	0	1	3	1	0
Amnesia	3	1	0	2	1	0
Nervousness	0	1	1	1	1	0
Respiratory system						
Dyspnea	3	0	2	2	2	1
Special senses						
Blurry vision[‡]	3	1	3	6	4	2
Abnormal vision	1	0	1	1	1	0

* PGB: pregabalin

† Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

‡ Investigator term; summary level term is amblyopia

Controlled Studies in Postherpetic Neuralgia

Adverse Reactions Leading to Discontinuation

In clinical trials in patients with postherpetic neuralgia, 14% of patients treated with LYRICA and 7% of patients treated with placebo discontinued prematurely due to adverse reactions. In the LYRICA treatment group, the most common reasons for discontinuation due to adverse reactions were dizziness (4%) and somnolence (3%). In comparison, less than 1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring in greater frequency in the LYRICA group than in the placebo group, were confusion (2%), as well as peripheral edema, asthenia, ataxia, and abnormal gait (1% each).

Most Common Adverse Reactions

Table 4 lists all adverse reactions, regardless of causality, occurring in ≥ 1% of patients with neuropathic pain associated with postherpetic neuralgia in the combined LYRICA group for which the incidence was greater in this combined LYRICA group than in the placebo group. In addition, an event is included, even if the incidence in the all LYRICA group is not greater than in the placebo group, if the incidence of the event in the 600 mg/day group is more than twice that in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse reactions with a maximum intensity of "mild" or "moderate". Overall, 12.4% of all pregabalin-treated patients and 9.0% of all placebo-treated patients had at least one severe event

while 8% of pregabalin-treated patients and 4.3% of placebo-treated patients had at least one severe treatment-related adverse event.

Table 4 Treatment-emergent adverse reaction incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all LYRICA than in the placebo group)

Body system - Preferred term	75 mg/d [N=84] %	150 mg/d [N=302] %	300 mg/d [N=312] %	600 mg/d [N=154] %	All PGB* [N=852] %	Placebo [N=398] %
Body as a whole						
Infection	14	8	6	3	7	4
Headache	5	9	5	8	7	5
Pain	5	4	5	5	5	4
Accidental injury	4	3	3	5	3	2
Flu syndrome	1	2	2	1	2	1
Face edema	0	2	1	3	2	1
Digestive system						
Dry mouth	7	7	6	15	8	3
Constipation	4	5	5	5	5	2
Flatulence	2	1	2	3	2	1
Vomiting	1	1	3	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	0	8	16	16	12	4
Weight gain	1	2	5	7	4	0
Edema	0	1	2	6	2	1
Musculoskeletal system						
Myasthenia	1	1	1	1	1	0
Nervous system						
Dizziness	11	18	31	37	26	9
Somnolence	8	12	18	25	16	5
Ataxia	1	2	5	9	5	1
Abnormal gait	0	2	4	8	4	1
Confusion	1	2	3	7	3	0
Thinking abnormal†	0	2	1	6	2	2
Incoordination	2	2	1	3	2	0
Amnesia	0	1	1	4	2	0
Speech disorder	0	0	1	3	1	0
Respiratory system						
Bronchitis	0	1	1	3	1	1
Special senses						
Blurry vision‡	1	5	5	9	5	3
Diplopia	0	2	2	4	2	0
Abnormal vision	0	1	2	5	2	0
Eye Disorder	0	1	1	2	1	0

Urogenital System						
Urinary Incontinence	0	1	1	2	1	0

* PGB: pregabalin

† Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

‡ Investigator term; summary level term is amblyopia

Controlled Add-On Studies in Adjunctive Therapy for Adult Patients with Partial Onset Seizures

Adverse Reactions Leading to Discontinuation

Approximately 15% of patients receiving LYRICA and 6% of patients receiving placebo in add-on epilepsy trials discontinued prematurely due to adverse reactions. In the LYRICA treatment group, the adverse reactions most frequently leading to discontinuation were dizziness (6%), ataxia (4%), and somnolence (3%). In comparison, <1% of patients in the placebo group withdrew due to each of these events. Other adverse reactions that led to discontinuation of at least 1% of patients in the LYRICA group and at least twice as frequently compared to the placebo group were asthenia, diplopia, blurred vision, thinking abnormal, nausea, tremor, vertigo, headache, and confusion (which each led to withdrawal in 2% or less of patients).

Most Common Adverse Reactions

Table 5 lists all dose-related adverse reactions occurring in at least 2% of all LYRICA-treated patients. Dose-relatedness was defined as the incidence of the adverse event in the 600 mg/day group was at least 2% greater than the rate in both the placebo and 150 mg/day groups. In these studies, 758 patients received LYRICA and 294 patients received placebo for up to 12 weeks. Because patients were also treated with 1 to 3 other AEDs, it is not possible to determine whether the following adverse reactions can be ascribed to LYRICA alone, or the combination of LYRICA and other AEDs. A majority of pregabalin-treated patients in clinical studies had adverse reactions with a maximum intensity of "mild" or "moderate".

Table 5. Dose-related treatment-emergent adverse reaction incidence in controlled trials in adjunctive therapy for adult patients with partial onset seizures (Events in at least 2% of all LYRICA-treated patients and the adverse reaction in the 600 mg/day group was ≥2% the rate in both the placebo and 150 mg/day groups

Body System - Preferred Term	**150 mg/d [N = 185] %**	**300 mg/d [N = 90] %**	**600 mg/d [N = 395] %**	**All PGB* [N = 670]† %**	**Placebo [N = 294] %**
Body as a Whole					
Accidental Injury	7	11	10	9	5
Pain	3	2	5	4	3
Digestive System					
Increased Appetite	2	3	6	5	1
Dry Mouth	1	2	6	4	1
Constipation	1	1	7	4	2

Metabolic and Nutritional Disorders					
Weight Gain	5	7	16	12	1
Peripheral Edema	3	3	6	5	2
Nervous System					
Dizziness	18	31	38	32	11
Somnolence	11	18	28	22	11
Ataxia	6	10	20	15	4
Tremor	3	7	11	8	4
Thinking Abnormal[‡]	4	8	9	8	2
Amnesia	3	2	6	5	2
Speech Disorder	1	2	7	5	1
Incoordination	1	3	6	4	1
Abnormal Gait	1	3	5	4	0
Twitching	0	4	5	4	1
Confusion	1	2	5	4	2
Myoclonus	1	0	4	2	0
Special Senses					
Blurred Vision[§]	5	8	12	10	4
Diplopia	5	7	12	9	4
Abnormal Vision	3	1	5	4	1

* PGB: pregabalin

† Excludes patients who received the 50 mg dose in Study E1.

‡ Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

§ Investigator term; summary level term is amblyopia.

Controlled Studies with Fibromyalgia

Adverse Reactions Leading to Discontinuation

In clinical trials of patients with fibromyalgia, 19% of patients treated with pregabalin (150–600 mg/day) and 10% of patients treated with placebo discontinued prematurely due to adverse reactions. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse reactions were dizziness (6%) and somnolence (3%). In comparison, <1% of placebo-treated patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin treatment group than in the placebo treatment group, were fatigue, headache, balance disorder, and weight increased. Each of these adverse reactions led to withdrawal in approximately 1% of patients.

Most Common Adverse Reactions

Table 6 lists all adverse reactions, regardless of causality, occurring in ≥2% of patients with fibromyalgia in the ‘all pregabalin’ treatment group for which the incidence was greater than in the placebo treatment group. A majority of pregabalin-treated patients in clinical studies experienced adverse reactions with a maximum intensity of "mild" or "moderate".

Table 6 Treatment-emergent adverse reaction incidence in controlled trials in Fibromyalgia (Events in at least 2% of all LYRICA-treated patients and occurring more frequently in the all pregabalin-group than in the placebo treatment group)

System Organ Class - Preferred term	150 mg/d [N=132] %	300 mg/d [N=502] %	450 mg/d [N=505] %	600 mg/d [N=378] %	All PGB* [N=1517] %	Placebo [N=505] %
Ear and Labyrinth Disorders						
Vertigo	2	2	2	1	2	0
Eye Disorders						
Vision blurred	8	7	7	12	8	1
Gastrointestinal Disorders						
Dry mouth	7	6	9	9	8	2
Constipation	4	4	7	10	7	2
Vomiting	2	3	3	2	3	2
Flatulence	1	1	2	2	2	1
Abdominal distension	2	2	2	2	2	1
General Disorders and Administrative Site Conditions						
Fatigue	5	7	6	8	7	4
Edema peripheral	5	5	6	9	6	2
Chest pain	2	1	1	2	2	1
Feeling abnormal	1	3	2	2	2	0
Edema	1	2	1	2	2	1
Feeling drunk	1	2	1	2	2	0
Infections and Infestations						
Sinusitis	4	5	7	5	5	4
Investigations						
Weight increased	8	10	10	14	11	2
Metabolism and Nutrition Disorders						
Increased appetite	4	3	5	7	5	1
Fluid retention	2	3	3	2	2	1
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	4	3	3	6	4	2
Muscle spasms	2	4	4	4	4	2
Back pain	2	3	4	3	3	3
Nervous System Disorders						
Dizziness	23	31	43	45	38	9
Somnolence	13	18	22	22	20	4
Headache	11	12	14	10	12	12
Disturbance in attention	4	4	6	6	5	1
Balance disorder	2	3	6	9	5	0
Memory impairment	1	3	4	4	3	0
Coordination abnormal	2	1	2	2	2	1
Hypoaesthesia	2	2	3	2	2	1
Lethargy	2	2	1	2	2	0
Tremor	0	1	3	2	2	0
Psychiatric Disorders						
Euphoric Mood	2	5	6	7	6	1
Confusional state	0	2	3	4	3	0
Anxiety	2	2	2	2	2	1
Disorientation	1	0	2	1	2	0

Depression	2	2	2	2	2	2
Respiratory, Thoracic and Mediastinal Disorders						
Pharyngolaryngeal pain	2	1	3	3	2	2

* PGB: pregabalin

Other Adverse Reactions Observed During the Clinical Studies of LYRICA

Following is a list of treatment-emergent adverse reactions reported by patients treated with LYRICA during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse reactions are those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the *Warnings and Precautions* section (5).

Body as a Whole – *Frequent:* Abdominal pain, Allergic reaction, Fever, *Infrequent:* Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction, *Rare:* Anaphylactoid reaction, Ascites, Granuloma, Hangover effect, Intentional Injury, Retroperitoneal Fibrosis, Shock

Cardiovascular System – *Infrequent:* Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope; *Rare:* ST Depressed, Ventricular Fibrillation

Digestive System – *Frequent:* Gastroenteritis, Increased appetite; *Infrequent:* Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema; *Rare:* Aphthous stomatitis, Esophageal Ulcer, Periodontal abscess

Hemic and Lymphatic System – *Frequent:* Ecchymosis; *Infrequent:* Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; *Rare:* Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocythemia

Metabolic and Nutritional Disorders – *Rare:* Glucose Tolerance Decreased, Urate Crystalluria

Musculoskeletal System – *Frequent:* Arthralgia, Leg cramps, Myalgia, Myasthenia; *Infrequent:* Arthrosis; *Rare:* Chondrodystrophy, Generalized Spasm

Nervous System – *Frequent:* Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching; *Infrequent:* Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia, *Rare:* Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions,

Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Guillain-Barré syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Personality disorder, Psychotic depression, Schizophrenic reaction, Sleep disorder, Torticollis, Trismus

Respiratory System – *Rare:* Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn

Skin and Appendages – *Frequent:* Pruritus, *Infrequent:* Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; *Rare:* Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Nail Disorder, Petechial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule

Special senses – *Frequent:* Conjunctivitis, Diplopia, Otitis media, Tinnitus; *Infrequent:* Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; *Rare:* Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis

Urogenital System – *Frequent:* Anorgasmia, Impotence, Urinary frequency, Urinary incontinence; *Infrequent:* Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, Urine abnormality; *Rare:* Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis, Ovarian disorder, Pyelonephritis

Comparison of Gender and Race

The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

6.2 Post-marketing Experience

The following adverse reactions have been identified during postapproval use of LYRICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous System Disorders -– Headache

Gastrointestinal Disorders – Nausea, Diarrhea

Reproductive System and Breast Disorders – Gynecomastia, Breast Enlargement

7 DRUG INTERACTIONS

Since LYRICA is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. *In vitro* and *in vivo* studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between LYRICA and commonly used antiepileptic drugs *[see Clinical Pharmacology (12)]*.

Pharmacodynamics

Multiple oral doses of LYRICA were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when LYRICA was co-administered with these drugs. No clinically important effects on respiration were seen.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) ≥5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at ≥1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established.

When pregnant rabbits were given LYRICA (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD.

In a study in which female rats were dosed with LYRICA (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at ≥ 100 mg/kg and offspring

survival was decreased at ≥250 mg/kg. The effect on offspring survival was pronounced at doses ≥1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at ≥250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD.

There are no adequate and well-controlled studies in pregnant women. Use LYRICA during pregnancy only if the potential benefit justifies the potential risk to the fetus.

To provide information regarding the effects of in utero exposure to LYRICA, physicians are advised to recommend that pregnant patients taking LYRICA enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

8.2 Labor and Delivery

The effects of LYRICA on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures ≥50 times the mean human exposure ($AUC_{(0–24)}$ of 123 µg·hr/mL) at the maximum recommended clinical dose of 600 mg/day.

8.3 Nursing Mothers

It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, decide whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of pregabalin in pediatric patients have not been established.

In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses ≥50 mg/kg. The neurobehavioral changes of acoustic startle persisted at ≥250 mg/kg and locomotor activity and water maze performance at ≥500 mg/kg in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established.

8.5 Geriatric Use

In controlled clinical studies of LYRICA in neuropathic pain associated with diabetic peripheral neuropathy, 246 patients were 65 to 74 years of age, and 73 patients were 75 years of age or older.

In controlled clinical studies of LYRICA in neuropathic pain associated with postherpetic neuralgia, 282 patients were 65 to 74 years of age, and 379 patients were 75 years of age or older.

In controlled clinical studies of LYRICA in epilepsy, there were only 10 patients 65 to 74 years of age, and 2 patients who were 75 years of age or older.

No overall differences in safety and efficacy were observed between these patients and younger patients.

In controlled clinical studies of LYRICA in fibromyalgia, 106 patients were 65 years of age or older. Although the adverse reaction profile was similar between the two age groups, the following neurological adverse reactions were more frequent in patients 65 years of age or older: dizziness, vision blurred, balance disorder, tremor, confusional state, coordination abnormal, and lethargy.

LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function. Because LYRICA is eliminated primarily by renal excretion, adjust the dose for elderly patients with renal impairment *[see Dosage and Administration (2.5)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

LYRICA is a Schedule V controlled substance.

LYRICA is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior).

9.2 Abuse

In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, LYRICA (450mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30mg, single dose). In controlled clinical studies in over 5500 patients, 4 % of LYRICA-treated patients and 1 % of placebo-treated patients overall

reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%.

9.3 Dependence

In clinical studies, following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache or diarrhea *[see Warnings and Precautions (5.8)]*, suggestive of physical dependence.

10 OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

There is limited experience with overdose of LYRICA. The highest reported accidental overdose of LYRICA during the clinical development program was 8000 mg, and there were no notable clinical consequences.

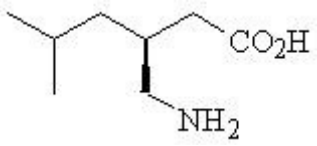
Treatment or Management of Overdose

There is no specific antidote for overdose with LYRICA. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; observe usual precautions to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. Contact a Certified Poison Control Center for up-to-date information on the management of overdose with LYRICA.

Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

11 DESCRIPTION

Pregabalin is described chemically as (*S*)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23. The chemical structure of pregabalin is:



Pregabalin is a white to off-white, crystalline solid with a pK_{a1} of 4.2 and a pK_{a2} of 10.6. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is – 1.35.

LYRICA (pregabalin) Capsules are administered orally and are supplied as imprinted hard-shell capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg of pregabalin, along with lactose monohydrate, cornstarch, and talc as inactive ingredients. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells. The imprinting ink contains shellac, black iron oxide, propylene glycol, and potassium hydroxide.

LYRICA (pregabalin) oral solution, 20 mg/mL, is administered orally and is supplied as a clear, colorless solution contained in a 16 fluid ounce white HDPE bottle with a polyethylene-lined closure. The oral solution contains 20 mg/mL of pregabalin, along with methylparaben, propylparaben, monobasic sodium phosphate anhydrous, dibasic sodium phosphate anhydrous, sucralose, artificial strawberry #11545 and purified water as inactive ingredients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LYRICA (pregabalin) binds with high affinity to the alpha$_2$-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin has not been fully elucidated, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha$_2$-delta subunit may be involved in pregabalin's anti-nociceptive and antiseizure effects in animals. In animal models of nerve damage, pregabalin has been shown to reduce calcium-dependent release of pro-nociceptive neurotransmitters in the spinal cord, possibly by disrupting alpha$_2$-delta containing-calcium channel trafficking and/or reducing calcium currents. Evidence from other animal models of nerve damage and persistent pain suggest the anti-nociceptive activities of pregabalin may also be mediated through interactions with descending noradrenergic and serotonergic pathways originating from the brainstem that modulate pain transmission in the spinal cord.

While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to $GABA_A$, $GABA_B$, or benzodiazepine receptors, does not augment $GABA_A$ responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

12.3 Pharmacokinetics

Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours.

Absorption and Distribution

Following oral administration of LYRICA capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is ≥90% and is independent of dose. Following single- (25 to 300 mg) and multiple- dose (75 to 900 mg/day) administration, maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data.

The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in C_{max} of approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats.

Metabolism and Elimination

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CLcr) *[see Dosage and Administration, (2.5)]*.

Pharmacokinetics in Special Populations

Race

In population pharmacokinetic analyses of the clinical studies in various populations, the pharmacokinetics of LYRICA were not significantly affected by race (Caucasians, Blacks, and Hispanics).

Gender

Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and LYRICA drug exposure is similar between genders.

Renal Impairment and Hemodialysis

Pregabalin clearance is nearly proportional to creatinine clearance (CLcr). Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified [*see Dosage and Administration (2.5)*].

Elderly

Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CLcr. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function [*see Dosage and Administration, (2.5)*].

Pediatric Pharmacokinetics

Pharmacokinetics of pregabalin have not been adequately studied in pediatric patients.

Drug Interactions

In Vitro Studies

Pregabalin, at concentrations that were, in general, 10-times those attained in clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. In vitro drug interaction studies demonstrate that pregabalin does not induce CYP1A2 or CYP3A4 activity. Therefore, an increase in the metabolism of coadministered CYP1A2 substrates (e.g. theophylline, caffeine) or CYP 3A4 substrates (e.g. midazolam, testosterone) is not anticipated.

In Vivo Studies

The drug interaction studies described in this section were conducted in healthy adults, and across various patient populations.

Gabapentin

The pharmacokinetic interactions of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single-dose administration of 100-mg pregabalin and 300-mg gabapentin and in 18 healthy subjects following concomitant multiple-dose administration of 200-mg pregabalin every 8 hours and 400-mg gabapentin every 8 hours. Gabapentin pharmacokinetics following single- and multiple-dose administration were unaltered by

pregabalin coadministration. The extent of pregabalin absorption was unaffected by gabapentin coadministration, although there was a small reduction in rate of absorption.

Oral Contraceptive

Pregabalin coadministration (200 mg three times a day) had no effect on the steady-state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 µg, respectively) in healthy subjects.

Lorazepam

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of lorazepam single-dose pharmacokinetics and single-dose administration of lorazepam (1 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Oxycodone

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of oxycodone single-dose pharmacokinetics. Single-dose administration of oxycodone (10 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Ethanol

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of ethanol single-dose pharmacokinetics and single-dose administration of ethanol (0.7 g/kg) had no effect on the steady-state pharmacokinetics of pregabalin.

Phenytoin, carbamazepine, valproic acid, and lamotrigine

Steady-state trough plasma concentrations of phenytoin, carbamazepine and carbamazepine 10,11 epoxide, valproic acid, and lamotrigine were not affected by concomitant pregabalin (200 mg three times a day) administration.

Population pharmacokinetic analyses in patients treated with pregabalin and various concomitant medications suggest the following:

Therapeutic class	**Specific concomitant drug studied**
Concomitant drug has no effect on the pharmacokinetics of pregabalin	
Hypoglycemics	Glyburide, insulin, metformin
Diuretics	Furosemide
Antiepileptic Drugs	Tiagabine
Concomitant drug has no effect on the pharmacokinetics of pregabalin and pregabalin has no effect on the pharmacokinetics of concomitant drug	

Therapeutic class	Specific concomitant drug studied
Antiepileptic Drugs	Carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for two years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD.

Mutagenesis

Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro*, was not clastogenic in mammalian systems *in vitro* and *in vivo*, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Impairment of Fertility

In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3–4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

In addition, adverse reactions on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD.

In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established.

Human Data

In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo- and pregabalin-treated subjects in mean percent sperm with normal motility was <4% and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied.

13.2 Animal Toxicology and/or Pharmacology

Dermatopathy

Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies.

Ocular Lesions

Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) ≥2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year.

14 CLINICAL STUDIES

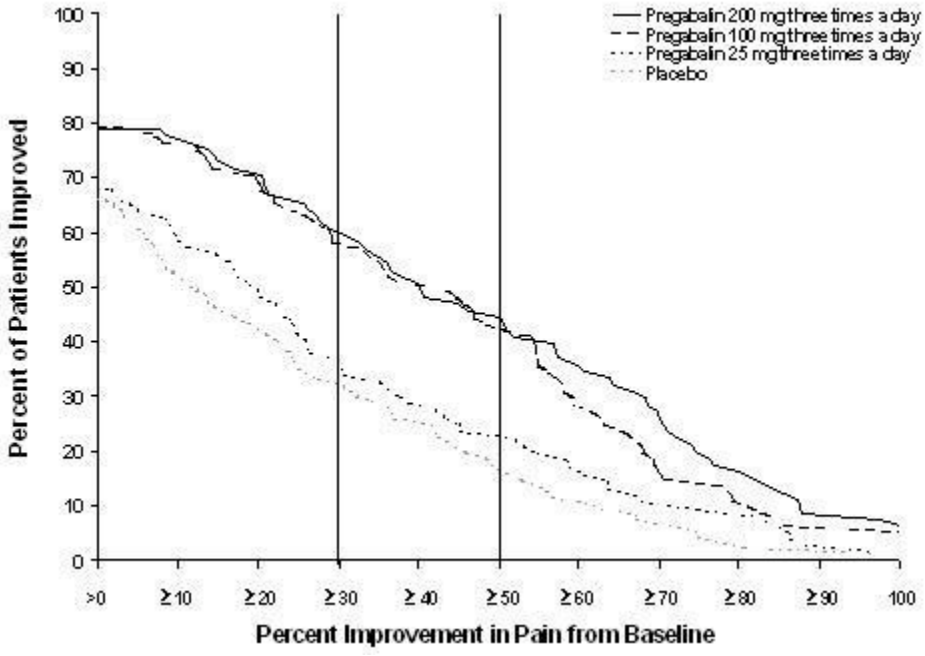
14.1 Neuropathic pain associated with diabetic peripheral neuropathy

The efficacy of the maximum recommended dose of LYRICA for the management of neuropathic pain associated with diabetic peripheral neuropathy was established in three double-blind, placebo-controlled, multicenter studies with three times a day dosing, two of which studied the maximum recommended dose. Patients were enrolled with either Type 1 or Type 2

diabetes mellitus and a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for 1 to 5 years. A total of 89% of patients completed Studies DPN 1 and DPN 2. The patients had a minimum mean baseline pain score of ≥4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). The baseline mean pain scores across the two studies ranged from 6.1 to 6.7. Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to pregabalin. Patients recorded their pain daily in a diary.

Study DPN 1: This 5-week study compared LYRICA 25, 100, or 200 mg three times a day with placebo. Treatment with LYRICA 100 and 200 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. There was no evidence of a greater effect on pain scores of the 200 mg three times a day dose than the 100 mg three times a day dose, but there was evidence of dose dependent adverse reactions *[see Adverse Reactions (6.1)]*. For a range of degrees of improvement in pain from baseline to study endpoint, Figure 1 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

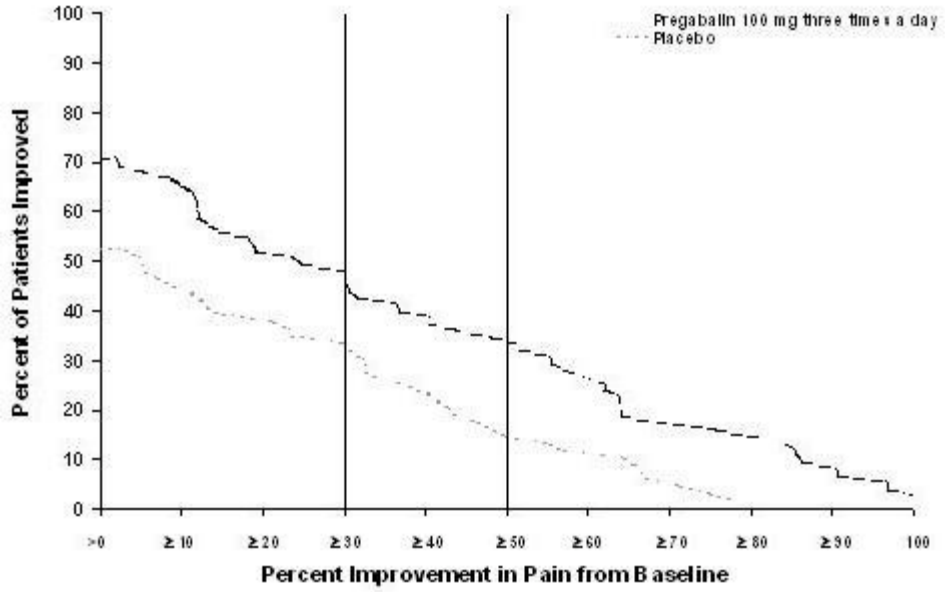
Figure 1: Patients Achieving Various Levels of Pain Relief – Study DPN 1



Study DPN 2: This 8-week study compared LYRICA 100 mg three times a day with placebo. Treatment with LYRICA 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figure 2 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study

were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 2: Patients Achieving Various Levels of Pain Relief – Study DPN 2



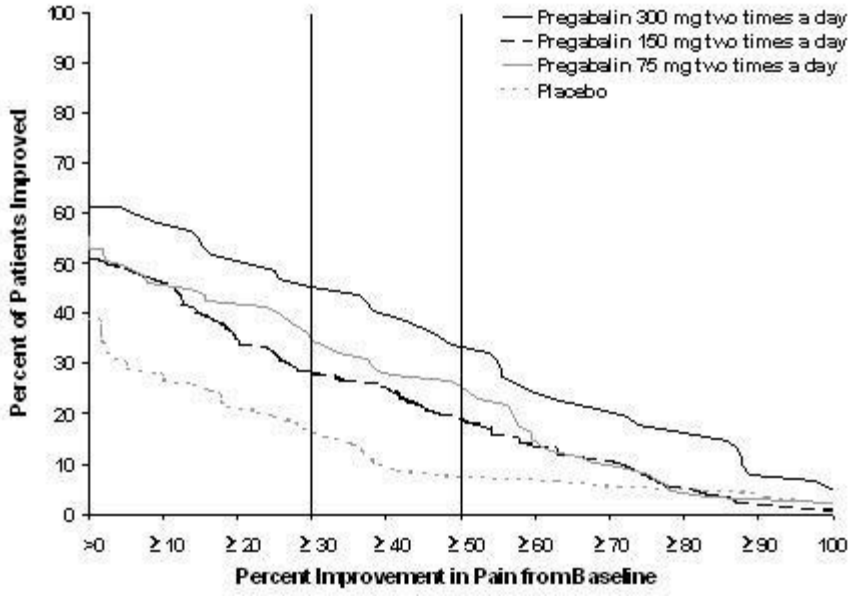
14.2 Postherpetic Neuralgia

The efficacy of LYRICA for the management of postherpetic neuralgia was established in three double-blind, placebo-controlled, multicenter studies. These studies enrolled patients with neuralgia persisting for at least 3 months following healing of herpes zoster rash and a minimum baseline score of ≥4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). Seventy-three percent of patients completed the studies. The baseline mean pain scores across the 3 studies ranged from 6 to 7. Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to pregabalin. Patients recorded their pain daily in a diary.

Study PHN 1: This 13-week study compared LYRICA 75, 150, and 300 mg twice daily with placebo. Patients with creatinine clearance (CLcr) between 30 to 60 mL/min were randomized to 75 mg, 150 mg, or placebo twice daily. Patients with creatinine clearance greater than 60 mL/min were randomized to 75 mg, 150 mg, 300 mg or placebo twice daily. In patients with creatinine clearance greater than 60 mL/min treatment with all doses of LYRICA statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Despite differences in dosing based on renal function, patients with creatinine clearance between 30 to 60 mL/min tolerated LYRICA less well than patients with creatinine clearance greater than 60 mL/min as evidenced by higher rates of discontinuation due to adverse reactions. For various degrees of improvement in pain from baseline to study endpoint, Figure 3 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not

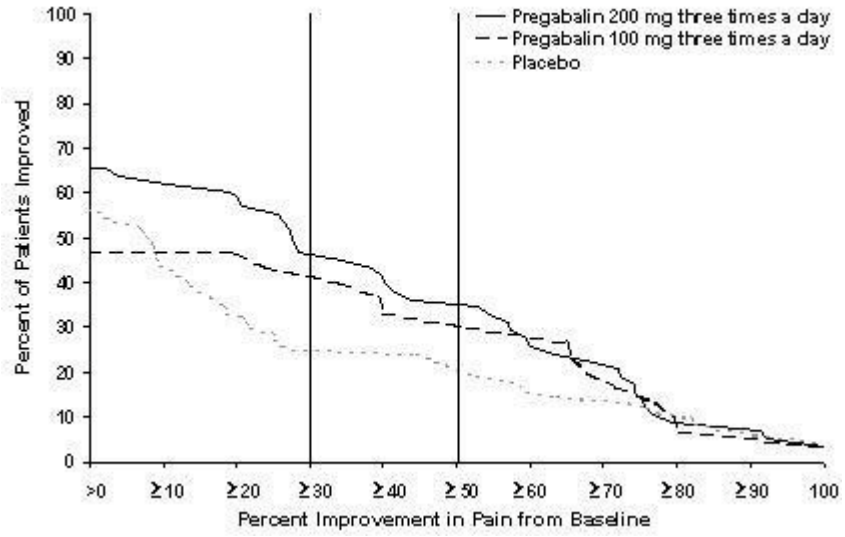
complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 3: Patients Achieving Various Levels of Pain Relief – Study PHN 1



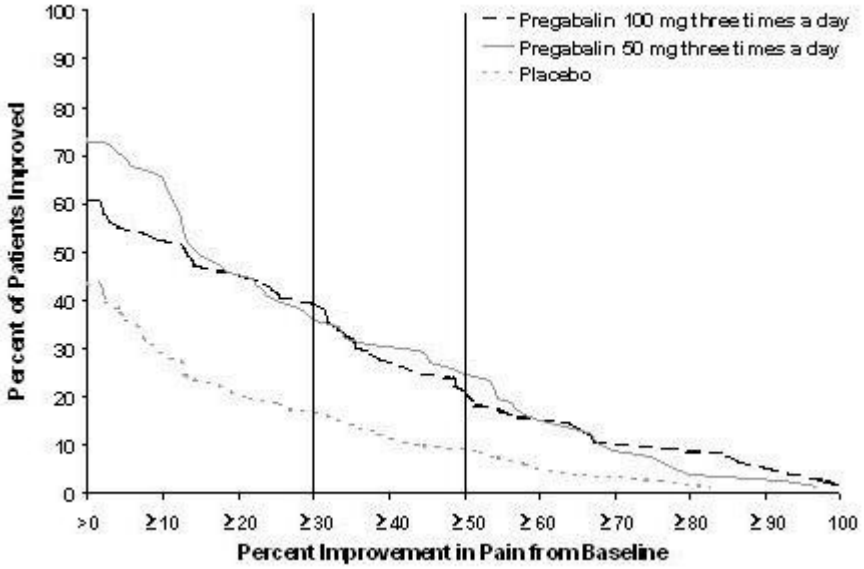
Study PHN 2: This 8-week study compared LYRICA 100 or 200 mg three times a day with placebo, with doses assigned based on creatinine clearance. Patients with creatinine clearance between 30 to 60 mL/min were treated with 100 mg three times a day, and patients with creatinine clearance greater than 60 mL/min were treated with 200 mg three times daily. Treatment with LYRICA statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figure 4 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 4: Patients Achieving Various Levels of Pain Relief – Study PHN 2



Study PHN 3: This 8-week study compared LYRICA 50 or 100 mg three times a day with placebo with doses assigned regardless of creatinine clearance. Treatment with LYRICA 50 and 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Patients with creatinine clearance between 30 to 60 mL/min tolerated LYRICA less well than patients with creatinine clearance greater than 60 mL/min as evidenced by markedly higher rates of discontinuation due to adverse reactions. For various degrees of improvement in pain from baseline to study endpoint, Figure 5 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 5: Patients Achieving Various Levels of Pain Relief – Study PHN 3



14.3 Adjunctive Therapy for Adult Patients with Partial Onset Seizures

The efficacy of LYRICA as adjunctive therapy in partial onset seizures was established in three 12-week, randomized, double-blind, placebo-controlled, multicenter studies in adult patients. Patients were enrolled who had partial onset seizures with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant antiepileptic drugs (AEDs). Patients taking gabapentin were required to discontinue gabapentin treatment 1 week prior to entering baseline. During an 8-week baseline period, patients had to experience at least 6 partial onset seizures with no seizure-free period exceeding 4 weeks. The mean duration of epilepsy was 25 years in these 3 studies and the mean and median baseline seizure frequencies were 22.5 and 10 seizures per month, respectively. Approximately half of the patients were taking 2 concurrent AEDs at baseline. Among the LYRICA-treated patients, 80% completed the double-blind phase of the studies.

Table 7 shows median baseline seizure rates and median percent reduction in seizure frequency by dose.

Table 7: Seizure Response in Controlled, Add-On Epilepsy Studies

Daily Dose of Pregabalin	Dosing Regimen	N	Baseline Seizure Frequency/mo	Median % Change from Baseline	p-value, vs. placebo
Study E1					
Placebo	BID	100	9.5	0	
50 mg/day	BID	88	10.3	-9	0.4230
150 mg/day	BID	86	8.8	-35	0.0001
300 mg/day	BID	90	9.8	-37	0.0001
600 mg/day	BID	89	9.0	-51	0.0001
Study E2					
Placebo	TID	96	9.3	1	
150 mg/day	TID	99	11.5	-17	0.0007
600 mg/day	TID	92	12.3	-43	0.0001
Study E3					
Placebo	BID/TID	98	11	-1	
600 mg/day	BID	103	9.5	-36	0.0001
600 mg/day	TID	111	10	-48	0.0001

In the first study (E1), there was evidence of a dose-response relationship for total daily doses of Lyrica between 150 and 600 mg/day; a dose of 50 mg/day was not effective. In the first study (E1), each daily dose was divided into two equal doses (twice a day dosing). In the second study (E2), each daily dose was divided into three equal doses (three times a day dosing). In the third study (E3), the same total daily dose was divided into two equal doses for one group (twice a day dosing) and three equal doses for another group (three times a day dosing). While the three times a day dosing group in Study E3 performed numerically better than the twice a day dosing group, this difference was small and not statistically significant.

A secondary outcome measure included the responder rate (proportion of patients with ≥50% reduction from baseline in partial seizure frequency). The following figure displays responder rate by dose for two of the studies.

Figure 6. Responder rate by add-on epilepsy study

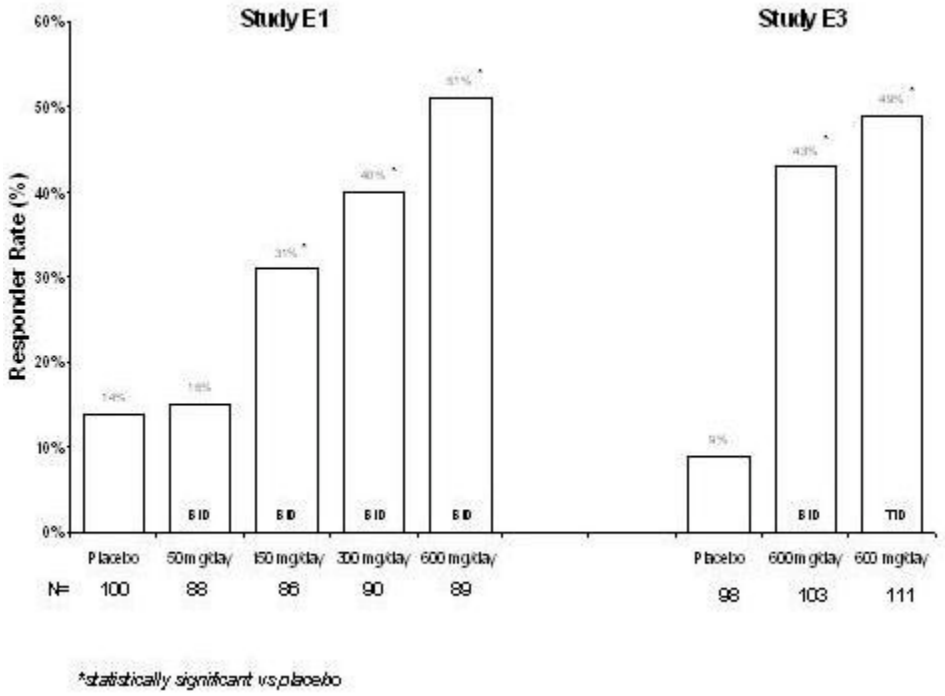
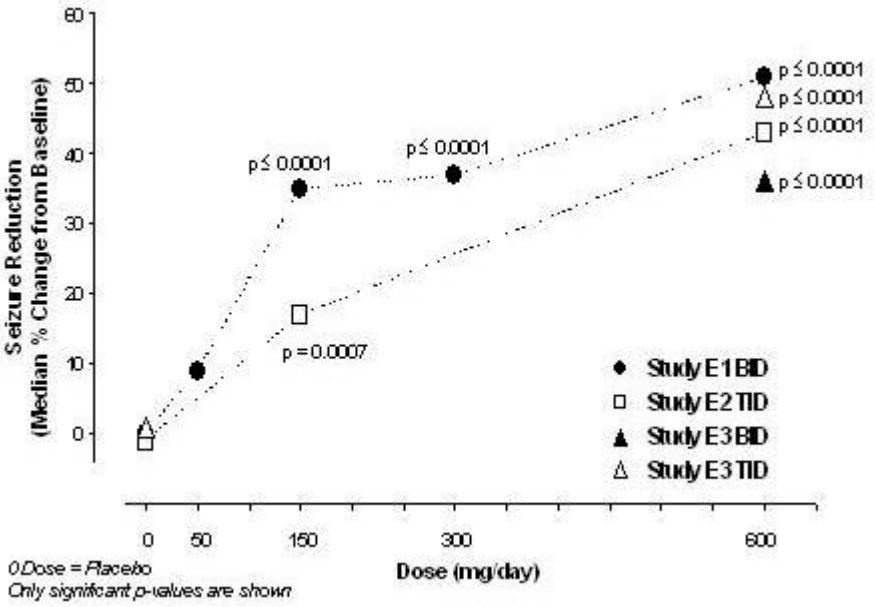


Figure 7. Seizure Reduction by Dose (All Partial Onset Seizures) for Studies E1, E2, and E3



Subset evaluations of the antiseizure efficacy of LYRICA showed no clinically important differences as a function of age, gender, or race.

14.4 Management of Fibromyalgia

The efficacy of LYRICA for management of fibromyalgia was established in one 14-week, double-blind, placebo-controlled, multicenter study (F1) and one six-month, randomized withdrawal study (F2). Studies F1 and F2 enrolled patients with a diagnosis of fibromyalgia using the American College of Rheumatology (ACR) criteria (history of widespread pain for 3 months, and pain present at 11 or more of the 18 specific tender point sites). The studies showed a reduction in pain by visual analog scale. In addition, improvement was demonstrated based on a patient global assessment (PGIC), and on the Fibromyalgia Impact Questionnaire (FIQ).

Study F1: This 14-week study compared LYRICA total daily doses of 300 mg, 450 mg and 600 mg with placebo. Patients were enrolled with a minimum mean baseline pain score of greater than or equal to 4 on an 11-point numeric pain rating scale and a score of greater than or equal to 40 mm on the 100 mm pain visual analog scale (VAS). The baseline mean pain score in this trial was 6.7. Responders to placebo in an initial one-week run-in phase were not randomized into subsequent phases of the study. A total of 64% of patients randomized to LYRICA completed the study. There was no evidence of a greater effect on pain scores of the 600 mg daily dose than the 450 mg daily dose, but there was evidence of dose-dependent adverse reactions [*see Adverse Reactions (6.1)*]. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study. The results are summarized in Figure 8 and Table 8.

For various degrees of improvement in pain from baseline to study endpoint, Figure 8 shows the fraction of patients achieving that degree of improvement. The figure is cumulative. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 8: Patients Achieving Various Levels of Pain Relief – Fibromyalgia Study F1

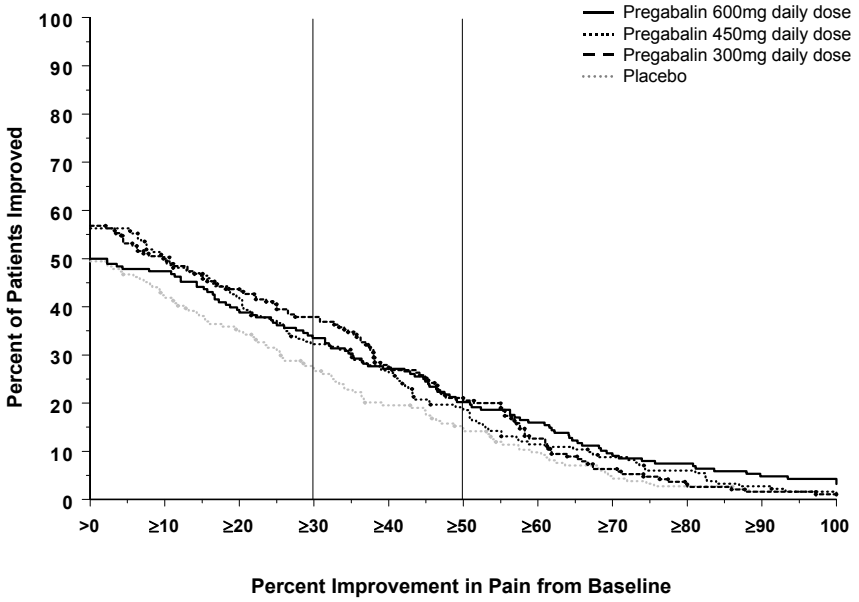


Table 8: Patient Global Response in Fibromyalgia Study F1		
Patient Global Impression of Change		
Treatment Group (mg/day)	**% Any Improvement**	**95% CI**
Placebo	47.6	(40.0,55.2)
PGB 300	68.1	(60.9, 75.3)
PGB 450	77.8	(71.5, 84.0)
PGB 600	66.1	(59.1, 73.1)
PGB = Pregabalin		

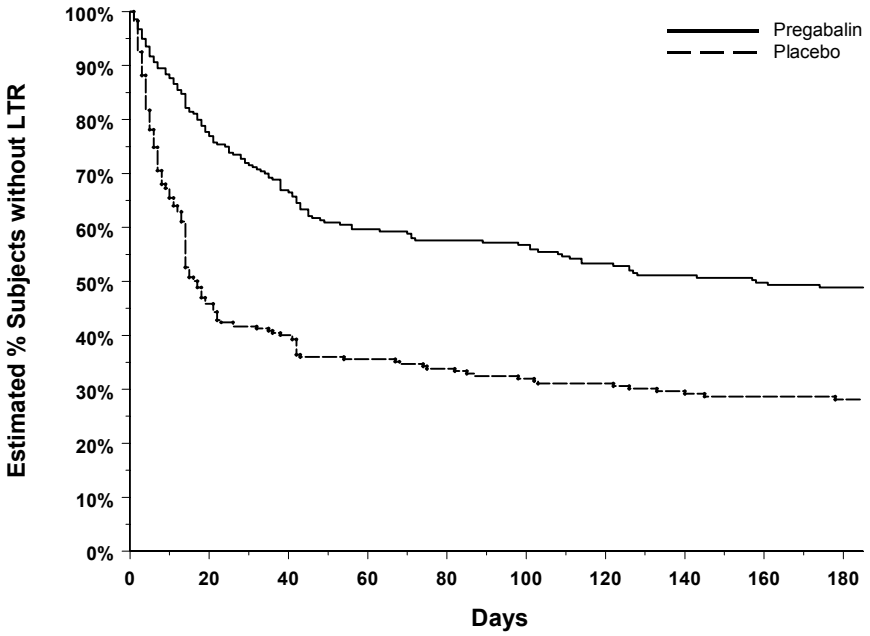
Study F2: This randomized withdrawal study compared LYRICA with placebo. Patients were titrated during a 6-week open-label dose optimization phase to a total daily dose of 300 mg, 450 mg, or 600 mg. Patients were considered to be responders if they had both: 1) at least a 50% reduction in pain (VAS) and, 2) rated their overall improvement on the PGIC as "much improved" or "very much improved." Those who responded to treatment were then randomized in the double-blind treatment phase to either the dose achieved in the open-label phase or to placebo. Patients were treated for up to 6 months following randomization. Efficacy was assessed by time to loss of therapeutic response, defined as 1) less than 30% reduction in pain (VAS) from open-label baseline during two consecutive visits of the double-blind phase, or 2) worsening of FM symptoms necessitating an alternative treatment. Fifty-four percent of patients were able to titrate to an effective and tolerable dose of LYRICA during the 6-week open-label phase. Of the patients entering the randomized treatment phase assigned to remain on LYRICA, 38% of patients completed 26 weeks of treatment versus 19% of placebo-treated patients.

When considering return of pain or withdrawal due to adverse events as loss of response (LTR), treatment with LYRICA resulted in a longer time to loss of therapeutic response than treatment with placebo. Fifty-three percent of the pregabalin-treated subjects compared to 33% of placebo patients remained on study drug and maintained a therapeutic response to Week 26 of the study. Treatment with LYRICA also resulted in a longer time to loss of response based on the FIQ[1], and longer time to loss of overall assessment of patient status, as measured by the PGIC[2].

[1] Time to worsening of the FIQ was defined as the time to a 1-point increase from double-blind baseline in each of the subscales, and a 5-point increase from double-blind baseline evaluation for the FIQ total score.

[2] Time to PGIC lack of improvement was defined as time to PGIC assessments indicating less improvement than "much improvement."

Figure 9: Time to Loss of Therapeutic Response, Fibromyalgia Study F2 (Kaplan-Meier Analysis)



16 HOW SUPPLIED/STORAGE AND HANDLING

25 mg capsules:

White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 25" on the body; available in:

Bottles of 90: NDC 0071-1012-68

50 mg capsules:

White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 50" and an ink band on the body, available in:

Bottles of 90: NDC 0071-1013-68

Unit-Dose Blister Packages of 100: NDC 0071-1013-41

75 mg capsules:

White/orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 75" on the body; available in:

Bottles of 90: NDC 0071-1014-68

Unit-Dose Blister Packages of 100: NDC 0071-1014-41

100 mg capsules:

Orange, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 100" on the body, available in:

Bottles of 90: NDC 0071-1015-68

Unit-Dose Blister Packages of 100: NDC 0071-1015-41

150 mg capsules:

White hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 150" on the body, available in:

Bottles of 90: NDC 0071-1016-68

Unit-Dose Blister Packages of 100: NDC 0071-1016-41

200 mg capsules:

Light orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 200" on the body, available in:

Bottles of 90: NDC 0071-1017-68

225 mg capsules:

White/light orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 225" on the body; available in:

Bottles of 90: NDC 0071-1019-68

300 mg capsules:

White/orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 300" on the body, available in:

Bottles of 90: NDC 0071-1018-68

20 mg/mL oral solution:

16 fluid ounce white high density polyethylene (HDPE) bottle with a polyethylene-lined closure:

16 fluid ounce bottle NDC 0071-1020-01

Storage and Handling

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).

See FDA-Approved Medication Guide

17 PATIENT COUNSELING INFORMATION

17.1 Medication Guide

Inform patients of the availability of a Medication Guide, and instruct them to read the Medication Guide prior to taking LYRICA. Instruct patients to take LYRICA only as prescribed.

17.2 Angioedema

Advise patients that LYRICA may cause angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Instruct patients to discontinue LYRICA and immediately seek medical care if they experience these symptoms [*see Warnings and Precautions (5.1)*].

17.3 Hypersensitivity

Advise patients that LYRICA has been associated with hypersensitivity reactions such as wheezing, dyspnea, rash, hives, and blisters. Instruct patients to discontinue LYRICA and immediately seek medical care if they experience these symptoms *[see Warnings and Precautions (5.2)*].

17.4 Suicidal Thinking and Behavior

Patients, their caregivers, and families should be counseled that AEDs, including LYRICA, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Report behaviors of concern immediately to healthcare providers *[see Warnings and Precautions (5.4)]*.

17.5 Dizziness and Somnolence

Counsel patients that LYRICA may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, advise patients not to drive, operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on LYRICA to

gauge whether or not it affects their mental, visual, and/or motor performance adversely. *[see Warnings and Precautions (5.6)]*.

17.6 Weight Gain and Edema

Counsel patients that LYRICA may cause edema and weight gain. Advise patients that concomitant treatment with LYRICA and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure. *[see Warnings and Precautions (5.5 and 5.7)]*.

17.7 Abrupt or Rapid Discontinuation

Advise patients to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, or diarrhea. *[see Warnings and Precautions (5.8)]*.

17.8 Ophthalmological Effects

Counsel patients that LYRICA may cause visual disturbances. Inform patients that if changes in vision occur, they should notify their physician *[see Warnings and Precautions (5.10)]*.

17.9 Creatine Kinase Elevations

Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. *[see Warnings and Precautions (5.11)]*.

17.10 CNS Depressants

Inform patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines that they may experience additive CNS side effects, such as somnolence.

17.11 Alcohol

Tell patients to avoid consuming alcohol while taking LYRICA, as LYRICA may potentiate the impairment of motor skills and sedating effects of alcohol.

17.12 Use in Pregnancy

Instruct patients to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy *[see Use In Specific Populations (8.1) and (8.3)]*.

Encourage patients to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 *[see Use In Specific Populations (8.1)]*.

17.13 Male Fertility

Inform men being treated with LYRICA who plan to father a child of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain *[see Nonclinical Toxicology (13.1)]*.

17.14 Dermatopathy

Instruct diabetic patients to pay particular attention to skin integrity while being treated with LYRICA. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with LYRICA was observed in clinical trials *[see Nonclinical Toxicology (13.2)]*.

Capsules manufactured by:
Pfizer Pharmaceuticals LLC
Vega Baja, PR 00694

Oral Solution manufactured by:
Pfizer Inc
Kalamazoo, MI 49001

Distributed by
Parke-Davis
Division of Pfizer Inc, NY, NY 10017

LAB-0294-21.0
Revised: 6/2011

MEDICATION GUIDE

LYRICA (LEER-i-kah)

(pregabalin)

Capsules and Oral Solution, CV

Read this Medication Guide before you start taking LYRICA and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about LYRICA, ask your healthcare provider or pharmacist.

What is the most important information I should know about LYRICA?

LYRICA may cause serious side effects including:

- **Serious, even life-threatening, allergic reactions**
- **Suicidal thoughts or actions**
- **Swelling of your hands, legs and feet**
- **Dizziness and sleepiness**

These serious side effects are described below:

1. **Serious, even life-threatening, allergic reactions.**

   Stop taking LYRICA and call your healthcare provider right away if you have any of these signs of a serious allergic reaction:
   - swelling of your face, mouth, lips, gums, tongue, throat or neck
   - trouble breathing
   - rash, hives (raised bumps) or blisters

2. **Like other antiepileptic drugs, LYRICA may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

   Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
   - thoughts about suicide or dying
   - attempts to commit suicide
   - new or worse depression
   - new or worse anxiety
   - feeling agitated or restless
   - panic attacks
   - trouble sleeping (insomnia)
   - new or worse irritability
   - acting aggressive, being angry, or violent

- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

If you have suicidal thoughts or actions, do not stop LYRICA without first talking to a healthcare provider.

- Stopping LYRICA suddenly can cause serious problems.
- Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

3. **Swelling of your hands, legs and feet**. This swelling can be a serious problem for people with heart problems.

4. **Dizziness and sleepiness.**
   Do not drive a car, work with machines, or do other dangerous activities until you know how LYRICA affects you. Ask your healthcare provider about when it will be okay to do these activities.

What is LYRICA?

LYRICA is a prescription medicine used in adults, 18 years and older, to treat:

- pain from damaged nerves (neuropathic pain) that happens with diabetes
- pain from damaged nerves (neuropathic pain) that follows healing of shingles
- partial seizures when taken together with other seizure medicines
- fibromyalgia (pain all over your body)

LYRICA has not been studied in children under 18 years of age.

Who Should Not Take LYRICA?

Do not take LYRICA if you are allergic to pregabalin or any of the ingredients in LYRICA.

See “What is the most important information I should know about LYRICA?” for the signs of an allergic reaction.

See the end of this leaflet for a complete list of ingredients in LYRICA.

What should I tell my healthcare provider before taking LYRICA?

Before taking LYRICA, tell your healthcare provider about all your medical conditions, including if you:

- have or have had depression, mood problems or suicidal thoughts or behavior
- have kidney problems or get kidney dialysis
- have heart problems including heart failure
- have a bleeding problem or a low blood platelet count
- have abused prescription medicines, street drugs, or alcohol in the past
- have ever had swelling of your face, mouth, tongue, lips, gums, neck, or throat (angioedema)
- plan to father a child. Animal studies have shown that pregabalin, the active ingredient in LYRICA, made male animals less fertile and caused sperm to change. Also, in animal studies, birth defects were seen in the offspring (babies) of male animals treated with pregabalin. It is not known if these problems can happen in people who take LYRICA.
- **are pregnant or plan to become pregnant. It is not known if LYRICA will harm your unborn baby.** You and your healthcare provider will have to decide if you should take LYRICA while you are pregnant. If you become pregnant while taking LYRICA, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.
- **are breastfeeding. It is not known if LYRICA passes into breast milk and if it can harm your baby.** You and your healthcare provider should discuss whether you should take LYRICA or breast-feed, but you should not do both

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins or herbal supplements. LYRICA and other medicines may affect each other causing side effects. Especially tell your healthcare provider if you take:

- angiotensin converting enzyme (ACE) inhibitors, which are used to treat many conditions, including high blood pressure. You may have a higher chance for swelling and hives if these medicines are taken with LYRICA. See "What is the most important information I should know about LYRICA?"

- Avandia (rosiglitazone), Avandamet (contains rosiglitazone and metformin), or Actos (pioglitazone) for diabetes. You may have a higher chance of weight gain or swelling of your hands or feet if these medicines are taken with LYRICA. See "What are the possible side effects of LYRICA."
- any narcotic pain medicine (such as oxycodone), tranquilizers or medicines for anxiety (such as lorazepam). You may have a higher chance for dizziness and sleepiness if these medicines are taken with LYRICA.
- any medicines that make you sleepy

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist each time you get a new medicine. Do not start a new medicine without talking with your healthcare provider.

How should I take LYRICA?

- Take LYRICA exactly as prescribed. Your healthcare provider will tell you how much LYRICA to take and when to take it. Take LYRICA at the same times each day.
- LYRICA may be taken with or without food.
- Your healthcare provider may change your dose. Do not change your dose without talking to your healthcare provider.
- Do not stop taking LYRICA without talking to your healthcare provider. If you stop taking LYRICA suddenly you may have headaches, nausea, diarrhea or trouble sleeping. If you have epilepsy and you stop taking LYRICA suddenly, you may have seizures more often. Talk with your healthcare provider about how to stop LYRICA slowly.
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, just skip the missed dose. Take the next dose at your regular time. **Do not take two doses at the same time.**
- If you take too much LYRICA, call your healthcare provider or poison control center, or go to the nearest emergency room right away.

What should I avoid while taking LYRICA?

- **Do not drive a car, work with machines, or do other dangerous activities until you know how LYRICA affects you.**
- **Do not drink alcohol while taking LYRICA.** LYRICA and alcohol can affect each other and increase side effects such as sleepiness and dizziness.

What are the possible side effects of LYRICA?

LYRICA may cause serious side effects, including:

- See “What is the most important information I should know about LYRICA?"

- **muscle problems, muscle pain, soreness, or weakness**. If you have these symptoms, especially if you feel sick and have a fever, tell your healthcare provider right away.
- **problems with your eyesight, including blurry vision.** Call your healthcare provider if you have any changes in your eyesight.
- **weight gain.** If you have diabetes, weight gain may affect the management of your diabetes. Weight gain can also be a serious problem for people with heart problems.
- **feeling "high"**

The most common side effects of LYRICA are:

- dizziness
- blurry vision
- weight gain
- sleepiness
- trouble concentrating
- swelling of hands and feet
- dry mouth

LYRICA caused skin sores in animal studies. Skin sores did not happen in studies in people. If you have diabetes, you should pay attention to your skin while taking LYRICA and tell your healthcare provider about any sores or skin problems.

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of LYRICA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LYRICA?

- Store LYRICA capsules and oral solution at room temperature, 59°F to 86°F (15°C to 30°C) in its original package.
- Safely throw away any LYRICA that is out of date or no longer needed.
- **Keep LYRICA and all medicines out of the reach of children.**

General information about LYRICA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LYRICA for a condition for which it was not prescribed. Do not give LYRICA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about LYRICA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about LYRICA that is written for health professionals.

You can also visit the LYRICA website at www.LYRICA.com or call 1-866-459-7422 (1-866-4LYRICA).

What are the ingredients In LYRICA?

Active ingredient: pregabalin

Inactive ingredients:

LYRICA capsules: lactose monohydrate, cornstarch, talc

Capsule shell: gelatin and titanium dioxide; Orange capsule shell: red iron oxide; White capsule shell: sodium lauryl sulfate, colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells.

Imprinting ink: shellac, black iron oxide, propylene glycol, potassium hydroxide.

LYRICA oral solution: methylparaben, propylparaben, monobasic sodium phosphate anhydrous, dibasic sodium phosphate anhydrous, sucralose, artificial strawberry #11545 and purified water.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Vega Baja, PR 00694

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