

Fibromyalgia Management

Prepared for West Virginia Medicaid by ACS Rx Delivery Services

Initial Study

Follow-up/Restudy

EXECUTIVE SUMMARY

Purpose: Fibromyalgia Syndrome (FMS) is estimated to affect 5 million Americans age 18 years and older, 80% to 90% of them women.¹ It is the second most common disorder seen by rheumatologists in the United States (after osteoarthritis); however, it is estimated that they provide care for less than 20% of those with FMS.² FMS patients typically present with widespread musculoskeletal pain, sleep disturbances, and fatigue. The recommendations in this intervention are based on the treatment guidelines published by the American Pain Society and other current literature.³⁻⁵

Why Issue was Selected: During a recent 30 day period, there were approximately 800 patients identified who had a diagnosis of FMS in the West Virginia Medicaid population and who were receiving pharmacotherapy related to that diagnosis.

Program Specific Information:	Performance Indicators	Exceptions
	• Trial of low-dose tricyclic compounds as first-line therapy in FMS	76
	• Use of milnacipran without a diagnosis of FMS	21
	• Pharmacotherapy for FMS at higher than recommended dose	13
	• Chronic use of sedative/hypnotic agents in FMS	117
	• Use of opiates or NSAIDs for pain management in FMS	122

Setting & Population: All patients with a diagnosis of fibromyalgia in the past 2 years receiving therapy with targeted medications (see Appendix A) in the past 30 days.

Type of Intervention: Cover letter and Modified Profiles.

Main Outcome Measures: The performance indicators in this proposal will be reassessed.

Anticipated Results: Improve the overall care of FMS patients through the following:

- Reduce the risk of adverse events that may occur with the use of high daily doses of pharmacotherapy for FMS,
- Improve the cost-benefit ratio of FMS therapy by encouraging use of TCAs as first-line therapy for FMS,
- Identify use of milnacipran for unproven off-label uses,
- Minimize the chronic use of sedative/hypnotic agents in the management of sleep disturbances associated with FMS,
- Encourage appropriate pain management therapy in patients with FMS.

PURPOSE OF INTERVENTION

Fibromyalgia Syndrome (FMS) is estimated to affect 5 million Americans age 18 years and older, 80% to 90% of them women.¹ It is the second most common disorder seen by rheumatologists in the United States (after osteoarthritis); however, it is estimated that they provide care for less than 20% of those with FMS.² FMS patients typically present with widespread musculoskeletal pain, sleep disturbances, and fatigue. The recommendations in this intervention are based on the treatment guidelines published by the American Pain Society and other current literature.³⁻⁵

WHY HAS THIS CLINICAL ISSUE BEEN SELECTED FOR REVIEW?

Fibromyalgia means connective tissue and muscle pain. The disorder is characterized by widespread chronic pain. However, since it frequently involves many other symptoms, fibromyalgia is now more commonly called fibromyalgia syndrome (FMS). It is a syndrome rather than a disease, meaning it is a collection of signs and symptoms that tend to occur together but are not related to a specific, identifiable cause.¹ In addition to pain; sleep disturbances, fatigue, and morning stiffness are present in over 73% of FMS patients. Other common symptoms include headaches, cognitive impairment, depression, paresthesias, bowel or bladder symptoms, and anxiety.⁶

The treatment of FMS is symptomatic and supportive, and pharmacotherapy is commonly employed. Non-pharmacologic measures are also very important, but are beyond the scope of this discussion. Pharmacotherapy for FMS can be challenging, and approximately 500 peer-reviewed articles were published before any medications gained FDA approval to treat the indication.³ Since 2007, three agents have received the indication for this condition: Lyrica® (pregabalin), an anticonvulsant which gained the indication in 2007; Cymbalta® (duloxetine), an antidepressant which gained the indication in 2008; and Savella® (milnacipran), which received FDA approval in January of 2009 specifically for the treatment of FMS.⁷⁻⁹

In 2004, before any agents gained official approval for this indication, the American Pain Society issued evidence-based treatment guidelines for the management of FMS.³ They recommended a stepwise approach to management that emphasized education, medications, exercise, and cognitive therapy. The medications rated as having “strong evidence for efficacy” were amitriptyline (a tricyclic antidepressant or TCA) and cyclobenzaprine (a tricyclic compound FDA approved as a muscle relaxant). Those rated as having “modest evidence for efficacy” were the analgesic tramadol, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and pregabalin. The three agents that now have FDA approval for this indication, pregabalin and the two SNRIs duloxetine and milnacipran, were each the subject of one randomized controlled trial at the time the treatment guidelines were published.

Response to pharmacotherapy in FMS is generally not robust. According to official prescribing information: with pregabalin approximately 25% of patients experienced a 50% or greater reduction in symptoms; with duloxetine approximately 35% experienced a 50% or greater reduction; while with milnacipran approximately 25% experienced a 50% or greater reduction of symptoms.⁷⁻⁹ These rates are very similar to those documented in studies over the years with the older agents: 25% to 37% for tricyclic compounds or tramadol.³ A recent meta-analysis of antidepressant efficacy in FMS found improvement with several agents and yielded the following standardized mean differences:⁵

Medication	Pain (95% CI)	Fatigue (95% CI)	Sleep (95% CI)
Tricyclic Antidepressants	-1.64 (-2.57 to -0.71) P = <0.001	-1.12 (-1.87 to -0.38) P = 0.003	-1.84 (-2.62 to -1.06) P = <0.001
SSRIs	-0.39 (-0.77 to -0.01) P = 0.04	-0.17 (-0.47 to 0.12) P = 0.25	-0.23 (-0.56 to 0.10) P = 0.18
SNRIs	-0.36 (-0.46 to -0.25) P = <0.001	-0.06 (-0.20 to -0.06) P = 0.23	-0.31 (-0.47 to -0.14) P = <0.001

The response rates for all agents used to treat FMS appear to be similar, although the exact symptoms that respond best and an individual patient’s response might be different with different agents. Therefore, the 2004 guidelines recommending a trial of a tricyclic compound appear to still be valid.⁴ In addition, when

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improvement rates are similar, cost of therapy should be considered when choosing an agent. Such a consideration definitely favors a tricyclic compound.

Regardless of which agent is chosen, dose is an important consideration. For the tricyclic antidepressants lower definitely appears to be better, both in terms of response and tolerability.^{3,5} For TCAs, doses as low as 10 to 25 mg/day have been reported to be beneficial while doses above 150 mg/day tend to have limited benefit and an increased risk of adverse effects. For the newer, FDA approved agents, effective doses for FMS also appear to be lower than doses that may be needed when treating other conditions for which they are effective. In pregabalin studies three doses were evaluated, 300mg, 450mg, and 600mg/day. There was no evidence of greater efficacy for the 600mg/day dose over the lower doses while the higher dose was associated with more adverse effects. The maximum recommended dose for FMS is 450 mg/day.⁷ Duloxetine was studied at 60 to 120 mg/day and again the higher dose did not demonstrate additional benefits and was associated with more adverse effects. The recommended duloxetine dose for FMS is 60 mg/day.⁸ Milnacipran is only FDA approved for FMS. It was studied at doses of 100 or 200 mg/day with similar results. The recommended dose is 100 mg/day but, based on individual response the dose may be increased to 200 mg/day.⁹

Pain is the most common complaint in FMS and is one of the primary target symptoms for most patients. When first-line therapies discussed above do not provide adequate pain relief, additional analgesics may be necessary and appropriate. However, the selection of appropriate agent should be guided by the literature which indicates tramadol is the analgesic of choice in FMS.^{3,4,11} Other commonly used analgesic agents, such as the nonsteroidal anti-inflammatory drugs (NSAIDs) or opiate analgesics, have not been shown to be effective for the pain of FMS. Sleep disturbances are also common in FMS patients, and different first-line agents for FMS appear to have different efficacy for these symptoms.^{3,10} The TCAs appear to be among the most effective agents for treating sleep disturbance in FMS.⁵ Among the newer agents, duloxetine and pregabalin appear to be more beneficial than milnacipran.¹⁰ Traditional sedative hypnotic agents may be useful as adjunctive therapy for sleep complaints in FMS patients. However, they have no effect on other FMS symptoms and their use should be limited and not chronic.^{3,11}

SETTING AND POPULATION

Date Range of Analysis:	To be determined for each client.
Business Units Reviewed:	To be determined for each client.
Estimated Date of Mailing:	To be determined for each client.

PERFORMANCE INDICATORS

Indicator #1: Trial of Low-Dose Tricyclic Compound as First-Line FMS Therapy

Why has this indicator been selected?	Treatment guidelines and other current literature continue to recommend low-dose tricyclic therapy as first-line for FMS. In the absence of comorbid conditions that would provide an additional indication for newer agents, a tricyclic trial is indicated. ³⁻⁵
How will the patients be selected?	
Candidates (denominator):	Patients with a diagnosis of fibromyalgia syndrome in the past 2 years who have been receiving duloxetine, milnacipran, or pregabalin therapy in the past 30 days.
Exception criteria (numerator):	Candidates who lack therapy with a TCA or cyclobenzaprine in the past 730 days, or do not have the following comorbid condition to justify the use of a non-tricyclic compound as first-line for FMS: <ul style="list-style-type: none">- duloxetine = major depression, generalized anxiety disorder, or neuropathic pain- milnacipran = no other indications- pregabalin = seizure disorder or neuropathic pain

Indicator #2: Use of Milnacipran Without a Diagnosis of FMS

Why has this indicator been selected? Milnacipran, a serotonin-norepinephrine reuptake inhibitor, is only FDA approved for the management of fibromyalgia.⁹

How will the patients be selected?

Candidates (denominator): Patients who have been receiving milnacipran therapy in the past 30 days.
Exception Criteria (numerator): Candidates who do not with a diagnosis of fibromyalgia syndrome in the past 2 years.

Indicator #3: Pharmacotherapy for FMS at Higher than Recommended Daily Dose

Why has this indicator been selected? The daily doses shown to be effective in the management of FMS are frequently lower than when the same medications are used to treat other approved indications.^{3,5,7-9}

How will the patients be selected?

Candidates (denominator): Patients with a diagnosis of fibromyalgia syndrome in the past 2 years who have been receiving duloxetine, milnacipran, pregabalin or tricyclic therapy in the past 30 days.
Exception Criteria (numerator): Candidates whose daily dose is higher than the recommended daily dose for FMS (see Appendix B) unless the following comorbid conditions are present to justify the use of a higher daily dose:

- duloxetine = major depression, generalized anxiety disorder, or neuropathic pain
- milnacipran = no other indications
- pregabalin = seizure disorder or neuropathic pain
- tricyclic antidepressant = major depression

Indicator #4: Chronic Use of a Sedative/Hypnotic Agent in FMS

Why has this indicator been selected? Traditional sedative hypnotic agents may be useful as adjunctive therapy for sleep complaints in FMS patients, however, they have no effect on other FMS symptoms and their use should be limited and not chronic.^{3,11}

How will the patients be selected?

Candidates (denominator): Patients with a diagnosis of fibromyalgia syndrome in the past 2 years who have been receiving benzodiazepine or non-benzodiazepine sedative/hypnotic therapy in the past 30 days.
Exception Criteria (numerator): Candidates who have received more than 35 days of sedative/hypnotic therapy in the past 60 days and have not received a tricyclic compound.

Indicator #5: Use of Opiates or NSAIDs for Pain Management in FMS

Why has this indicator been selected? Pain is a common target symptom in FMS but the literature indicates NSAIDs or opiate analgesics are minimally effective in these patients, with tramadol being the analgesic of choice in FMS.^{3,4,11}

How will the patients be selected?

Candidates (denominator): Patients with a diagnosis of fibromyalgia syndrome in the past 2 years who have been receiving opiate or NSAID therapy in the past 30 days.
Exception Criteria (numerator): Candidates who have not received therapy with tramadol in the past 730 days AND have received more than 60 days of opiate or NSAID therapy in the past 90 days but do not have a diagnosis of another chronic pain condition.

INTERVENTION MATERIAL

The intervention will consist of a cover letter and modified profiles.

OUTCOMES MEASUREMENT

The outcomes associated with this initiative will be measured when six months of post-initiative data are available, and will include evaluation of the targeted initiative group.

ANTICIPATED RESULTS

This intervention will focus on the clinical management of fibromyalgia syndrome. It is anticipated that as a result of this intervention, more FMS patients will receive a trial with a tricyclic compound as they have been demonstrated to be among the most effective agents for this condition. Adverse events relating to FMS therapy will be reduced through reduction of high-dose medication use. In addition, the use of opiate analgesics or NSAIDs for pain management will be discouraged as will the chronic use of sedative/hypnotic agents in FMS patients.

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Template Name: Fibromyalgia Management

APPENDIX A

First-Line Medications for FMS

Generic Name	Brand Name	HICL
Anticonvulsants		
Pregabalin	Lyrica	026470
Serotonin-Norepinephrine Reuptake Inhibitors		
Duloxetine	Cymbalta	026521
Milnacipran	Savella	021229
Tricyclic Antidepressants		
Amtriptyline	Elavil	001643
Desipramine	Norpramin	001645
Doxepin	Sinequan	001650
Imipramine	Tofranil	001641
Nortriptyline	Pamelor	001644
Tricyclic Muscle Relaxant		
Cyclobenzaprine	Flexeril	001950

APPENDIX B

Maximum Doses Recommended for FMS Treatment

Medication	Max Daily Dose
Duloxetine	60 mg/day
Milnacipran	200 mg/day
Pregabalin	450 mg/day
Tricyclic Antidepressant	150 mg/day