CHRONIC PAIN PERSPECTIVES™

A SUPPLEMENT TO THE JOURNAL OF FAMILY PRACTICE

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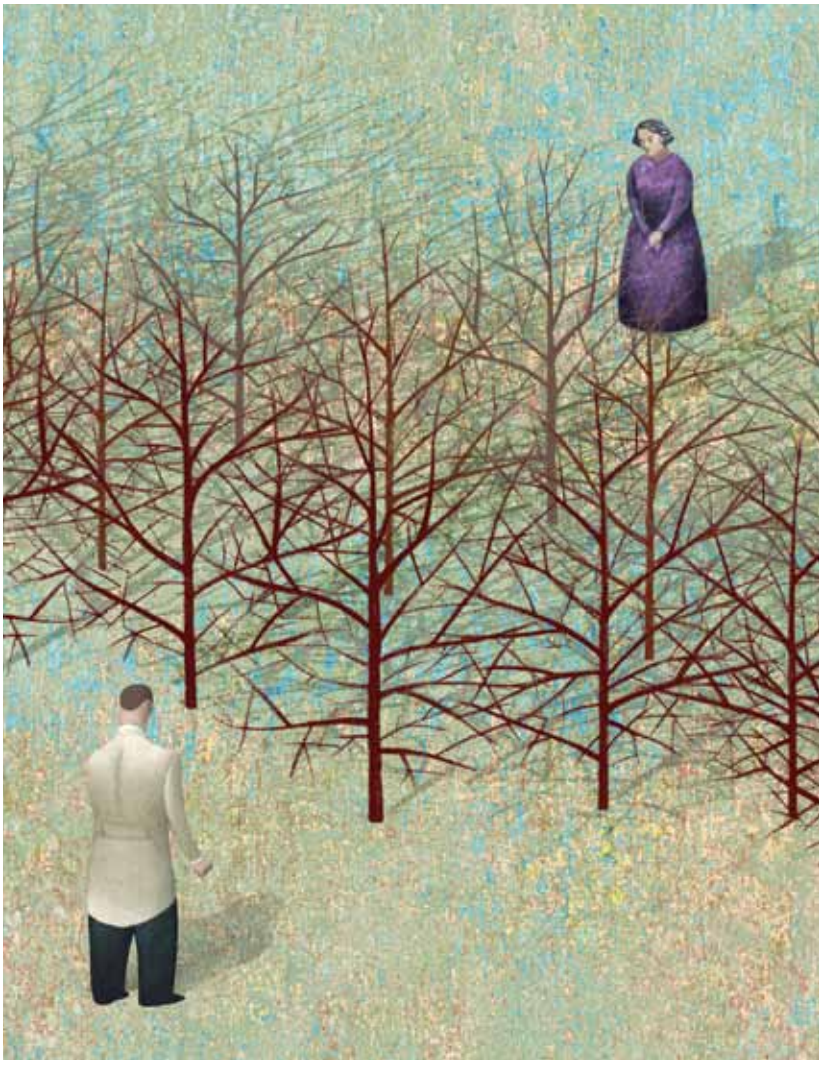
Managing chronic pain in older adults: 6 steps to overcoming medication barriers



Sickle cell disease: Gaining control over the pain

Treating herpes zoster and postherpetic neuralgia: An evidence-based approach

For the management of fibromyalgia

Savella relieves symptoms of fibromyalgia

- **Delivers simultaneous improvements on 3 measures of fibromyalgia[1]**
  - Pain reduction
  - Improvement in patient global fibromyalgia assessment
  - Improvement in physical function
- **Decrease in pain as early as week 1 of treatment with a stable dose in some patients who reported global improvement[1]**
  - Primary endpoint was assessed at week 15
- **Low potential for pharmacokinetic drug-drug interactions[1]**
  - Clinically important interactions may occur with MAOIs, serotonergic drugs (including other SSRIs, SNRIs, lithium, tryptophan, antipsychotics, and dopamine antagonists), triptans, catecholamines (epinephrine and norepinephrine), CNS-active drugs (including clomipramine), and select cardiovascular agents (digoxin and clonidine)
- **A dual reuptake inhibitor that blocks the uptake of norepinephrine over serotonin with approximately 3 times greater potency in vitro[1]**
  - The clinical significance of in vitro data is unknown
- **Widely available on managed care formularies[2]**

Savella®
milnacipran HCl
12.5 mg, 25 mg, 50 mg, 100 mg tablets
For the management of fibromyalgia

IMPORTANT SAFETY INFORMATION

Savella is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), similar to some drugs used for the treatment of depression and other psychiatric disorders. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of such drugs in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on Savella should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of drug therapy or at times of dose changes, either increases or decreases. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Savella is not approved for use in the treatment of major depressive disorder. Savella is not approved for use in pediatric patients.

References: 1. Savella (milnacipran HCl) prescribing information. Forest Pharmaceuticals, Inc. St Louis, MO. **2.** MediMedia Database as of April 2011 for Savella.

Contraindications

- Savella is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) concomitantly or within 14 days of discontinuing treatment with an MAOI. There have been reports of serious, sometimes fatal, reactions in patients started on an MAOI who were receiving or had recently discontinued a serotonin reuptake inhibitor. At least 5 days should be allowed after stopping Savella before starting an MAOI.
- Savella is contraindicated in patients with uncontrolled narrow-angle glaucoma and should be used with caution in patients with controlled narrow-angle glaucoma. In clinical trials, Savella was associated with an increased risk of mydriasis.

Warnings and Precautions

- Prescriptions for Savella should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.
- Development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SSRIs and SNRIs alone, including Savella, but particularly with concomitant use of serotonergic drugs (including triptans), drugs that impair metabolism of serotonin (including MAOIs), or antipsychotics or other dopamine antagonists. The management of these reactions should include immediate discontinuation of Savella and the concomitant agent and supportive symptomatic treatment. The concomitant use of Savella with serotonin precursors is not recommended.
- SNRIs, including Savella, have been associated with cardiovascular effects, including cases of elevated blood pressure, requiring immediate treatment. In clinical trials, sustained increases in systolic and diastolic blood pressure occurred more frequently in Savella-treated patients compared to placebo. Among patients who were non-hypertensive at baseline, approximately twice as many patients receiving Savella, vs placebo, became hypertensive at the end of the study. Clinically significant increases in pulse (≥20 bpm) occurred more frequently in Savella-treated than placebo-treated patients. Blood pressure and heart rate should be monitored prior to initiating treatment with Savella and periodically throughout treatment. Pre-existing hypertension, tachyarrhythmias, and other cardiac diseases should be treated before starting therapy with Savella. Savella should be used with caution in patients with significant hypertension or cardiac disease. Concomitant use of Savella with drugs that increase blood pressure and pulse has not been evaluated, and such combinations should be used with caution. For patients who experience a sustained increase in blood pressure or heart rate while receiving Savella, either dose reduction or discontinuation should be considered.
- Savella should be prescribed with caution in patients with a history of seizure disorder or mania.
- Savella has been associated with mild elevations of ALT and AST (1 to 3 times the upper limit of normal). Rarely, reports of serious liver injury, including fulminant hepatitis, have been reported in patients treated with milnacipran. Savella should be discontinued in patients who develop jaundice or other evidence of liver dysfunction and should not be resumed unless another cause can be established.
- As with other SNRIs and SSRIs, withdrawal symptoms have been observed following discontinuation of milnacipran. A gradual dose reduction is recommended.
- Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Savella. Elderly patients may be at greater risk. Discontinuation should be considered for patients with symptomatic hyponatremia.
- SSRIs and SNRIs, including Savella, may increase the risk of bleeding events. Patients should be cautioned regarding the risk of bleeding associated with concomitant use of Savella and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation.
- Savella can affect urethral resistance and micturition. Caution is advised in the use of Savella in patients with a history of dysuria, notably in male patients with a history of obstructive uropathies as these patients may experience higher rates of genitourinary adverse events.
- Savella should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Use in Specific Populations

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

Adverse Reactions

- In clinical trials, the most frequently occurring adverse reaction was nausea (37% vs 20% for placebo). The most commonly occurring adverse reactions (≥5% and greater than placebo) were headache (18% vs 14%), constipation (16% vs 4%), dizziness (10% vs 6%), insomnia (12% vs 10%), hot flush (12% vs 2%), hyperhidrosis (9% vs 2%), vomiting (7% vs 2%), palpitations (7% vs 2%), heart rate increased (6% vs 1%), dry mouth (5% vs 2%), and hypertension (5% vs 2%).

Please see brief summary of Prescribing Information on the following pages.

Please also see Full Prescribing Information at www.Savella.com.

Savella®
milnacipran HCl
12.5 mg, 25 mg, 50 mg, 100 mg tablets
For the management of fibromyalgia

Licensed from Pierre Fabre and Cypress Bioscience, Inc.

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

Cypress Bioscience, Inc.

SAVELLA® (milnacipran HCl) Tablets **Rx Only**
Brief Summary of Full Prescribing Information
Initial U.S. Approval: 2009

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS Savella is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), similar to some drugs used for the treatment of depression and other psychiatric disorders. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of such drugs in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on Savella should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Savella is not approved for use in the treatment of major depressive disorder. Savella is not approved for use in pediatric patients [*see Warnings and Precautions, Use in Specific Populations*].

INDICATIONS AND USAGE: Savella is indicated for the management of fibromyalgia. Savella is not approved for use in pediatric patients [*see Use in Specific Populations*].

CONTRAINDICATIONS: Monoamine Oxidase Inhibitors-Concomitant use of Savella in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. In patients receiving a serotonin reuptake inhibitor in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of Savella and MAOIs have not been evaluated in humans. Therefore, it is recommended that Savella should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 5 days should be allowed after stopping Savella before starting an MAOI [see *Dosage and Administration, Warnings and Precautions*]. **Uncontrolled Narrow-Angle Glaucoma-**In clinical trials, Savella was associated with an increased risk of mydriasis. Mydriasis has been reported with other dual reuptake inhibitors of norepinephrine and serotonin; therefore, do not use Savella in patients with uncontrolled narrow-angle glaucoma.

WARNINGS AND PRECAUTIONS: Suicide Risk-Savella is a selective serotonin and norepinephrine reuptake inhibitor (SNRI), similar to some drugs used for the treatment of depression and other psychiatric disorders. Patients, both adult and pediatric, with depression or other psychiatric disorders may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking these medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants, including drugs that inhibit the reuptake of norepinephrine and/or serotonin, may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. In the placebo-controlled clinical trials of adults with fibromyalgia, among the patients who had a history of depression at treatment initiation, the incidence of suicidal ideation was 0.5% in patients treated with placebo, 0% in patients treated with Savella 100 mg/day, and 1.3% in patients treated with Savella 200 mg/day. No suicides occurred in the short-term or longer-term (up to 1 year) fibromyalgia trials. Pooled analyses of short-term placebo-controlled trials of drugs used to treat depression (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with these drugs compared to placebo in adults beyond age 24; there was a reduction in suicidality risk with antidepressants compared to placebo in adults age 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 drugs used to treat depression in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug versus placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1 of the full prescribing information. There were 14 additional cases reported in patients under the age of 18, while 5 additional cases were reported in patients between 18 and 24 years of age. Patients between 25 and 64 years of age reported 1 fewer case of suicidality, while patients 65 years of age and over reported 6 fewer cases. No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with drugs inhibiting the reuptake of norepinephrine and/or serotonin for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, have been reported in adult and pediatric patients being treated with drugs inhibiting the reuptake of norepinephrine and/or serotonin for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who may experience worsening depressive symptoms, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe or abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment due to worsening depressive symptoms or emergent suicidality, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can produce withdrawal symptoms *[see Dosage and Administration* and *Warnings and Precautions]*. **Families and caregivers of patients being treated with drugs inhibiting the reuptake of norepinephrine and/or serotonin for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Savella should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions-**The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Savella, but particularly with concomitant use of serotonergic drugs (including triptans), with drugs which impair metabolism of serotonin (including MAOIs) or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) *[see Drug Interactions]*. Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. The concomitant use of Savella with MAOIs is contraindicated *[see Contraindications]*. If concomitant treatment of Savella with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions]*. The concomitant use of Savella with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions]*. Treatment with Savella and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated. **Effects on Blood Pressure-**Inhibition of the reuptake of norepinephrine (NE) and serotonin (5-HT) can lead to cardiovascular effects. SNRIs, including Savella, have been associated with reports of increase in blood pressure. In a double-blind, placebo-controlled clinical pharmacology study in healthy subjects designed to evaluate the effects of milnacipran on various parameters, including blood pressure at supratherapeutic doses, there was evidence of mean increases in supine blood pressure at doses up to 300 mg twice daily (600 mg/day). At the highest 300 mg twice daily dose, the mean increase in systolic blood pressure was up to 8.1 mm Hg for the placebo group and up to 10.0 mm Hg for the Savella treated group over the 12 hour steady state dosing interval. The corresponding mean increase in diastolic blood pressure over this interval was up to 4.6 mm Hg for placebo and up to 11.5 mm Hg for the Savella treated group. In the 3-month placebo-controlled fibromyalgia clinical trials, Savella treatment was associated with mean increases of up to 3.1 mm Hg in systolic blood pressure (SBP) and diastolic blood pressure (DBP) [*see Adverse Reactions*]. In the placebo-controlled trials, among fibromyalgia patients who were non-hypertensive at baseline, approximately twice as many patients in the Savella treatment arms became hypertensive at the end of the study (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) compared with the placebo patients: 7.2% of patients in the placebo arm versus 19.5% of patients treated with Savella 100 mg/day and 16.6% of patients treated with Savella 200 mg/day. Among patients who met systolic criteria for pre-hypertension at baseline (SBP 120-139 mmHg), more patients became hypertensive at the end of the study in the Savella treatment arms than placebo: 9% of patients in the placebo arm versus 14% in both the Savella 100 mg/day and the Savella 200 mg/day treatment arms. Among fibromyalgia patients who were hypertensive at baseline, more patients in the Savella treatment arms had a >15 mmHg increase in SBP than placebo at the end of the study: 1% of patients in the placebo arm versus 7% in the Savella 100 mg/day and 2% in the Savella 200 mg/day treatment arms. Similarly, more patients who were hypertensive at baseline and were treated with Savella had DBP increases > 10 mmHg than placebo at the end of study: 3% of patients in the placebo arm versus 8% in the Savella 100 mg/day and 6% in the Savella 200 mg/day treatment arms. Sustained increases in SBP (increase of ≥ 15 mmHg on three consecutive post-baseline visits) occurred in 2% of placebo patients versus 9% of patients receiving Savella 100 mg/day and 6% of patients receiving Savella 200 mg/day. Sustained increases in DBP (increase of ≥ 10 mmHg on 3 consecutive post-baseline visits) occurred in 4% of patients receiving placebo versus 13% of patients receiving Savella 100 mg/day and 10% of patients receiving Savella 200 mg/day. Sustained increases in blood pressure could have adverse consequences. Cases of elevated blood pressure requiring immediate treatment have been reported. Concomitant use of Savella with drugs that increase blood pressure and pulse has not been evaluated and such combinations should be used with caution *[see Drug Interactions]*. Effects of Savella on blood pressure in patients with significant hypertension or cardiac disease have not been systematically evaluated. Savella should be used with caution in these patients. Blood pressure should be measured prior to initiating treatment and periodically measured throughout Savella treatment. Pre-existing hypertension and other cardiovascular disease should be treated before starting therapy with Savella. For patients who experience a sustained increase in blood pressure while receiving Savella, either dose reduction or discontinuation should be considered. **Effects on Heart Rate-**SNRIs have been associated with reports of increase in heart rate. In clinical trials, relative to placebo, Savella treatment was associated with mean increases in pulse rate of approximately 7 to 8 beats per minute [*see Adverse Reactions*]. Increases in pulse ≥ 20 bpm occurred more frequently in Savella-treated patients when compared to placebo: 0.3% in the placebo arm versus 8% in the Savella 100 mg/day and 8% in the 200 mg/day treatment arms. The effect of Savella on heart rate did not appear to increase with increasing dose. Savella has not been systematically evaluated in patients with a cardiac rhythm disorder. Heart rate should be measured prior to initiating treatment and periodically measured throughout Savella treatment. Pre-existing tachyarrhythmias and other cardiac disease should be treated before starting therapy with Savella. For patients who experience a sustained increase in heart rate while receiving Savella, either dose reduction or discontinuation should be considered. **Seizures-**Savella has not been systematically evaluated in patients with a seizure disorder. In clinical trials evaluating Savella in patients with fibromyalgia, seizures/convulsions have not been reported. However, seizures have been reported infrequently in patients treated with Savella for disorders other than fibromyalgia. Savella should be prescribed with care in patients with a history of a seizure disorder. **Hepatotoxicity-**In the placebo-controlled fibromyalgia trials, increases in the number of patients treated with Savella with mild elevations of ALT or AST (1-3 times the upper limit of normal, ULN) were observed. Increases in ALT were more frequently observed in the patients treated with Savella 100 mg/day (6%) and Savella 200 mg/day (7%), compared to the patients treated with placebo (3%). One patient receiving Savella 100 mg/day (0.2%) had an increase in ALT greater than 5 times the upper limit of normal but did not exceed 10 times the upper limit of normal. Increases in AST were more frequently observed in the patients treated with Savella 100 mg/day (3%) and Savella 200 mg/day (5%) compared to the patients treated with placebo (2%). The increases of bilirubin observed in the fibromyalgia clinical trials were not clinically significant. No case met the criteria of elevated ALT > 3x ULN and associated with an increase in bilirubin ≥ 2x ULN. There have been cases of increased liver enzymes and reports of severe liver injury, including fulminant hepatitis with milnacipran from foreign postmarketing experience. In the cases of severe liver injury, there were significant underlying clinical conditions and/or the use of multiple concomitant medications. Because of underreporting, it is impossible to provide an accurate estimate of the true incidence of these reactions. Savella should be discontinued in patients who develop jaundice or other evidence of liver dysfunction. Treatment with Savella should not be resumed unless another cause can be established. Savella should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease. **Discontinuation of Treatment with Savella-**Withdrawal symptoms have been observed in clinical trials following discontinuation of milnacipran, as with other SNRIs and SSRIs. During marketing of milnacipran, and other SNRIs and SSRIs, there have been spontaneous reports of adverse events indicative of withdrawal and physical dependence occurring upon discontinuation of these drugs, particularly when discontinuation is abrupt. The adverse events include the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe. Patients should be monitored for these symptoms when discontinuing treatment with Savella. Savella should be tapered and not abruptly discontinued after extended use. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate *[see Dosage and Administration]*. **Hyponatremia-**Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Savella. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SNRIs, SSRIs, or Savella. Also, patients taking diuretics or who are otherwise volume-depleted may be at greater risk [*see Geriatric Use*]. Discontinuation of Savella should be considered in patients with symptomatic hyponatremia. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hal-

lucination, syncope, seizure, coma, respiratory arrest, and death. **Abnormal Bleeding-**SSRIs and SNRIs, including Savella, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Savella and NSAIDs, aspirin, or other drugs that affect coagulation. **Activation of Mania-**No activation of mania or hypomania was reported in the clinical trials evaluating effects of Savella in patients with fibromyalgia. However those clinical trials excluded patients with current major depressive episode. Activation of mania and hypomania have been reported in patients with mood disorders who were treated with other similar drugs for major depressive disorder. As with these other agents, Savella should be used cautiously in patients with a history of mania. **Patients with a History of Dysuria-**Because of their noradrenergic effect, SNRIs including Savella, can affect urethral resistance and micturition. In the controlled fibromyalgia trials, dysuria occurred more frequently in patients treated with Savella (1%) than in placebo-treated patients (0.5%). Caution is advised in use of Savella in patients with a history of dysuria, notably in male patients with prostatic hypertrophy, prostatitis, and other lower urinary tract obstructive disorders. Male patients are more prone to genitourinary adverse effects, such as dysuria or urinary retention, and may experience testicular pain or ejaculation disorders. **Controlled Narrow-Angle Glaucoma-**Mydriasis has been reported in association with SNRIs and Savella; therefore, Savella should be used cautiously in patients with controlled narrow-angle glaucoma. Do not use Savella in patients with Uncontrolled Narrow-Angle Glaucoma *[see Contraindications]*. **Concomitant Use with Alcohol-**In clinical trials, more patients treated with Savella developed elevated transaminases than did placebo-treated patients [see *Warnings and Precautions*]. Because it is possible that milnacipran may aggravate pre-existing liver disease, Savella should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

ADVERSE REACTIONS: Clinical Trial Data Sources-Savella was evaluated in three double-blind placebo-controlled trials involving 2209 fibromyalgia patients (1557 patients treated with Savella and 652 patients treated with placebo) for a treatment period up to 29 weeks. The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. 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. **Adverse Reactions Leading to Discontinuation-**In placebo-controlled trials in patients with fibromyalgia, 23% of patients treated with Savella 100 mg/day, 26% of patients treated with Savella 200 mg/day discontinued prematurely due to adverse reactions, compared to 12% of patients treated with placebo. The adverse reactions that led to withdrawal in ≥ 1% of patients in the Savella treatment group and with an incidence rate greater than that in the placebo treatment group were nausea (milnacipran 6%, placebo 1%), palpitations (milnacipran 3%, placebo 1%), headache (milnacipran 2%, placebo 0%), constipation (milnacipran 1%, placebo 0%), heart rate increased (milnacipran 1%, placebo 0%), hyperhidrosis (milnacipran 1%, placebo 0%), vomiting (milnacipran 1%, placebo 0%), and dizziness (milnacipran 1% and placebo 0.5%). Discontinuation due to adverse reactions was generally more common among patients treated with Savella 200 mg/day compared to Savella 100 mg/day. **Most Common Adverse Reactions-**In the placebo-controlled fibromyalgia patient trials, the most frequently occurring adverse reaction in clinical trials was nausea. The most common adverse reactions (incidence ≥ 5% and twice placebo) in patients treated with Savella were constipation, hot flush, hyperhidrosis, vomiting, palpitations, heart rate increased, dry mouth, and hypertension. Table 2 lists all adverse reactions that occurred in at least 2% of patients treated with Savella at either 100 or 200 mg/day and at an incidence greater than that of placebo. Table 2 in the full PI shows the incidence of common adverse reactions that occurred in at least 2% of patients treated with Savella at either 100 or 200 mg/day and at an incidence greater than that of placebo. Savella 100 mg/day (n=632); Savella 200 mg/day (n=934); All Savella (n=1557); Placebo (n=652): **Cardiac Disorders:** Palpitations (8%; 7%; 7%; 2%); Tachycardia (3%; 2%; 2%; 1%); **Eye Disorders:** Vision blurred (1%; 2%; 2%; 1%); **Gastrointestinal Disorders:** Nausea (35%; 39%; 37%; 20%); Constipation (16%; 15%; 16%; 4%); Vomiting (6%; 7%; 7%; 2%); Dry mouth (5%; 5%; 5%; 2%); Abdominal pain (3%; 3%; 3%; 2%); **General Disorders:** Chest pain (3%; 2%; 2%; 2%); Chills (1%; 2%; 2%; 0%); Chest discomfort (2%; 1%; 1%; 1%); **Infections:** Upper respiratory tract infection (7%; 6%; 6%; 6%); **Investigations:** Heart rate increased (5%; 6%; 6%; 1%); Blood pressure increased (3%; 3%; 3%; 1%); **Metabolism and Nutrition Disorders:** Decreased appetite (1%; 2%; 2%; 0%); **Nervous System Disorders:** Headache (19%; 17%; 18%; 14%); Dizziness (11%; 10%; 10%; 6%); Migraine (6%; 4%; 5%; 3%); Paresthesia (2%; 3%; 2%; 2%); Tremor (2%; 2%; 2%; 1%); Hypoesthesia (1%; 2%; 1%; 1%); Tension headache (2%; 1%; 1%; 1%); **Psychiatric Disorders:** Insomnia (12%; 12%; 12%; 10%); Anxiety (5%; 3%; 4%; 4%); **Respiratory Disorders:** Dyspnea (2%; 2%; 2%; 1%); **Skin Disorders:** Hyperhidrosis (8%; 9%; 9%; 2%); Rash (3%; 4%; 3%; 2%); Pruritus (3%; 2%; 2%; 2%); **Vascular Disorders:** Hot flush (11%; 12%; 12%; 2%); Hypertension (7%; 4%; 5%; 2%); Flushing (2%; 3%; 3%; 1%). **Weight Changes-**In placebo-controlled fibromyalgia clinical trials, patients treated with Savella for up to 3 months experienced a mean weight loss of approximately 0.8 kg in both the Savella 100 mg/day and the Savella 200 mg/day treatment groups, compared with a mean weight loss of approximately 0.2 kg in placebo-treated patients. **Genitourinary Adverse Reactions in Males-**In the placebo-controlled fibromyalgia studies, the following treatment-emergent adverse reactions related to the genitourinary system were observed in at least 2% of male patients treated with Savella, and occurred at a rate greater than in placebo-treated male patients: dysuria, ejaculation disorder, erectile dysfunction, ejaculation failure, libido decreased, prostatitis, scrotal pain, testicular pain, testicular swelling, urinary hesitation, urinary retention, urethral pain, and urine flow decreased. **Other Adverse Reactions Observed During Clinical Trials of Savella in Fibromyalgia-**Following is a list of frequent (those occurring on one or more occasions in at least 1/100 patients) treatment-emergent adverse reactions reported from 1824 fibromyalgia patients treated with Savella for periods up to 68 weeks. The listing does not include those events already listed in Table 2, 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. Adverse reactions are categorized by body system and listed in order of decreasing frequency. Adverse reactions of major clinical importance are described in the *Warnings and Precautions* section. Gastrointestinal Disorders – diarrhea, dyspepsia, gastroesophageal reflux disease, flatulence, abdominal distension; General Disorders – fatigue, peripheral edema, irritability, pyrexia; Infections – urinary tract infection, cystitis; Injury, Poisoning, and Procedural Complications – contusion, fall; Investigations – weight decreased or increased; Metabolism and Nutrition Disorders – hypercholesterolemia; Nervous System Disorders – somnolence, dysgeusia; Psychiatric Disorders – depression, stress; Skin Disorders – night sweats. **Post-marketing Spontaneous Reports-**The following additional adverse reactions have been identified from spontaneous reports of Savella received worldwide. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to Savella. However, because these adverse reactions were 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. These events include: Blood and Lymphatic System Disorders – leukopenia, neutropenia, thrombocytopenia; Cardiac Disorders – supraventricular tachycardia; Eye Disorders – accommodation disorder; Endocrine Disorders – hyperprolactinemia; Hepatobiliary Disorders – hepatitis; Metabolism and Nutrition Disorders – anorexia, hyponatremia; Musculoskeletal and Connective Tissue Disorders – rhabdomyolysis; Nervous System Disorders – convulsions (including grand mal), loss of consciousness, Parkinsonism; Psychiatric Disorders – delirium, hallucination; Renal and Urinary Disorders – acute renal failure; Reproductive System and Breast Disorders – galactorrhea; Skin Disorders – erythema multiforme, Stevens Johnson syndrome; Vascular Disorders – hypertensive crisis.

DRUG INTERACTIONS: Milnacipran undergoes minimal CYP450 related metabolism, with the majority of the dose excreted unchanged in urine (55%), and has a low binding to plasma proteins (13%). In vitro and in vivo studies showed that Savella is unlikely to be involved in clinically significant pharmacokinetic drug interactions *[see Pharmacokinetics in Special Populations]*. **Monoamine Oxidase Inhibitors** - *[See Contraindications]* **Serotonergic Drugs** - Due to the mechanism of action of SNRIs and SSRIs, including Savella, and the potential for serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)–like reactions, caution is advised when Savella is co-administered with other drugs that may affect the serotonergic neurotransmitter systems. This includes drugs such as triptans, lithium, tryptophan, anti-psychotics and dopamine antagonists. Co-administration of Savella with other inhibitors of serotonin re-uptake may result in hypertension and coronary artery vasoconstriction, through additive serotonergic effects. Concomitant use of Savella with other SSRIs, SNRIs, or tryptophan is not recommended [*see Warnings and Precautions*]. **Triptans** - There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Savella with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [*see Warnings and Precautions*]. **Catecholamines** - Savella inhibits the reuptake of norepinephrine. Therefore concomitant use of Savella with epinephrine and norepinephrine may be associated with paroxysmal hypertension and possible arrhythmia [*see Warnings and Precautions*]. **CNS-active drugs** - Given the primary CNS effects of Savella, caution should be used when it is taken in combination with other centrally acting drugs, including those with a similar mechanism of action. *Clomipramine:* In a drug-drug interaction study, an increase in euphoria and postural hypotension was observed in patients who switched from clomipramine to Savella. **Clinically Important Interactions with Select Cardiovascular Agents** - *Digoxin:* Use of Savella concomitantly with digoxin may be associated with potentiation of adverse hemodynamic effects. Postural hypotension and tachycardia have been reported in combination therapy with intravenously administered digoxin (1 mg). Co-administration of Savella and intravenous digoxin should be avoided [*see Warnings and Precautions*]. *Clonidine:* Because Savella inhibits norepinephrine reuptake, co-administration with clonidine may inhibit clonidine's anti-hypertensive effect.

USE IN SPECIFIC POPULATIONS: Pregnancy-Pregnancy Category C. Milnacipran increased the incidence of dead fetuses in utero in rats at doses of 5 mg/kg/day (0.25 times the MRHD on a mg/m^2 basis). Administration of milnacipran to mice and rabbits during the period of organogenesis did not result in embryotoxicity or teratogenicity at doses up to 125 mg/kg/day in mice (3 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m^2 basis) and up to 60 mg/kg/day in rabbits (6 times the MRHD of 200 mg/day on a mg/m^2 basis). In rabbits, the incidence of the skeletal variation, extra single rib, was increased following administration of milnacipran at 15 mg/kg/day during the period of organogenesis. There are no adequate and well-controlled studies in pregnant women. Savella should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To provide information regarding the exposure to Savella during pregnancy, physicians are advised to recommend that pregnant patients taking Savella enroll in the Savella Pregnancy Registry. Enrollment is voluntary and may be initiated by pregnant patients or their healthcare providers by contacting the registry at 1-877-643-3010 or by email at registries@kendle.com. Data forms may also be downloaded from the registry website at www.savellapregnancyregistry.com. Nonteratogenic Effects; Neonates exposed to dual reuptake inhibitors of serotonin and norepinephrine, or selective serotonin reuptake inhibitors late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of these classes of drugs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions*]. In rats, a decrease in pup body weight and viability on postpartum day 4 were observed when milnacipran, at a dose of 5 mg/kg/day (approximately 0.2 times the MRHD on a mg/m^2 basis), was administered orally to rats during late gestation. The no-effect dose for maternal and offspring toxicity was 2.5 mg/kg/day (approximately 0.1 times the MRHD on a mg/m^2 basis). **Labor and Delivery-**The effect of milnacipran on labor and delivery is unknown. The use of Savella during labor and delivery is not recommended. **Nursing Mothers-**There are no adequate and well-controlled studies in nursing mothers. It is not known if milnacipran is excreted in human milk. Studies in animals have shown that milnacipran or its metabolites are excreted in breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from milnacipran, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. Because the safety of Savella in infants is not known, nursing while on Savella is not recommended. **Pediatric Use-**Safety and effectiveness of Savella in a fibromyalgia pediatric population below the age of 17 have not been established [*see Box Warning* and *Warnings and Precautions*]. The use of Savella is not recommended in pediatric patients. **Geriatric Use-**In controlled clinical studies of Savella, 402 patients were 60 years or older, and no overall differences in safety and efficacy were observed between these patients and younger patients. In view of the predominant excretion of unchanged milnacipran via kidneys and the expected decrease in renal function with age, renal function should be considered prior to use of Savella in the elderly [*see Dosage and Administration*]. SNRIs, SSRIs, and Savella, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [*see Warnings and Precautions*].

DRUG ABUSE AND DEPENDENCE: Controlled Substance-Milnacipran is not a controlled substance. **Abuse-**Milnacipran did not produce behavioral signs indicative of abuse potential in animal or human studies. **Dependence-**Milnacipran produces physical dependence, as evidenced by the emergence of withdrawal symptoms following drug discontinuation, similar to other SNRIs and SSRIs. These withdrawal symptoms can be severe. Thus, Savella should be tapered and not abruptly discontinued after extended use [*see Warnings and Precautions*].

OVERDOSAGE: There is limited clinical experience with Savella overdose in humans. In clinical trials, cases of acute ingestions up to 1000 mg, alone or in combination with other drugs, were reported with none being fatal. In postmarketing experience, fatal outcomes have been reported for acute overdoses primarily involving multiple drugs but also with Savella only. The most common signs and symptoms included increased blood pressure, cardio-respiratory arrest, changes in the level of consciousness (ranging from somnolence to coma), confusional state, dizziness, and increased hepatic enzymes. **Management of Overdose-**There is no specific antidote to Savella, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug. An adequate airway, oxygenation, and ventilation should be assured and cardiac rhythm and vital signs should be monitored. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Because there is no specific antidote for Savella, symptomatic care and treatment with gastric lavage and activated charcoal should be considered as soon as possible for patients who experience a Savella overdose. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial. In managing overdose, the possibility of multiple drug involvement should be considered. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

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Sickle cell disease: Gaining control over the pain

Ongoing adjustments to the medication regimen and careful attention to lifestyle and support systems are critical to helping patients manage the pain of sickle cell disease.

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Truman Medical Centers, Kansas City, Mo

Sickle cell disease affects an estimated 100,000 patients in the United States.[1] By the time just one of these patients reaches the age of 45, his or her health care costs will reach nearly $1 million.[2]

Pain is the primary reason patients seek treatment for this disorder. Individuals with sickle cell disease have pain that is characterized as chronic with intermittent episodes of acute pain crises. The pain during a crisis is related to the ischemia the sickle-shaped red blood cells cause as they aggregate, resulting in decreased blood flow to distal tissues. (For more on other factors that can influence sickle cell pain, see "The role of age and depression in sickle cell crises"[3] on page S6.)

Continued on page S6

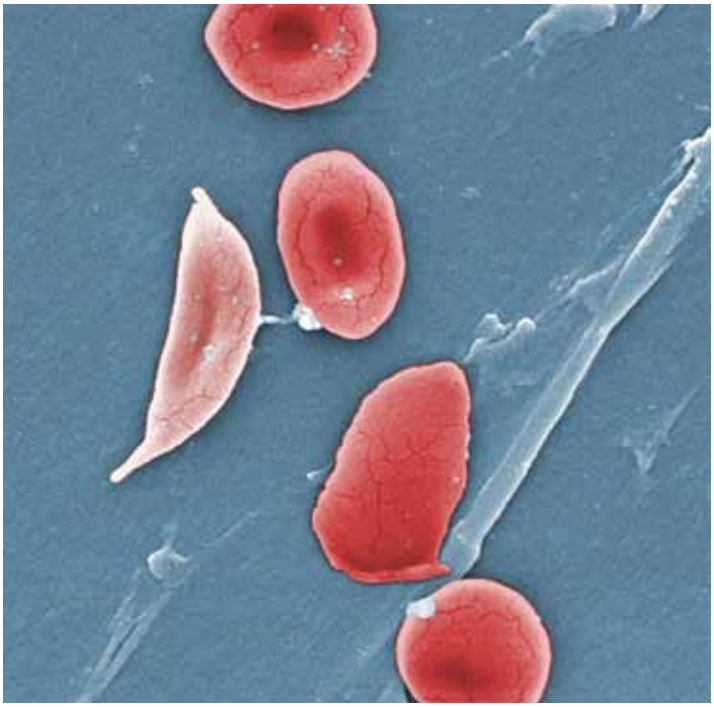

Photo: Janice Haney Carr

Disclosure
The author reports that he serves on the speakers' bureau of Aventine HealthSciences, a medical communications agency for pain and neuroscience.

THE ROLE OF AGE AND DEPRESSION IN SICKLE CELL CRISES

Sickle cell pain is primarily due to ischemia; however, there are other factors that may play a role. The PiSCES project was an epidemiologic longitudinal cohort of adults with sickle cell pain designed to address the relationship between sickle cell pain and the individual response to pain.[3] Researchers enrolled 260 patients and compared the genotype of sickle cell, sex of patient, presence of depression, and age with location of pain, number of associated painful crises, and overall health care utilization for pain management.

Researchers found that the areas of the body associated with the most painful episodes were the lower back, knee/shin area, and hips. Interestingly, more pain sites were reported by those with depression (3.8 vs 3.1 for those with no depression; *P*=.0011) and by those who were 45 years and older (2.7 pain sites [<25 years old]; 3.3 pain sites [25-44 years old]; 4.0 pain sites [≥45 years old]; *P*=0.0120 for overall test for older patients vs those <45 years).[3]

Patients ≥45 years and those suffering from depression had more pain sites than younger patients and those with no depression.

In the review that follows, I'll describe the mainstays of pharmacologic treatment to address this pain and provide strategies to help minimize patients' time in the hospital and maximize their quality of life. But first, a brief review of what occurs during a sickle cell crisis.

What you'll see during a crisis

Dehydration, infection, stress, and changes in body temperature are common triggers of a sickle cell crisis.[4] Once set into motion, a crisis unfolds in 4 distinct phases:

Prodromal. During this phase, patients typically become lethargic and experience mild pain in a single localized area, such as the lower back, hips, or legs. There are no hematologic changes at this point and the pain can be managed using oral analgesics.

Initial infarctive. At this point, the pain increases from mild to moderate intensity. This phase is marked by a decrease in hemoglobin and alterations in mood, such as increased anxiety or irritability. The laboratory findings often occur much later than the patient's report of symptoms. Prompt attention by the physician when the patient begins to experience the symptoms is key to initial management.

Post-infarctive/inflammatory. The peak of severe pain occurs during this phase. The pain is intense enough to cause patients to seek emergency services or hospitalization for pain relief. Laboratory changes include an increase in reticulocyte count, lactate dehydrogenase, and C-reactive protein. CRP levels, for instance, will rise to 70 mg/L during a crisis. Patients with sickle cell disease normally average 32.2 mg/L; non-sickle cell patients average 10 mg/L.[5]

Resolving. After adequate fluid hydration and intravenous analgesics, the pain of a crisis will return to a moderate intensity.

Pain management centers on opioids

Opioids form the foundation of sickle cell pain management, both in acute crisis management and for the chronic pain that patients experience as the disease progresses. (See "Case study: Helping Annie stay out of the hospital" on page S7.) Opioids like codeine and tramadol are typically used to treat moderate pain, whereas drugs such as morphine, oxycodone, hydrocodone, and hydromorphone have a more prominent role in severe and breakthrough pain management.

What to use—and when—during a crisis

In order to manage acute painful episodes, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and adequate hydration are standard. Parenteral NSAIDs are beneficial because of their opioid-sparing effects; they can also lead to a more efficient transition to oral analgesics.

A Cochrane review of the medical management of pain associated with a sickle cell crisis[6] acknowledges the opioid-sparing effects of parenteral NSAIDs in the initial phases of a crisis. This review also suggests that:

- The use of parenteral opioids with their fast onset in a pain crisis should be transitioned to oral sustained-release opioids once the patient is able to tolerate oral medications.
- Short-acting oral opioids are appropriate for intermittent (breakthrough) pain during a crisis, while sustained-release opioids are useful for persistent (baseline) pain.
- Parenteral corticosteroids may be of some benefit during the crisis phases, but data related to their efficacy are lacking after the first 48 hours of the crisis.

PCA can make a big difference to patients

Many opioids such as morphine, fentanyl, and hydromorphone are available for delivery via patient-controlled analgesia (PCA). This allows the patient to give him- or herself a dose of opioid when the pain intensity is greater than baseline. During the inflammatory phase of a crisis, the PCA opioids are preferred by many patients because of their convenient dosing and the ease

CASE STUDY Helping Annie stay out of the hospital

Annie is a 29-year-old African American woman with sickle cell disease. She arrives at the local emergency department (ED) and tells the staff that she's there because of her "usual sickle cell pain." She has pain (9/10) in her lower back, hips, and lower extremities. She says the pain is sharp, constant, and localized—with no radiation to other areas. She has no chest pain or shortness of breath.

A review of systems is negative, except for what was documented in the history of her present illness. Annie's home medications include oxycodone extended release 40 mg twice daily, oxycodone immediate release 5 to 10 mg every 4 hours as needed for pain, and ibuprofen 600 mg as needed.

Before coming into the ED, Annie says she took her morning oxycodone extended release dose and oxycodone 40 mg immediate release over the past 24 hours with little relief. Her vital signs in the ED are blood pressure, 150/85 mm Hg; heart rate, 95 beats per minute; respiratory rate, 14 breaths per minute; temperature 99.2°F.

The patient has scleral icterus and bilateral mild lower extremity swelling. Her lab work reveals a serum creatinine concentration of 1.4 mg/dL and lactate dehydrogenase level of 256 IU/L.

During her 8-hour stay in the ED, Annie receives hydromorphone 2 mg IV every 30 minutes for 3 doses, 3 liters of IV rehydration, and 25 mg oral diphenhydramine for itching with the third dose of hydromorphone. She is discharged to home after rating her pain as 5/10, which she finds tolerable. Discharge instructions indicate that she should follow up with her primary care provider.

One week later, Annie goes to see her family physician. Because she's been taking her oxycodone prescriptions as directed and has still ended up in the ED twice in the past 3 weeks, her physician talks to her about increasing her oxycodone extended release to 80 mg twice a day and the immediate release to 10 to 15 mg every 4 hours as needed.

During their conversation, Annie mentions that as her use of oxycodone has gone up, the number of bowel movements has gone down. So her physician prescribes a stimulant laxative (senna with docusate) twice a day.

The physician also talks to Annie about restarting her hydroxyurea, which she hasn't been taking for the past few months. Before Annie leaves, her physician reminds her to stay hydrated, pointing out that it will not only prevent dehydration, but it will aid with bowel regulation.

of self-titration to adequate analgesia. Once the resolving phase begins, the patient can decrease his or her breakthrough PCA opioid use and return to the pre-crisis amount of opioids.

Hydroxyurea can help with crisis prevention

The use of hydroxyurea in the maintenance of sickle cell disease and the prevention of crises has been documented in the literature.[7] Hydroxyurea increases the circulating amounts of fetal hemoglobin, which has been shown to inhibit the sickling of mature red blood cells. In one study, patients on hydroxyurea had fewer crises (5.1 per year vs 7.9 with placebo) and their risk of death was reduced by approximately 40% during a 6- to 8-year observation period.[8]

Long-term data are lacking and other novel approaches to outpatient maintenance and prevention of sickle cell crises are still being discovered. Relative contraindications to hydroxyurea therapy include bone marrow suppression, impaired renal or hepatic function, and pregnancy.[9]

Pharmacologic management of chronic pain

Patients with sickle cell disease are typically managed using opioids and other pharmacologic agents, such as NSAIDs and acetaminophen, along with nonpharmacologic strategies. The goal of sickle cell management is to enable the patient to resume activities of daily living.

Some patients have a very high tolerance to opioids and are subsequently on large doses of long-acting and short-acting opioids. Patients who are on long-term opiates should have an opioid agreement in place to monitor adherence to therapy and potential diversion, as well as to document potentially risky patient behaviors, such as a pattern of early refills in the absence of clinical change or prescription "problems," such as lost or stolen medications.[10]

Opioid agreements generally have language that indicates the patient will receive opioids from only one provider, utilize one pharmacy to fill prescriptions for opioids, and inform the clinic if he or she receives care from another provider who is also prescribing opioids. These agreements can also include specific language related to urine drug screening practices, medi-

SUPPORT GROUPS FOR SICKLE CELL PATIENTS

- http://www.sicklecellsupportgroup.org/
- http://www.ascaa.org/support-groups.php
- http://www.cdc.gov/ncbddd/sicklecell/documents/SickleCellDIRECTORY_508.pdf

cation counts, and consequences of breaking the treatment agreement. It is good practice to institute opioid agreements for all patients on long-term opiates in order to ensure consistency within the clinic.

Addressing the pain from many angles

Management of the chronic underlying pain requires a multifaceted approach to ensure patient adherence to treatment and adequate management of symptoms. Chronic pain involves modulation of the afferent nociceptive pathways in the spinal cord (such as the spinothalamic tract), which are responsible for transmission of pain from the periphery to the brain for processing. Medications that can alter the perception of pain in the spinothalamic tract include opioids, serotonin norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants. The SNRIs duloxetine and milnacipran have indications for chronic pain—although not for sickle cell pain. No tricyclics are FDA approved for chronic pain, though they are routinely used for this purpose as an adjunct to nonpharmacologic therapy for chronic neuropathic pain.

Nonpharmacologic management strategies include minimizing caffeine intake, avoiding or minimizing intake of alcohol, and adequate rest. Also, because dehydration can lead to a crisis, it's important to avoid—whenever possible—the use of diuretics in these patients.

Multidisciplinary patient management offers additional treatment strategies such as social support, assistance with activities of daily living, and "day hospitals" for management of patients in a subacute setting. The day hospital model, which originated in 1989,[11] provides patients with access to a controlled environment where they can receive parenteral medication and hydration for the purpose of avoiding emergency care or inpatient hospitalization.

A 5-year-study of this model showed that patients were admitted to the hospital 5 times less often from the day hospital than from the emergency department. Also, the inpatient length of stay dropped by 1.5 days once the day hospital model was put into place.[11]

In one study, patients on hydroxyurea had fewer crises and their risk of death was reduced by about 40%.

Patients need help coping

The long-term effects of pain on physiology and psychology are well documented. Patients living with chronic pain may also have comorbidities such as anxiety, depression, and/or substance abuse. A tricyclic antidepressant or an SNRI may be worth considering for patients with sickle cell disease who are suffering from depression.

Many sickle cell patients feel isolated from others because of their constant pain and fear of the next sickle cell crisis.[12] A strong network of friends and family, empathetic health care providers, and a support network of other sickle cell patients who "truly understand" the pain of sickle cell disease can have a positive impact on the sickle cell patient. (For more on support groups, see the box on page S7.) Shifting the focus away from inpatient hospitalization for pain management and onto outpatient maintenance and prevention of future crises will increase the overall quality of life of these patients.

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Treating herpes zoster and postherpetic neuralgia: An evidence-based approach

When are corticosteroids appropriate for patients with herpes zoster? Which tricyclics are best for frail and elderly patients with PHN pain? And when should you consider opioids? Read on.

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Postherpetic neuralgia (PHN) is a management challenge—because of its severity, long duration, and potential for debilitation, often in the highly vulnerable elderly population. And, as the most common complication of an acute episode of herpes zoster (shingles) in an immunocompetent person, PHN is likely no stranger to your practice.

Herpes zoster is one of the most common neurological problems, with an incidence of up to 1 million new cases per year in the United States.[1] Although the precise number for the prevalence of PHN in the United States is unknown, investigators estimate it at 500,000 to 1 million.[2]

Major risk factors for development of PHN after an episode of herpes zoster include:

- older age

Disclosure
The authors reported no potential conflict of interest relevant to this article.

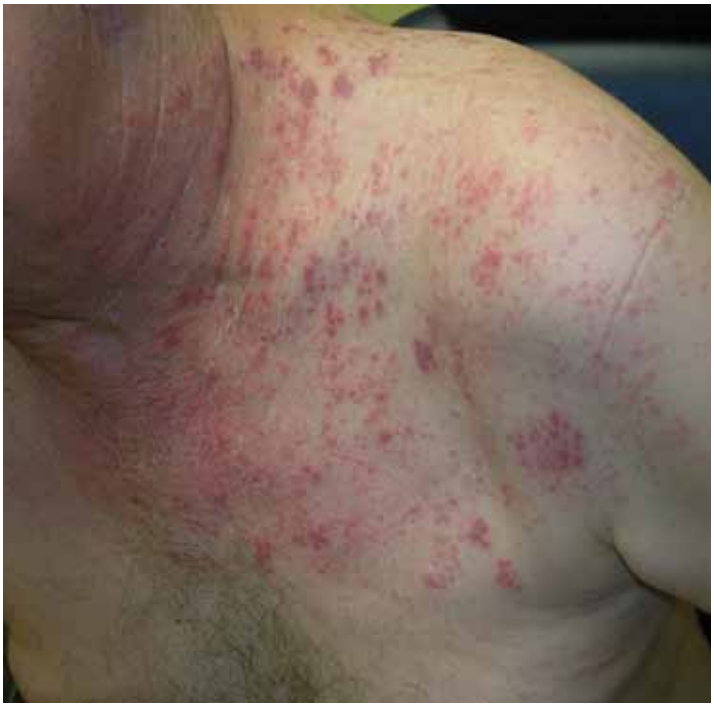

Photo courtesy of Richard Usatine, MD

- greater acute pain during herpes zoster
- greater severity of rash.[3,4]

PHN is commonly defined as "dermatomal pain that persists 120 days or more after the onset of rash."[5] The pain of PHN has been characterized as a stimulus-dependent continuous burning, throbbing, or episodic sharp electric shock-like sensation[6] and as a stimulus-dependent tactile allodynia (ie, pain after normally nonpainful stimulus) and hyperalgesia (exaggerated response to a painful stimulus). In addition, some patients experience myofascial pain secondary to excessive muscle guarding. Chronic pruritus can be present.

More than 90% of patients who have PHN have allodynia,[7] which tends to occur in areas where sensation is relatively preserved. Patients also feel spontaneous pain in areas where sensation is lost or impaired.

In this article, we review the evidence for the range of treatments for acute herpes zoster and PHN, as well offer preventive strategies for herpes zoster.

Gabapentin or pregabalin, followed by a tricyclic antidepressant, can be added if conventional analgesics are not effective for herpes zoster pain.

Acute herpes zoster: Start antivirals early

Evidence-based treatment of acute herpes zoster includes antiviral drugs and analgesics.

Antiviral agents suppress viral replication and have a beneficial effect on acute and chronic pain. Acyclovir (800 mg, 5 times a day), valacyclovir (1000 mg, every 8 hours), and famciclovir (500 mg, every 8 hours) are antivirals commonly used to treat herpes zoster. All 3 drugs have comparable efficacy and safety profiles.

In a meta-analysis of patients older than 50 years who were treated with acyclovir or placebo, pain persisted in 15% of the acyclovir-treated group, compared with 35% of the placebo group.[8] In terms of duration, a study comparing famciclovir treatment with placebo showed that subjects in the placebo group had persistent pain for 163 days, whereas famciclovir-treated patients had pain for 63 days.[9]

Based on this evidence, antiviral medications are strongly recommended for treating herpes zoster, especially for patients at increased risk of developing PHN. Antiviral treatment should be started within 72 hours of the onset of the rash.

No good evidence supports the efficacy of antiviral treatment administered 72 hours after the onset of rash. One uncontrolled trial, however, examined the effectiveness of acyclovir started before vs after 72 hours; the difference in pain persistence was not significant between the groups, suggesting acyclovir has benefit even when given after 72 hours.[10]

In clinical practice, the diagnosis of herpes zoster is often not made within 72 hours of symptom onset; nevertheless, it is important to identify patients who could still benefit from antiviral medication even when treatment is started relatively late in the disease course. This is especially true in ocular zoster, because viral shedding may continue beyond 72 hours.[11]

Analgesics are part of a practical approach for managing herpes zoster–associated pain that begins with a short-acting opioid in combination with acetaminophen or a nonsteroidal anti-inflammatory (NSAID) agent. Gabapentin or pregabalin, followed by a tricyclic antidepressant, can be added if conventional analgesics are not entirely effective. The analgesic regimen should be tailored to the patient's needs and tolerance of adverse effects. If pain control is inadequate or adverse effects are intolerable, consider referring the patient to a pain management center for possible interventional modalities.

Corticosteroids are not recommended routinely for treatment of herpes zoster; you can try them in otherwise healthy older adults, however, if antiviral therapy and analgesics do not relieve pain. In 2 double-blind controlled trials, a combination of acyclovir and corticosteroids for 21 days did not decrease the incidence of PHN—although some benefit was seen in terms of patients' return to normal activities, cessation of analgesic therapy, and improved sleep.[12,13]

Evidence-based treatment options for PHN

Pharmacotherapy for PHN includes anticonvulsants, tricyclic antidepressants, opioids, and topical agents. Invasive interventions have a limited but important role in the management of PHN pain in clinical practice.

Calcium channel-blocking anticonvulsants gabapentin and pregabalin are safe and relatively well tolerated. They can be used as first-line agents for PHN, starting with a low dosage and titrating up, based on effectiveness and tolerability.

Gabapentin is FDA approved for the treatment of PHN. The starting dosage is 100 to 300 mg taken at night, titrated as needed by 100 to 300 mg every 3 to 5 days, to as high a dosage as 1800 to 3600 mg/d in 3 or 4 divided doses. In 2 large, randomized controlled trials,

gabapentin produced a statistically significant reduction in pain ratings and improved sleep and quality of life.[14,15] Adverse effects include somnolence, dizziness, peripheral edema, visual adverse effects, and gait and balance problems.

Because gabapentin is excreted by the kidneys, take care when using it in patients with renal insufficiency. Gabapentin clearance is linearly related to creatinine clearance and is decreased in the elderly and in individuals with impaired renal function. Hence, the gabapentin dose and the frequency of dosing must be adjusted in these patients.

In patients on hemodialysis, plasma gabapentin levels can be maintained by giving a dose of 200 to 300 mg 4 hours after hemodialysis.[16]

Extended-release gabapentin. The FDA recently approved an extended-release gabapentin formulation for PHN. Approval was based on a 12-week pivotal study and 2 adjunct studies. In a multicenter, randomized, double-blind, parallel-group, placebo-controlled, 12-week study evaluating the efficacy, safety, and dose response of 3 doses, extended-release gabapentin was effective at 1200 mg/d dosing. The initial recommended dose is 600 mg, once daily for 3 days, followed by 600 mg, twice daily, beginning on Day 4.[17] The premise is that the extended-release preparation improves bioavailability of the active drug and, therefore, reduces the incidence of adverse effects, compared with regular gabapentin.

Overall, evidence is mixed. Two randomized controlled trials of extended-release gabapentin showed benefit (ie, reduced pain score on a numerical rating scale) with twice-a-day dosing (600 mg in the morning and 1200 mg at night), compared with a once-daily 1800-mg dose as well as placebo, for reduction in intensity of pain[18] and specific pain quality.[19] In another trial, however, extended-release gabapentin, 1800 mg once daily, did not show any benefit compared with placebo.[20]

Pregabalin is also FDA approved for PHN. The effective dosage range is 150 to 600 mg/d. Pregabalin provided significantly superior pain relief and improved sleep scores compared with placebo in 776 patients with PHN. [21] Adverse effects include weight gain, dizziness, and somnolence. Titrate the dosage slowly in the elderly.

Sodium channel-blocking anticonvulsants topiramate, lamotrigine, carbamazepine, oxcarbazepine, levetriacetam, and valproic acid are *not* FDA approved for PHN. These agents may be a treatment option, however, for patients with PHN who do not respond to conventional therapy. In an 8-week randomized controlled trial, patients treated with divalproex sodium (valproic acid and sodium valproate), 1000 mg/d, experienced significant pain relief compared with placebo-treated patients.[22] Adverse effects included vertigo, hair loss, headache, nausea, and diarrhea.

Tricyclic antidepressants, including amitriptyline, desipramine, and nortriptyline, might work by (1) inhibiting norepinephrine and serotonin uptake, (2) sodium-channel blockade, or (3) another mechanism that is unclear. Although amitriptyline is the most studied tricyclic antidepressant for PHN, available evidence and clinical experience suggest that nortriptyline and desipramine have comparable efficacy and are better tolerated.[23,24]

Nortriptyline and desipramine are preferred in frail and elderly patients. Start therapy with 10 to 25 mg nightly, titrating as tolerated every 2 weeks to 75 to 150 mg as a single daily dose. Adverse effects include dry mouth, fatigue, dizziness, sedation, urinary retention, orthostatic hypotension, weight gain, blurred vision, QT interval prolongation, constipation, and sexual dysfunction.

Serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants. Use of such agents as duloxetine and venlafaxine in PHN patients is extrapolated from their proven efficacy in treating diabetic neuropathy and other neuropathic pain conditions. Try duloxetine if your patient does not respond to or tolerate a tricyclic. The recommended dosage is 60 to 120 mg/d in 2 divided doses.[25]

Two randomized, 12-week, double-blind, placebo-controlled trials using duloxetine 60 mg once a day and 60 mg twice a day for diabetic peripheral neuropathy concluded that 120 mg was safe and effective in treating diabetic peripheral neuropathy, but 120 mg was not as well tolerated as 60 mg once a day.[25]

Monitor liver function periodically in patients taking duloxetine. Alternatively, you can give venlafaxine; the recommended dosage is 75 to 225 mg/d.[26]

Opioid analgesics are recommended as second- and third-line agents for PHN. Adverse effects include nausea, pruritus, sedation, confusion, constipation, hypogonadism, and risk of developing tolerance and abuse.

A double-blind crossover trial evaluated the analgesic efficacy of oral oxycodone; treatment resulted in significant reduction of allodynia, steady pain, and spontaneous paroxysmal pain. Oxycodone treatment resulted in superior scores

Available evidence and clinical experience suggest that nortriptyline and desipramine have comparable efficacy and are better tolerated than amitriptyline for PHN.

of global effectiveness, disability reduction, and patient preference, compared with placebo.[27]

In a randomized crossover trial, the combination of gabapentin and morphine was superior to either of these medications alone in relieving pain in PHN.[28]

Tramadol, an atypical opioid, has a weak μ-opioid receptor agonist effect and inhibits reuptake of serotonin and norepinephrine. Avoid using it in patients with a history of seizures. The maximum recommended dosage is 400 mg/d. An extended-release formulation of tramadol is also available.

Tramadol provided superior pain relief and improved quality of life in PHN patients in a randomized placebo-controlled trial.[29]

Tapentadol has weak μ-opioid receptor agonist activity; norepinephrine reuptake inhibition is more predominant than serotonin reuptake inhibition. This drug is also available as an extended-release formulation. The maximum recommended dosage is 600 mg/d.

Avoid using tapentadol in patients with a history of seizures. *Note:* Although there is no scientific evidence regarding the use of tapentadol in neuropathic pain, we use it often in our practice.

Acupuncture and transcutaneous electrical nerve stimulation do not appear to be effective for PHN relief.

Topical therapies

Treating PHN with a topical agent is associated with relatively fewer adverse effects than what has been seen with oral therapy because systemic absorption is minimal.

Lidocaine is available as a transdermal patch and as a topical gel ointment. The 5% lidocaine patch is FDA approved for treating PHN. Lidocaine, a sodium-channel blocker, is useful for treating patients with clinical evidence of allodynia. You can cut a patch to fit the affected area; a maximum of 3 patches can be used simultaneously for 12 hours on, 12 hours off. If helpful, the patch can be left in place for 18 hours.[30]

In 2 open-labeled, nonrandomized prospective studies, patients treated with the lidocaine patch had reduced intensity of pain and improved quality of life.[31,32]

If lidocaine patches are not available, or affordable, or if a patient has difficulty applying them, use 5% lidocaine gel instead.

Capsaicin topical cream is sold in 2 concentrations: 0.025% and 0.075%. An extract of hot chili peppers, capsaicin acts as an agonist at the vanilloid receptors. The recommended dosage is 3 or 4 times a day. Initial application causes burning to become worse, but repeated use results in diminished pain and hyperalgesia.

A 6-week, blinded parallel study, followed by a 2-year open label follow-up, showed that the 0.075% dose of topical capsaicin cream relieved pain in 64% of patients; pain was relieved in 25% of placebo-treated patients.[33]

An 8% capsaicin patch is FDA approved for treating PHN. The patch must be applied by a health care professional in a monitored setting. Prepare the affected area by pretreating it with a local anesthetic cream; then apply the patch and leave it in place for 1 hour. As many as 4 patches can be used at once. A single application can provide pain relief for as long as 12 weeks. Adverse effects are mostly mild and transient.

In a double-blind, randomized, placebo-controlled trial with an open-label extension, the score on a numeric pain-rating scale declined from baseline in both the high-concentration capsaicin group and the placebo group during Week 1; however, the capsaicin-treated group experienced long-term improvement through Week 12.[34]

(See TABLE 1[14-21, 23, 24, 27-34] for a summary of pharmacotherapeutic options.)

Alternative modalities to reduce pain

Acupuncture and transcutaneous electrical nerve stimulation (TENS) have been tried for the relief of PHN without consistent evidence of efficacy. There are no significant adverse effects associated with these therapies; however, the cost of treatment may be an issue. Acupuncture is not covered by many insurance carriers. Mental-health interventions, including cognitive and behavioral therapy, might help with overall physical and emotional functioning and quality of life.

Invasive interventions

Researchers have examined several interventional modalities for treating PHN that is refractory to medication.

Sympathetic nerve blocks. Retrospective studies have shown that sympathetic nerve block provides short-term improvement in pain in 40% to 50% of patients with PHN.[35]

Intercostal nerve block has been reported to provide long-lasting pain relief in patients with thoracic PHN.[36]

Neuraxial use of intrathecal methylprednisone is supported by moderately good evidence

TABLE 1
Pharmacotherapeutic options for managing postherpetic neuralgia[14-21, 23, 24, 27-34]

Medication	Starting dose	Dose titration	Common adverse effects	Cautions and comments
Anticonvulsants				
Gabapentin	100-300 mg	Start at bedtime and increase to tid dosing; increase by 100-300 mg every 3-5 days to total dose of 1800-3600 mg/d in 3 or 4 divided doses	Somnolence, dizziness, fatigue, ataxia, peripheral edema, weight gain, visual adverse effects	Decrease dose in patients with renal impairment Dialysis patients: Every-other-day dosing; dosed on the day of dialysis Avoid sudden discontinuation
Extended-release gabapentin	600 mg daily for 3 days, then 600 mg bid beginning Day 4	600 mg bid	Somnolence, dizziness	Recently approved by FDA for PHN; not much clinical experience as yet
Pregabalin	50 mg tid or 75 mg bid	300-600 mg/d in 2 divided doses for 7-10 days	Somnolence, fatigue, dizziness, peripheral edema and weight gain, blurred vision, and euphoria	Decrease dose in patients with renal impairment Titrate dosage slowly in elderly patients
Tricyclic antidepressants*				
Amitriptyline Desipramine Nortriptyline	10-25 mg at bedtime. Start at a lower dose in elderly	Increase as tolerated every 2 weeks, with a target dose of 75-150 mg as a single daily dose	Sedation, dry mouth, blurred vision, weight gain, urinary retention, constipation, sexual dysfunction	Cardiac arrhythmic disease, glaucoma, suicide risk, seizure disorder Risk of serotonin syndrome with concomitant use of tramadol, SSRIs, or SNRIs Amitriptyline has the most anticholinergic effects
Opioids				
Fentanyl patch† Methadone‡ Morphine Oxycodone	12 µg/hour 2.5 mg tid 15 mg q 6 hours prn 5 mg q 6 hours prn	Titrate at weekly intervals balancing analgesia and adverse effects. If patient tolerates the medications, can titrate faster	Nausea and vomiting, constipation, sedation, itching, risk of tolerance and abuse	Driving impairment and cognitive dysfunction during treatment initiation Be careful in patients with sleep apnea Additive effects of sedation with neuromodulating medications
Atypical opioids				
Tapentadol§	50 mg every 4-6 hours prn	Can titrate up to 100 mg q 4 hours. Maximum daily dose is 600 mg	Nausea and vomiting, constipation, drowsiness, and dizziness	Be careful in patients taking SSRIs, SNRIs, MAOIs, and TCAs Decrease dose in patients with moderate hepatic and renal impairment Avoid use in patients with a history of seizures
Tramadol	50 mg every 6 hours prn	Can titrate up to 100 mg q 6 hours. Maximum daily dose: 400 mg. Extended-release dosing once a day	Nausea and vomiting, constipation, drowsiness, dizziness	Be careful in patients with seizure disorder and concomitant use of SSRIs, SNRIs, and TCAs Decrease dose in patients with hepatic or renal disease
Topical agents				
Lidocaine patch	5% lidocaine patch	Can use up to 3 patches 12 hours/d	Local erythema, rash, blisters	Contraindicated in patients with known hypersensitivity to amide local anesthetics (eg, bupivacaine, mepivacaine) Do not use on skin with open lesions
Topical capsaicin	0.025% and 0.075% cream	Apply 3-4 times a day over affected region	No systemic adverse effects Burning and stinging sensation at the application site	Avoid contact with eyes, nose, and mouth Application of lidocaine gel locally may be helpful prior to capsaicin cream application
Capsaicin patch‖	8% single application patch	Need topical local anesthetic application prior to patch application. Patch applied for 1 hour	Local site irritation, burning, temporary increase in pain	Done in a physician's office under monitored circumstances Patient may need oral analgesics for a short period following application of the patch

*Obtain baseline EKG in patients with history of cardiac disease.
†May need to start a patient on short-acting opioid medications before changing over to a fentanyl patch.
‡Has a long and unpredictable half-life, hence the need for extra caution in elderly patients.
§Has not been studied in neuropathic pain; found to be effective in PHN and other chronic pain conditions.
‖Single application has been found to be effective for about 3 months.

MAOI, monoamine oxidase inhibitor; PHN, postherpetic neuralgia; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

of benefit in patients with intractable PHN.[37] Because this intervention poses significant risk of neurologic sequelae, we do not recommend that it be used in clinical practice.

Spinal cord stimulation was studied prospectively in a case series of 28 patients.[38] Long-term pain relief was obtained in 82%. Patients serve as their own controls by switching off the spinal cord stimulator and monitoring pain. Consider spinal cord stimulation for patients with well-established PHN that is refractory to conventional management.

Cryotherapy was used for facial neuralgia pain, without significant benefit.[39] Another trial showed short-term benefit in 11 of 14 patients who underwent cryotherapy of the intercostal nerves for thoracic PHN.[40]

Botulinium toxin A injection. An abstract presented at the February 2010 meeting of the American Academy of Pain Medicine described how subcutaneous injection of botulinium toxin A reduced pain in patients with PHN, compared with lidocaine and placebo injections. The pain relief was noted in 1 week and persisted for 90 days.[41]

Surgery. Many surgical interventions have been described and used to treat PHN, but none has a role in clinical practice.

Many surgical interventions have been used to treat PHN, but none has a role in clinical practice.

When should you refer to a pain management center?

Dermatomal pain that lasts for longer than 180 days after a herpes zoster rash can be considered "well-established PHN" to denote its refractory nature. As a primary care clinician, you can refer a patient with PHN to a pain management center at any stage of disease but especially when the:

- patient has a significant medical comorbidity and you think that he or she requires the services of a specialist to manage multimodal pharmacotherapy
- PHN pain is refractory to conventional treatment modalities
- patient needs an invasive intervention
- patient needs treatment with a high-dose capsaicin patch and you have not been trained to apply it.

Preventing herpes zoster and PHN

Obviously, preventing PHN is closely tied to preventing herpes zoster. To help prevent herpes zoster:

- vaccinate children with varicella vaccine to prevent primary varicella infection[42]
- use varicella-zoster immunoglobulin, as recommended by the CDC's Advisory Committee on Immunization Practices (ACIP), in immunocompromised, seronegative patients who were exposed recently to a person with chickenpox or herpes zoster[42]
- administer the herpes zoster vaccine to patients 60 years and older, as recommended by ACIP.[43] The FDA recently approved use of this vaccine for people 50 through 59 years, but ACIP has not changed its recommendations.[44]

As we've discussed, herpes zoster vaccination, antiviral therapy, and aggressive pain control can reduce the incidence, severity, and duration of acute herpes zoster and PHN.

A large multicenter, randomized, placebo-controlled trial demonstrated that herpes zoster vaccine decreases the likelihood of developing herpes zoster in immunocompetent individuals 60 years and older.[45] The vaccine reduced the incidence of herpes zoster by 51.3%; reduced the burden of illness by 61.1%; and reduced the incidence of PHN by 66.5%.[45] The live, attenuated vaccine is contraindicated in children, pregnant women, and immunocompromised individuals.

The number needed to treat for herpes zoster vaccine is 175; that is, 1 case of herpes zoster is avoided for every 175 people vaccinated.[1]

Newer tools mean a better outcome

We have improved our ability to diminish the incidence of herpes zoster and PHN and to manage postherpetic pain more effectively. These advances include the development of a herpes zoster vaccine; consensus that antiviral therapy and aggressive pain management can reduce the burden of PHN; identification of efficacious treatments for PHN; and recognition of PHN as a study model for neuropathic pain research.

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One case of herpes zoster is avoided for every 175 people vaccinated.

FEATURE ARTICLE

Managing chronic pain in older adults: 6 steps to overcoming medication barriers

These practical tips will help improve the likelihood of a successful analgesic trial in patients 65 and older.

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Managing chronic pain in an older adult can be a complicated task, with risks for adverse effects, under- or overmedication, and nonadherence. Pain can be alleviated in many cases, however, if you address potential complications and barriers to effective treatment when prescribing analgesic medications.

Pain is a part of daily life for many older adults

As many as 50% of community-dwelling older adults experience a chronic pain disorder, defined as pain on most days for at least 3 consecutive months.[1] Prevalence rates are typically higher (49%-84%) among residents of long-term care facilities.[2] Untreated chronic pain can

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lead to health consequences such as depression, decreased ability to socialize, impaired ambulation, impaired sleep, increased falls, malnutrition, and decreased quality of life.[1,3] Among older women, pain is the most common reported cause of impairment in activities of daily living.[4]

Arthritis and arthritis-related diseases (such as back pain) are common causes of chronic pain in older adults.[5] Other causes include neuropathies, vertebral compression fractures, cancer and cancer treatments, and advanced chronic diseases such as end-stage heart, lung, and kidney disease.[6-10]

Substantial literature documents that chronic pain is underdetected and undertreated with advancing age[11,12] and strongly supports efforts to improve pain care in later life. Treatment guidelines recommend a multimodal approach, including evidence-based nonpharmacologic treatments such as cognitive-behavioral therapy, exercise, and physical therapy.[1] At the same time, pharmacotherapies remain the primary treatment used by physicians,[13] and studies indicate that older people use analgesics frequently:

- When 551 older black and non-Hispanic white adults with osteoarthritis were interviewed, more than 80% of each group reported regular use of prescription and over-the-counter (OTC) analgesic medications.[14]
- In a cross-sectional study of 272 community-dwelling older adults with chronic pain from diverse causes, 59% reported routine use of an analgesic medication.[15]

The following 6 steps can improve the likelihood of a successful analgesic trial when managing chronic pain in people ages 65 and older. They take into account barriers you are likely to encounter, including polypharmacy, multimorbidity, cognitive and sensory impairment, sociodemographic factors, specific health beliefs about pain and pain treatments, and age-related physiologic changes.

Step 1. Conduct a comprehensive pain history

The first step in pain management is to perform a comprehensive pain assessment. Without a proper pain assessment, it will be difficult to effectively treat and monitor response to treatment. Whichever pain scale you decide to use, it is important to use the same pain scale consistently each time a pain assessment takes place.[3] The numeric rating scale and verbal descriptor scales (or pain thermometer) are widely used and have been shown to be preferred in the older adult population.[3,16] The numeric rating scale asks a patient to rate his or her pain on a scale of 0 to 10, with 0 being no pain and 10 being the most severe pain imaginable. The verbal descriptor scale is a measure of pain intensity on a vertical scale (typically a thermometer) from "no pain" to "excruciating."[3]

Recommendations. In addition to assessing the intensity of the pain using a pain assessment tool, it is important to determine certain characteristics of the pain. What is the location and quality of the pain? Ask patients how the pain limits them. What prior treatments have been tried and failed? What has worked the best? What treatment/coping strategies are they using now? Have they had any intolerable adverse effects from specific treatments? Reliable predictors of treatment response require further definition,[17] but a successful trial of a given analgesic in the past is often a good indicator of what might work again.

Step 2. Review the patient's problem list

Use of multiple medications. Polypharmacy—with 5 or more being a typical threshold criterion—is common in people ages 65 and older and frequently complicates the pharmacologic management of chronic pain.[16,18] Complications most often occur as a result of drug-drug interactions.

Multiple coexisting chronic conditions. Multimorbidity is common in older adults with chronic pain. Consider co-occurring diabetes, hypertension, and osteoporosis when initiating any trial of a pain medication. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be effective in treating pain syndromes, but their use can be hazardous in older individuals, particularly those with coexisting hypertension, cardiovascular disease, history of peptic ulcer disease or gastropathy, or impaired renal function. NSAID use has been implicated as a cause of approximately one-quarter of all hospitalizations related to drug adverse effects among adults over age 65.[1]

The geriatric syndrome of frailty is defined by deficits in physiologic reserve and decreased resistance to multiple stressors.[19] Risk of fracture is a particular concern of clinicians, older patients, and their caregivers. Opioids are the analgesic medications most often associated

NSAIDs can be effective in treating pain syndromes, but their use can be hazardous in older patients with hypertension, peptic ulcer disease, or impaired renal function.

with increased fracture risk. In a recent analysis of Medicare claims data, opioid users were found to have a significantly increased fracture risk compared with users of nonselective NSAIDs.[20] Mechanisms underlying this association include opioid-associated cognitive dysfunction and worsening gait/balance function.

Recommendations. Obtain a full list of the patient's medications, including all OTC and complementary preparations. Also consider chronic kidney problems, liver disease, movement disorders, and neurologic problems when selecting a pharmacologic agent. Consider what chronic conditions might be made worse by an analgesic trial or would operate as a contraindication to starting a specific pain medication. Establish which medications or comorbidities might modify your treatment choices.

Step 3. Establish the patient's treatment goals

We recommend shared decision-making when planning treatment and monitoring outcomes for older adults with chronic pain. Use your patient's reports of the experience of pain—including pain intensity and how pain affects daily functioning[1]—and identify his or her treatment goals, which might differ from yours. You may be aiming for the best pain relief possible, but your patient might be focused on practical issues such as increased mobility or ability to socialize. By talking openly, you can reach consensus and agree upon realistic treatment goals.

Fifty-six percent of nursing home residents with cognitive impairment received pain medications vs 80% of those with intact cognition.

This approach can improve patients' outcomes and satisfaction with treatment; it also has been shown to improve physician satisfaction when treating patients with chronic pain.[21] In a recent qualitative study, older individuals varied in how much they wanted to participate in making decisions and being a "source of control" in their pain treatment.[22] Some patients—particularly those ages 80 and older—prefer to have their physicians make treatment decisions for them, whereas others embrace active participation. Regardless of how much older individuals wish to share in treatment decisions, they all value being listened to and understood by their physicians.[21]

Recommendations. The patient's goals and expectations for treatment may or may not be the same as yours. Before starting a medication trial, address potential unrealistic expectations such as complete relief of pain or a belief that treatment is not likely to help. Come to a mutual decision as to what constitutes the most important outcomes, and you will then be able to monitor and assess treatment success.

Step 4. Identify barriers to initiating and adhering to therapy

Cognitive impairment is a strong risk factor for undertreatment of pain. It can lead to underreporting of pain by patients or difficulty for clinicians in assessing treatment response from those who are unable to communicate pain effectively. A study of nursing home residents found that only 56% of those with cognitive impairment received pain medications, compared with 80% of those with intact cognition.[23] Older patients with cognitive deficits and memory loss also may take analgesic medications inappropriately or forget when/if they took them, increasing the risk of undertreatment or overdosing.

Sensory impairment. Patients with visual deficits may have difficulty reading prescription bottle labels and information sheets. Those with auditory deficits may have trouble hearing, communicating, and understanding treatment instructions during a busy clinical encounter.

Sociodemographic factors. Many older adults live alone and have limited social support to encourage medication adherence.[24] Some have significant caregiving responsibilities of their own (such as a spouse in poor health), which can lead to stress and inconsistent use of prescribed medications.[25] Some older adults can't afford the costs of certain pain medications and may take less than the prescribed amount.

Many older adults lack the necessary skills to read and process basic health care information, including understanding pill bottle instructions, information that appears in patient handouts, and clinicians' instructions about possible adverse effects.[26,27] Low health literacy can lead to problems with medication adherence (taking too much or too little of an analgesic medication) and associated complications.

Health beliefs. Many older adults believe chronic pain is a natural part of aging; in one study, this was true of 61% of approximately 700 primary care patients with osteoarthritis pain.[28] Some older adults believe pain only gets worse over time,[28] and others believe treatment for pain is not likely to provide any meaningful benefit.[29,30] Beliefs such as these can lead

TABLE
Refine your approach to chronic pain in older patients with these 6 steps

1. Conduct a comprehensive pain history	Assess pain location and intensity, and ask how pain limits activity. What treatments have been tried? What worked best? Any intolerable adverse effects?
2. Review the problem list	Obtain a full medication list (OTC and supplements) to identify potential interactions. What chronic conditions (kidney or liver disease, movement disorders, neurologic problems) might worsen with analgesic medication or operate as a contraindication? Which drugs or comorbidities might affect treatment choices?
3. Establish treatment goals	Address potential unrealistic expectations (eg, complete relief of pain or no benefit from treatment). The patient's goals might differ from yours; come to a mutual decision about the most important outcomes.
4. Identify barriers to therapy	Be aware of how cognitive or sensory impairment, sociodemographic factors, or health beliefs may limit medication adherence. Elicit the patient's concerns about medications and discuss openly. Include the caregiver, as needed, when discussing treatments and monitoring outcomes.
5. Start low and go slow when initiating analgesia	Avoid "start low and stay low," which can contribute to undertreatment. If treatment goals are not met and the patient is tolerating therapy, advancing the dose is reasonable before trying another intervention.
6. Assess for effects and outcomes	Make certain that the patient (or caregiver) understands what adverse effects might occur, and create a plan to address them. Establish how often and when communication should occur. Encourage telephone calls and/or e-mail to communicate questions or concerns.

OTC, over the counter.

to stoicism or acceptance of the status quo.[31]

Older adults also may endorse beliefs about pain medications that are likely to decrease their willingness to engage in, or adhere to, recommended pharmacologic interventions. Some use pain medicines sparingly because they fear addiction or dependence.[32,33] Caregivers—often a spouse or adult child—also may express fears about the possibility of addiction.[32] Finally, some older adults believe that using prescription analgesic medications invariably results in adverse effects;[32] those who endorse this belief report minimizing medication use except when the pain is "very bad."[34]

Recommendations. Elicit concerns patients may have about using analgesic medications and discuss them openly. Although not all barriers (such as economic issues) are modifiable, most (such as beliefs that pain medications are addictive) can be successfully addressed through patient education.

If other social support, such as a family member or caregiver in the home, could positively affect analgesic engagement/adherence, include these facilitators when discussing treatment decisions and in monitoring for medication effectiveness and adverse effects.

Step 5. Start low and go slow when initiating analgesia

Advancing age is associated with increased sensitivity to the anticholinergic effects of many commonly prescribed and OTC medications, including NSAIDs and opioids.[35] Increasing the anticholinergic load can lead to cognitive impairments, including confusion, which can be particularly troublesome for older adults.[1]

Changes in pharmacokinetics (what the body does to the drug in terms of altering absorption, distribution, metabolism and excretion) and pharmacodynamics (what the drug does to the body in the form of adverse effects) occur as a function of advancing age.[1] Body fat increases by 20% to 40% on average, which increases the volume of distribution for fat-soluble medications.[16] Hepatic and renal clearance decrease, leading to an increased half-life and decreased excretion of medications cleared by the liver or kidneys. Age-associated changes

in gastrointestinal (GI) absorption and function include slower GI transit times and the possibility of increased opioid-related constipation from dysmotility problems.[1]

As a result of these physiologic changes, advancing age is associated with a greater incidence of drug-related adverse effects. Even so, individuals within the older population are highly heterogeneous, and no geriatric-specific dosing guidelines exist for prescribing pain medications to older adults.

Recommendations. We recommend the adage "start low and go slow" when initiating an analgesic trial for an older patient with chronic pain. This does not mean you should "start low and stay low," which can contribute to undertreatment.[36] If treatment goals are not being met and the patient is tolerating the therapy, advancing the dose is reasonable before moving on to another intervention.

We recommend that you "start low and go slow" but this does not mean that you should "start low and stay low."

Step 6. Assess for effects and outcomes outside the office

Adverse effects are a primary reason older adults discontinue an analgesic trial.[37] Make certain the patient (or caregiver, as appropriate) understands what adverse effects might occur, and create a plan to address them if they do.

Recommendations. Because many older people are reluctant to communicate with their physicians outside of an office visit, establish how often and when communication should occur. Telephone calls and/or e-mail are practical tools for patients to communicate questions or concerns to you, and you can enhance treatment outcomes with timely replies. In the near future, mobile health technologies may play a key role in monitoring for adverse effects and communicating positive treatment outcomes.

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PRIMARY CONSTIPATION

-VS-

OPIOID-INDUCED CONSTIPATION:

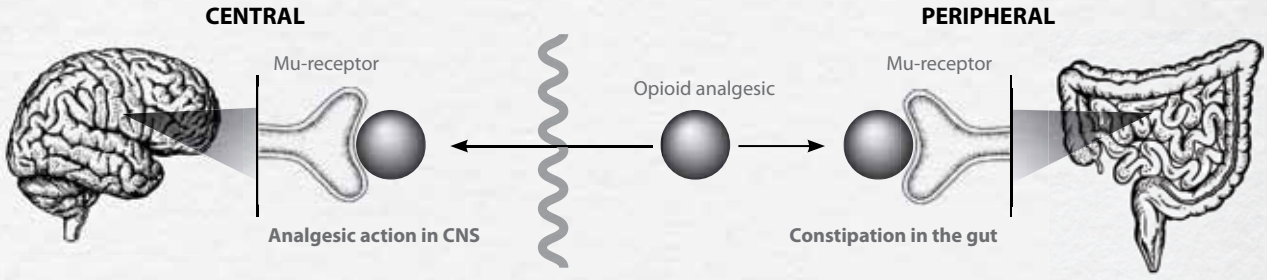
Same symptoms, different causes

Constipation is a common condition and may lead to serious complications due to the symptoms of straining and hard stools.[1] The most familiar form of constipation–primary constipation–can be caused by dietary factors, changes in routine, or abuse of laxatives.[1,2]

Another source of constipation is medication use, such as opioids for pain management.[2-4] This is called opioid-induced constipation and is a common side effect in patients taking opioid therapy.[5]

A distinct mechanism of constipation

Opioid-induced constipation is etiologically distinct from other types of constipation. It is principally a peripheral effect mediated by mu-opioid receptors in the gastrointestinal (GI) tract.[6] Nearly all opioids cause analgesia by binding to mu-opioid receptors in the central nervous system.[7,8] These binding targets are also located in the peripheral nervous system and along the GI tract; the intestinal wall is dense with these receptors.[9]



The agonist activity of opioids on these peripheral receptors causes a decrease in GI motility.[9] Because the GI tract is sensitive to opioids, this slowing of GI motility can even occur at lower opioid doses than those needed for analgesia.[5] In essence, the effects of opioids in the GI tract cause:

- Inhibition of propulsive motor activity of the intestine and slow intestinal transit, which causes constipation[8]
- Reduction of gut secretions and increases in fluid absorption contributes to constipation[8]

Recognition in your clinic

When providing therapy for treatment of constipation in your patients, it is important to note whether they are taking opioids. Knowing this can help you help your patients with opioid-induced constipation return to normal (consistent), regular, and comfortable bowel movements, occurring with a frequency reflective of their normal pattern prior to opioid therapy.[10]

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