ABSTRACT

Fibromyalgia syndrome (FMS) is characterized by widespread pain and tenderness, and is often accompanied by one or more comorbid conditions. Although the precise cause of FMS is unknown, both its clinical picture and the available evidence point to multifactorial etiologies, including several central pain processing abnormalities and a genetic predisposition. This article reviews the pain processing abnormalities implicated in FMS, various mechanisms of modulating pain responses, and the mechanisms of action and pharmacologic properties of 3 agents that were recently approved for the treatment of FMS. All 3 drugs target neurotransmitters to modulate pain responses. This article includes a case presentation to help healthcare providers and pharmacists formulate an appropriate treatment plan based on currently approved pharmacologic options, and incorporating nonpharmacologic modalities as needed.

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is associated with its own complexities. Three hypothesized abnormalities—dysfunction of the autonomic nervous system, peripheral and central sensitization, and hyper-windup—are briefly addressed here.

The first abnormality is the dysfunctional blunting of the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, which leads to an adaptive system that responds to stressors such as pain and trauma.\(^1\) This results in chemical and hormonal imbalances, and alters the response to substance P and serotonin.\(^1\) Another pain processing abnormality is central and peripheral tissue sensitization, which is associated with the release of glutamate, an excitatory neurotransmitter, and neuropeptides such as substance P and nerve growth factor.\(^1\) The third abnormality is hyper-windup, which is associated with extensive allodynia (lowered pain threshold), hyperalgesia (increased sensitivity to painful stimuli), and pain amplification via N-methyl-D-aspartate (NMDA) receptor activation.\(^1\)

**MECHANISMS OF MODULATING PAIN RESPONSES**

Modulating pain responses can improve the overall quality of life for patients with FMS. This can be accomplished by utilizing therapies that reduce pain due to central sensitization and peripheral nociceptive input from muscles, as well as by treating comorbid conditions.

Therapies that address central sensitization include cognitive-behavioral therapy, neurokinin and NMDA antagonists, and antiepileptic drugs.\(^1\) Motivated interactions between healthcare professionals and patients that provide support and guidance, in addition to reassurance that treatment options are available, are helpful in this situation.

Physical therapy, muscle relaxants, muscle injections, and anti-inflammatory agents are used to reduce peripheral nociceptive input from muscles, whereas serotonin-norepinephrine reuptake inhibitors (SNRIs) are used to treat certain comorbid states that intensify pain, such as depression, anxiety, and anger.\(^1\)

**FDA-APPROVED AGENTS**

Three drugs were recently approved by the US Food and Drug Administration (FDA) for the treatment of FMS: pregabalin, approved in June 2007; duloxetine, approved in June 2008; and milnacipran, approved in January 2009. Each of these agents is discussed in some detail in the following sections.

### PREGABALIN

Pregabalin is a \(\gamma\)-aminobutyric acid (GABA) analog that binds to the \(\alpha_2\)-\(\delta\) subunit of the voltage-gated presynaptic calcium channels in the CNS.\(^2,3\) It reduces the calcium-dependent release of neurotransmitters via modulation of calcium channel function, and inhibits the release of glutamate, norepinephrine, and substance P.\(^2,5\) It does not bind to GABA or benzodiazepine receptors, and is thought to have membrane stabilization activity.\(^2,5\)

The pharmacokinetics of pregabalin and its dosing information are summarized in Table 1.\(^4\) Patients taking 450 mg/day in divided doses might find it helpful to take 150 mg in the morning and 300 mg at night. Although there is no additional benefit with a higher daily dose of 600 mg, some patients with FMS may require it.

Adverse events associated with pregabalin include weight gain of approximately 7% above baseline; edema, especially in the lower extremities in patients over 60 years of age; elevated levels of creatine phosphokinase; dizziness; somnolence; blurred vision; decreased platelet counts; mild prolongation of the PR interval; and angioedema.\(^4\)

Drug interactions are uncommon because pregabalin is not metabolized by the cytochrome P450 sys-

### Table 1. Pregabalin Pharmacokinetics and Dosing Information

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
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<tbody>
<tr>
<td>Bioavailability: (\geq 90%)</td>
<td></td>
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<tr>
<td>Peak plasma concentrations within 1.5 hours</td>
<td></td>
</tr>
<tr>
<td>Vd: 0.5 L/kg (no protein binding)</td>
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<tr>
<td>Half-life: 6.3 hours</td>
<td></td>
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<tr>
<td>Negligible metabolism</td>
<td></td>
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<tr>
<td>90% excreted unchanged in urine</td>
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</table>

<table>
<thead>
<tr>
<th>Dosing Information</th>
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<tbody>
<tr>
<td>Initial dose: 75 mg BID (may be too high for some patients)</td>
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<tr>
<td>Increase dose weekly to a maximum of 450 mg/day (no additional benefit with 600 mg/day)</td>
<td></td>
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<tr>
<td>Therapeutic effect usually not seen until dose reaches 300 mg/day</td>
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<tr>
<td>Dose must be adjusted for patients with renal insufficiency</td>
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<tr>
<td>Dose must be tapered over at least 1 week</td>
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</tr>
<tr>
<td>FDA Schedule V</td>
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</table>

BID = twice a day; FDA = US Food and Drug Administration. Data from pregabalin [prescribing information].\(^4\)
However, there may be pharmacodynamic interactions whereby pregabalin may increase the sedative effects of CNS depressants such as alcohol, valerian root, kava, and St. John’s wort, and may enhance the fluid-retaining effects of the thiazolidinediones or glitazones.

**Duloxetine**

Duloxetine is a dual SNRI with slightly more inhibition of reuptake at the serotonin receptor than at the norepinephrine receptor, as well as weak inhibition of dopamine reuptake. The pharmacokinetics of duloxetine and its dosing information are summarized in Table 2.

Duloxetine is contraindicated in patients with uncontrolled narrow-angle glaucoma and should not be used within 14 days of a nonselective monoamine oxidase (MAO) inhibitor. Abrupt withdrawal of duloxetine is also contraindicated because it may precipitate agitation, dizziness, headache, fatigue, nausea and/or vomiting, hyperhidrosis, insomnia, and vertigo.

Adverse events reported to occur with duloxetine at a frequency of at least 10% are fatigue, somnolence, dizziness, nausea, xerostomia, constipation, diarrhea, insomnia, and headache. Adverse events reported less frequently include suicidal thoughts, agitation, hyperglycemia, orthostatic hypotension, syncope, syndrome of inappropriate antidiuretic hormone secretion, hyponatremia, decreased appetite, diaphoresis, and sexual dysfunction.

Because duloxetine is a substrate and a moderate inhibitor of CYP-1A2 and CYP-2D6, the possibility of drug interactions is a concern. Serum concentrations of duloxetine are increased in patients taking a CYP-1A2 inhibitor such as ciprofloxacin, fluvoxamine, or verapamil, or a CYP-2D6 inhibitor such as a selective serotonin reuptake inhibitor (SSRI) or bupropion.

Duloxetine should be used with caution in patients taking linezolid (an antibiotic with nonselective MAO inhibitor properties), tricyclic antidepressants, phe-nothiazines, or the antiarrhythmic agents propafenone or flecainide. Thioridazine use is contraindicated in patients taking duloxetine because of the increased risk of serious arrhythmia or sudden death. Providers should also monitor concentrations of tricyclic antidepressants in patients who are taking them along with duloxetine, and should be alert to thrombocytopenia or signs of bleeding in patients taking duloxetine and an anticoagulant. Rarely, the concomitant use of an SNRI and another agent that increases serotonin levels may cause serotonergic syndrome, which is discussed in greater detail in the following section.

**Milnacipran**

Milnacipran is a selective and equipotent inhibitor of both serotonin and norepinephrine reuptake, but does not directly affect the uptake of dopamine or other neurotransmitters. The pharmacokinetics of milnacipran and its dosing information are summarized in Table 3.

Milnacipran is contraindicated in patients with uncontrolled narrow-angle glaucoma, and should not be used within 14 days of an MAO inhibitor. As with the other FDA-approved therapies for FMS, milnacipran should not be withdrawn abruptly, but tapered off gradually.

The most common adverse events associated with milnacipran are increased blood pressure (occurring at a frequency of 2%–19.5%), increased heart rate (6%–8%), heart palpitations (7%), diaphoresis (9%), hot sweats (12%), constipation (16%), nausea (37%), vomiting (7%), xerostomia (5%), and headache (18%). Serious adverse events that have been reported are abnormal bleeding, depression, suicidal thoughts, and serotonergic syndrome. Because the latter occurs rarely, it can be classified in most cases as a theoretical risk rather than a true contraindication.

### Table 2. Duloxetine Pharmacokinetics and Dosing Information

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
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<tbody>
<tr>
<td>• Absorption: 30%–80%; delayed by food</td>
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<tr>
<td>• Protein binding: &gt;90%</td>
</tr>
<tr>
<td>• Half-life: 12 hours (extended in patients with liver failure)</td>
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<tr>
<td>• Extensively metabolized by CYP-1A2 and CYP-2D6 to inactive compounds</td>
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<table>
<thead>
<tr>
<th>Dosing Information</th>
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<tbody>
<tr>
<td>• Initiate with 30 mg/day for 1 week (may be too high for elderly patients or those with liver dysfunction)</td>
</tr>
<tr>
<td>• Titrate upward to usual effective dose of 60 mg/day</td>
</tr>
<tr>
<td>• Doses above 60 mg/day provide no additional benefit, but increase the incidence of adverse events</td>
</tr>
<tr>
<td>• May take several weeks to provide therapeutic effect</td>
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<tr>
<td>• Dose should be tapered over 2 weeks</td>
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Data from duloxetine [prescribing information].

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If treatment with both an SNRI (duloxetine or milnacipran) and a serotonin receptor agonist (ie, a triptan) is clinically necessary, the patient should be observed carefully, especially during the start of treatment and with dose escalation. The patient should be counseled about the signs and symptoms of serotonergic syndrome, which include increased blood pressure, tachycardia, hyperthermia, agitation, hallucinations, hyperreflexia, incoordination, nausea, vomiting, and diarrhea. In the most severe cases, serotonergic syndrome can result in coma and/or resemble neuroleptic malignant syndrome. When dispensing an SNRI and a serotonin receptor agonist concomitantly, the pharmacist or healthcare practitioner should always document that the patient was counseled about the signs and symptoms of serotonergic syndrome and instructed to call the healthcare practitioner or go to the emergency department if they occur.

Milnacipran can interact adversely with MAO inhibitors, producing CNS toxicity or serotonergic syndrome; with SSRIs, increasing the risk of serotonergic syndrome; with clopidogrel and dipyridamole, increasing the risk of bleeding; and to a lesser extent with nonsteroidal anti-inflammatory drugs, also increasing the risk of bleeding.

As with all drugs, for whatever medical condition, patients should be counseled about what to expect from pharmacotherapy and the adverse effects and drug interactions that may occur, particularly if they are taking multiple drugs. Physicians and pharmacists should document that such counseling has taken place and should note all patient reports of untoward effects resulting from drug therapy.

**Formulating a Treatment Plan**

The patient described in Table 4 is presented to help providers and pharmacists formulate an appropriate treatment plan based on currently approved therapies. The treatment plan should be tailored to the patient's needs.

Because the patient's symptoms include fatigue, dry skin, and thinning hair, the first recommendation is to check her thyroid function to rule out hypothyroidism. The second is to review her current medications and institute a treatment plan that removes agents that have not been helpful and adds an agent that is FDA approved for FMS. Nonpharmacologic modalities, such as cognitive-behavioral therapy, a suitable exercise program, massage, and/or acupuncture or acupressure, should always be attempted prior to, and then used concomitantly with, drug therapy.

Pharmacologic options for this patient would be to discontinue ibuprofen, add pregabalin 75 mg twice a day (increasing the dose by 150 mg/day every 7 days

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**Table 3. Milnacipran Pharmacokinetics and Dosing Information**

**Pharmacokinetics**
- Bioavailability: 85%–90%; not affected by food
- Protein binding: 13%
- Half-life: 6–8 hours (extended in patients with liver or renal failure)
- Metabolized in liver by glucuronidation to inactive metabolite
- Does not appear to be metabolized via the cytochrome P450 system

**Dosing Information**
- Recommended dose: 50 mg BID, with or without food (food may improve tolerability)
- Initiate and titrate dose as follows:
  - Day 1: 12.5 mg/day
  - Days 2–3: 12.5 mg BID
  - Days 4–7: 25 mg BID
  - After Day 7: 50 mg BID
- Dose may be increased to 100 mg BID based on individual patient response
- Reduce dose by 50% in patients with severe renal impairment
- Taper dose gradually; do not discontinue abruptly

BID = twice a day.

Data from milnacipran [prescribing information].

**Table 4. Case Presentation**

- 46-year-old woman with fibromyalgia for 12 years presents for follow-up care because of worsening pain and increasing fatigue.
- She says her current medications (ibuprofen 400 mg QID, cyclobenzaprine 10 mg TID as needed, and fluoxetine 40 mg/day) do not seem to be working anymore.
- Current symptoms include “pins and needles” tingling all over her body, painfully cold hands and feet, thinning hair, difficulty swallowing, fatigue, dry skin, and difficulty remembering appointments and times.
- She used to smoke, but drinks alcohol occasionally.

QID = 4 times a day; TID = 3 times a day.
to a maximum of 450 mg/day, titrating the doses as tolerated until there is symptomatic improvement), and consider changing fluoxetine to duloxetine or milnacipran. [Editor’s note: Duloxetine is FDA approved for FMS and major depressive disorder; milnacipran is approved for FMS only.]

CONCLUSIONS

Appropriate treatment of patients with FMS includes addressing all of the symptoms contributing to the pain syndrome and basing treatment options on multifactorial etiologies. Treatment of FMS per se should focus on FDA-approved therapies. Treatment should also be personalized to the individual patient, taking into account any comorbidities, as well as current and past medications that have been helpful. Patients should always be screened for allergies prior to adding drug therapy.

DISCUSSION

SEROTONERGIC SYNDROME

Dr Hahn: I know that many physicians are irritated when pharmacists call and hold up a prescription because of the possibility of serotonergic syndrome. That may be because we are now seeing the use of multiple agents that increase serotonin, but we are not really seeing the syndrome. I have seen it only once. Pharmacists certainly have to be concerned about it, but physicians seem to feel that pharmacists are going overboard with their calls.

Dr Lipman: Serotonergic syndrome is almost a class warning.

Dr Bainbridge: It truly is, but I think pharmacists need more education on how to counsel, how to document, and what to tell patients. But I agree that physicians get very upset when we call to question or hold up a prescription.

Dr Natelson: You have that increased risk with tricyclics and SSRIs, but I have never had a problem.

Dr Bainbridge: You also see this risk with triptans for migraine, so you have to go back to the half-life and the dose of the drug and whether it is used as a chronic medication or not. Longer-acting triptans may pose more of a problem than shorter-acting ones.

Dr Lipman: We have to keep adverse events and drug interactions in perspective. Otherwise, we are going to scare clinicians.

Dr Bainbridge: Adverse events and interactions that occur very rarely are theoretical. They can happen, and pharmacists should be aware of them, but very few patients on these medications will actually have a problem.

Dr Penna: The issue of pharmacists overcalling physicians is real, and has been mentioned as a problem by both parties. The problem is that if a potential or theoretical severe interaction is ignored, and it happens in a patient, then we have failed the patient. On the other hand, there are many reports showing that pharmacists routinely ignore interaction alerts because there are so many of them coming through. There are also reports that physicians with e-prescribing are being overburdened with interaction alerts. Yet, when these physicians were asked if they wanted the alerts turned off, they said no because they felt something important might come up.

Dr Swims: Physicians at the medical center often call me and say, “I have a patient on fluoxetine, but I want to add zolmitriptan for migraines and amitriptyline for neuropathic pain. What should I do?” I think patient education, from the physician and the pharmacist, is key. Both professionals can explain what serotonergic syndrome is, emphasize that it is rare, and review the signs and symptoms that warrant a trip to the emergency department. Pharmacists need to think about patient education before calling the doctor and holding up the prescription, unless it is for huge doses of 3 drugs that have the same properties.

FUTURE DIRECTIONS

Dr Natelson: The need to personalize therapy is so important. After I evaluate a patient, I ask her to name the most important thing I should focus on to help her, because my management is symptom based after all. Usually, the patient says pain relief. They very rarely say depression, but when I do see depression, I focus on that first because it is an illness multiplier.

Dr Lipman: If we look at where personalized medicine is going, it is very clear that in the foreseeable future we are going to have smart cards that contain patient-specific data on individuals’ major cytochrome P450 oxidase profiles. Thus, personalized really employs genetic single-nucleotide polymorphism data. Currently, we are individualizing on the basis of empirical observations and symptom polymorphism data. FMS and all the functional syndromes may well be a major focus for truly personalized medicine in the future. We already have it for drugs such as codeine. We also have half a dozen drugs in which 2D6 stratification matters
clinically, and we can individualize therapy easily and inexpensively.

**Dr Penna:** Clearly there are unmet needs in our ability to treat FMS. What drugs are in the pipeline that may offer more hope in the future?

**Dr Natelson:** The only drug I am aware of is sodium oxybate.

**Dr Lipman:** Work is currently being done on N-type calcium channel blockers for neuropathic pain, and there is some early preclinical work on drugs acting on acid-sensing ion channels. Whether these will apply to FMS is unclear. I think the future of treatment for FMS is going to rest on understanding its pathophysiology, probably from a genetic perspective.

**REFERENCES**

5. Duloxetine [prescribing information]. Indianapolis, IN: Eli Lilly and Company; 2009.