440
Myalgias and Myopathies

January 2016

Fibromyalgia
pp 11-15

Polymyalgia Rheumatica and Giant Cell Arteritis
pp 16-22

Drug-Induced Myalgias and Myopathies
pp 23-27

Rhabdomyolysis
pp 28-31
Myalgias and Myopathies

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Foreword

A few years ago, one of my patients developed generalized muscle aches and proximal weakness that made it difficult for her to walk up stairs or lift her arms over her head. She turned out to have a statin-induced myopathy, and gradually improved after the drugs were discontinued. As family physicians, we see many patients with muscle pains or weakness because these are common conditions with multiple etiologies. This edition of **FP Essentials™** focuses on myalgias and myopathies.

Section One covers the diagnosis and management of fibromyalgia. It is refreshing to know that an assessment of tender points is no longer required when using the latest diagnostic criteria for fibromyalgia. Although only three drugs currently are Food and Drug Administration-approved for treating fibromyalgia, the authors give helpful tips on effective pharmacotherapy and nonpharmacotherapy (eg, exercise) management. Section Two discusses the differences and similarities of two related inflammatory disorders: polymyalgia rheumatica and giant cell arteritis, where prompt diagnosis and treatment can make a world of difference for our patients. Section Three focuses on myalgias and myopathies due to drugs, the most prominent being the statins. With guidelines increasingly recommending statins for prevention of cardiovascular disease, I was encouraged to learn that several statins have a lower likelihood of causing myopathies. Section Four addresses rhabdomyolysis, a severe form of myopathy that can be accompanied by acute kidney injury, significant electrolyte disturbances, and other dangerous complications. Trauma, exercise, infections, and toxic drugs are common etiologies, and aggressive hydration is the mainstay of treatment.

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Karl T. Rew, MD, Associate Medical Editor
Assistant Professor, Departments of Family Medicine and Urology
University of Michigan Medical School, Ann Arbor

Learning Objectives

1. Apply the most current criteria to diagnose fibromyalgia.
2. Prescribe effective pharmacotherapy and nonpharmacotherapy treatment when managing fibromyalgia.
4. Avoid prescribing drugs or drug combinations that can precipitate myopathy.
5. Prevent acute kidney injury by aggressively hydrating patients with rhabdomyolysis.
<table>
<thead>
<tr>
<th>Contents</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreword</td>
<td>2</td>
</tr>
<tr>
<td>Learning Objectives</td>
<td>2</td>
</tr>
<tr>
<td>Tables and Figures</td>
<td>4</td>
</tr>
<tr>
<td>Editorial Mission and Policies</td>
<td>5</td>
</tr>
<tr>
<td>Pretest Questions</td>
<td>7</td>
</tr>
<tr>
<td>Pretest Answers</td>
<td>8</td>
</tr>
<tr>
<td>Key Practice Recommendations</td>
<td>9</td>
</tr>
<tr>
<td>SECTION ONE</td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>11</td>
</tr>
<tr>
<td>Overview</td>
<td>11</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>11</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>11</td>
</tr>
<tr>
<td>Laboratory Testing</td>
<td>12</td>
</tr>
<tr>
<td>Management</td>
<td>12</td>
</tr>
<tr>
<td>Nonpharmacologic Management</td>
<td></td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td></td>
</tr>
<tr>
<td>SECTION TWO</td>
<td></td>
</tr>
<tr>
<td>Polymyalgia Rheumatica and Giant Cell Arteritis</td>
<td>16</td>
</tr>
<tr>
<td>Overview</td>
<td>16</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>16</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>17</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>17</td>
</tr>
<tr>
<td>Laboratory Testing</td>
<td>18</td>
</tr>
<tr>
<td>Imaging</td>
<td>19</td>
</tr>
<tr>
<td>Temporal Artery Biopsy</td>
<td>20</td>
</tr>
<tr>
<td>Management</td>
<td>20</td>
</tr>
<tr>
<td>Relapse</td>
<td>20</td>
</tr>
<tr>
<td>Managing Adverse Effects of Steroids</td>
<td>22</td>
</tr>
<tr>
<td>SECTION THREE</td>
<td></td>
</tr>
<tr>
<td>Drug-Induced Myalgias and Myopathies</td>
<td>23</td>
</tr>
<tr>
<td>Overview</td>
<td>23</td>
</tr>
<tr>
<td>Etiology</td>
<td>23</td>
</tr>
<tr>
<td>Clinical Presentation and Evaluation</td>
<td>23</td>
</tr>
<tr>
<td>Statin-Induced Myopathy</td>
<td>24</td>
</tr>
<tr>
<td>Management Options</td>
<td></td>
</tr>
<tr>
<td>SECTION FOUR</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>28</td>
</tr>
<tr>
<td>Overview and Prevalence</td>
<td>28</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>28</td>
</tr>
<tr>
<td>Etiology and Risk Factors</td>
<td>28</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>29</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>30</td>
</tr>
<tr>
<td>Complications</td>
<td>30</td>
</tr>
<tr>
<td>Management</td>
<td>31</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>32</td>
</tr>
<tr>
<td>Suggested Reading</td>
<td>36</td>
</tr>
<tr>
<td>Posttest Questions</td>
<td>37</td>
</tr>
<tr>
<td>Posttest Answers</td>
<td>39</td>
</tr>
<tr>
<td>* websites accessed December 2015</td>
<td></td>
</tr>
</tbody>
</table>
Tables and Figures

Tables

1. Drugs to Manage Fibromyalgia .......................................................... 13
2. Diagnostic Criteria for Polymyalgia Rheumatica ................................. 18
3. Differential Diagnosis of Polymyalgia Rheumatica ................................ 19
4. American College of Rheumatology Diagnostic Criteria for Giant Cell Arteritis ........................................ 19
5. Management and Follow-Up Recommendations for PMR and GCA ........ 21
6. Polymyalgia Rheumatica Disease Activity Score ................................... 22
7. Differential Diagnosis for Drug-Induced Myalgias and Myopathies .......... 24
8. Risk Factors for Statin-Induced Myopathy ......................................... 25
9. In Vitro Cytotoxicity Ranking for Statins .......................................... 25
10. Clinical Factors That Increase the Risk of Renal Complications in Rhabdomyolysis ........................................... 31
**FP Essentials™ Editorial**

**Mission and Policies**

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The mission of *FP Essentials* is to provide practicing family physicians, family medicine residents, and other clinicians and trainees with high-quality, cost-effective educational content that emphasizes new advances in clinical practice.

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1. To provide learners with information on advances in clinical practice to aid them in providing up-to-date care for their patients.
2. To assist learners in preparing for the American Board of Family Medicine (ABFM) certification and recertification examinations. Each monthly edition of *FP Essentials* is part of a 9-year curriculum that presents topics with areas of emphasis similar to those on the ABFM examinations.
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4. To present the content of *FP Essentials* in both print and online formats, thus enabling learners to have access to information anywhere, anytime.

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1. Using the 2010 American College of Rheumatology criteria, which one of the following is true of fibromyalgia?
   ❏ A. It affects approximately 10% of the population.
   ❏ B. It is more common in women than in men.
   ❏ C. It is the most common disorder for which patients are referred to rheumatology subspecialists.

2. Which one of the following drugs is Food and Drug Administration-approved for management of fibromyalgia?
   ❏ A. Amitriptyline (tricyclic antidepressant).
   ❏ B. Cyclobenzaprine (muscle relaxant).
   ❏ C. Duloxetine (serotonin-norepinephrine reuptake inhibitor).
   ❏ D. Fluoxetine (selective serotonin reuptake inhibitor).
   ❏ E. Gabapentin (neurologic).

3. For the past week, a patient has had a temporal headache that is resistant to standard analgesics. Amaurosis fugax then develops. A swollen optic disc is present on funduscopic examination. Which one of the following conditions is most likely?
   ❏ A. Fibromyalgia.
   ❏ B. Giant cell arteritis.
   ❏ C. Polymyalgia rheumatica.
   ❏ D. Rhabdomyolysis.

4. Which one of the following is unusual for a patient with polymyalgia rheumatica and would lead to consideration of a different diagnosis?
   ❏ A. Age 75 years.
   ❏ B. Asymmetric nonerosive synovitis.
   ❏ C. Elevated erythrocyte sedimentation rate.
   ❏ D. Morning stiffness.
   ❏ E. Presence of cyclic citrullinated peptide antibodies.

5. Concomitant use of a statin with which one of the following drugs is the most likely etiology of statin-induced myopathy?
   ❏ A. Amlodipine (dihydropyridine calcium channel blocker).
   ❏ B. Cephalexin (cephalosporin antibiotic).
   ❏ C. Gemfibrozil (fibrate).

6. Which one of the following statins is least likely to cause a statin-induced myopathy?
   ❏ A. Atorvastatin.
   ❏ B. Fluvastatin.
   ❏ C. Lovastatin.
   ❏ D. Pravastatin.

7. In a patient with rhabdomyolysis, which one of the following conditions can lead to cardiac arrhythmias and cardiac arrest?
   ❏ A. Compartment syndrome.
   ❏ B. Elevated creatine kinase level.
   ❏ C. Hyperkalemia.
   ❏ D. Myoglobinuria.

8. To help prevent acute kidney injury during the initial management of rhabdomyolysis, intravenous saline typically is started as soon as possible with a goal of maintaining a urine output of at least which one of the following rates?
   ❏ A. 75 mL/hour.
   ❏ B. 150 mL/hour.
   ❏ C. 300 mL/hour.
   ❏ D. 600 mL/hour.
Pretest Answers

Question 1: The correct answer is B.
Fibromyalgia, as defined by the 2010 American College of Rheumatology criteria, affects approximately 5% of the population and is the second most common disorder, after osteoarthritis, for which patients are referred to rheumatology subspecialists. Fibromyalgia occurs more frequently among women than among men, with a 2.3:1 prevalence ratio. See page 11.

Question 2: The correct answer is C.
Only duloxetine, milnacipran (Savella), and pregabalin (Lyrica) currently are approved by the Food and Drug Administration for the management of fibromyalgia. See pages 12-13.

Question 3: The correct answer is B.
Giant cell arteritis tends to follow a subacute course; the most common presenting symptom is a temporal headache resistant to standard analgesics. Amaurosis fugax, a transient monocular visual loss, manifests in 10% to 15% of patients and can progress to total blindness in up to 20% to 60% of untreated patients. The funduscopic examination may reveal a swollen optic disc, which foreshadows vision loss if present at the time of diagnosis. See page 17.

Question 4: The correct answer is E.
Cyclic citrullinated peptide antibodies typically are not present in polymyalgia rheumatica but present in rheumatoid arthritis. See page 18.

Question 5: The correct answer is C.
Risk factors for statin-induced myopathy include concomitant use with drugs metabolized by the cytochrome P450 3A4 systems, which include fibrates (especially gemfibrozil). See Table 8.

Question 6: The correct answer is D.
Many statins, including simvastatin, fluvastatin, atorvastatin, and lovastatin, are metabolized by the microsomal hepatic cytochrome P450 (CYP) system. Concomitant use of another drug metabolized by the CYP system can lead to drug-drug interactions and increase the risk of statin-induced myopathy. However, pitavastatin (Livalo), pravastatin, and rosuvastatin (Crestor) are metabolized independently of the CYP system and have a lower risk of statin-induced myopathy. In vitro data support pravastatin as having the lowest cytotoxicity of statins currently available in the United States, with simvastatin having the highest. See page 25 and Table 9.

Question 7: The correct answer is C.
In patients with rhabdomyolysis, direct muscle injury causes breakdown of muscle cells, leading to potassium and phosphate release. Hyperkalemia, when severe, can cause cardiac arrhythmias and cardiac arrest. See page 30.

Question 8: The correct answer is C.
The initial goals of rhabdomyolysis management are to preserve renal function and address electrolyte abnormalities. Initiating intravenous fluids with normal saline (avoiding potassium- or lactate-containing solutions) as soon as possible, preferably within the first 6 hours, can help prevent acute kidney injury. Fluids should be administered at a rate that maintains a urine output of at least 300 mL/hour for at least 24 hours unless the patient has a medical condition that would be worsened by such a fluid load. See page 31.
Key Practice Recommendations

1. To diagnose patients with fibromyalgia, use the modified 2010 American College of Rheumatology criteria.

2. For patients with fibromyalgia, prescribe a graded exercise program to improve pain and other symptoms.

3. For patients with fibromyalgia for whom nonpharmacologic treatments are not sufficient for pain management, consider drugs with strong evidence for symptom improvement, including cyclobenzaprine, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors.

4. Patients with symptoms of polymyalgia rheumatica should receive initial treatment with 15 to 20 mg/day oral prednisone.

5. Patients with suspected uncomplicated giant cell arteritis should receive initial treatment with 40 to 60 mg/day oral prednisone.

6. For all patients, do not initiate simvastatin therapy at 80 mg/day.

7. To prevent acute kidney injury in patients with rhabdomyolysis, intravenous fluids should be administered within 6 hours after muscle injury. Fluids should be administered at a rate to maintain urine output of 300 mL/hour or more for at least 24 hours, unless the patient has a condition that precludes aggressive hydration.

Resources

1. Strength of evidence: SORT C

2. Strength of evidence: SORT A
   Source: *JAMA*, reference 1.
   Website: http://jama.jamanetwork.com/article.aspx?articleid=1860480

3. Strength of evidence: SORT A
   Sources: *JAMA, Arthritis Rheum, CNS Drugs*, references 1, 28, and 27.

4. Strength of evidence: SORT A
   Website: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60680-1/abstract

5. Strength of evidence: SORT C
   Website: http://www.nature.com/nrrheum/journal/v8/n9/abs/nrrheum.2012.97.html

6. Strength of evidence: SORT C
   Source: *Clin Pharmacol Ther*, reference 104
   Website: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4169720/?report=classic

7. Strength of evidence: SORT C
   Website: http://aop.sagepub.com/content/47/1/90.abstract
Myalgias and Myopathies

Strength of Recommendation Taxonomy (SORT)

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>• Recommendation based on consistent and good-quality patient-oriented evidence.</td>
</tr>
<tr>
<td>B</td>
<td>• Recommendation based on inconsistent or limited-quality patient-oriented evidence.</td>
</tr>
<tr>
<td>C</td>
<td>• Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening.</td>
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</tbody>
</table>

*Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life. Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvement in patient outcomes (eg, blood pressure, blood chemistry, physiologic function, pathologic findings). *(From Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy [SORT]: a patient-centered approach to grading evidence in the medical literature. Am Fam Physician. 2004;69:548-556.)*

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Fibromyalgia is a syndrome of chronic widespread pain typically accompanied by fatigue, nonrestorative sleep, cognitive dysfunction, and mood disorders. As defined by the 2010 American College of Rheumatology criteria, fibromyalgia affects approximately 5% of the population and is the second most common disorder, after osteoarthritis, for which patients are referred to rheumatology subspecialists. These criteria provide a framework for diagnosing fibromyalgia that does not require tender points and incorporates other symptoms of the syndrome in addition to pain. Extensive laboratory tests and imaging are not required to diagnose fibromyalgia. A patient-centered, multimodal approach that includes patient education, behavioral therapy, a graded exercise program, and pharmacotherapy should be used for patients with fibromyalgia. Prescribers must be mindful of adverse drug effects and should tailor therapy to the individual patient. Strong evidence of benefit exists for tricyclic antidepressants, cyclobenzaprine, and serotonin-norepinephrine reuptake inhibitors in fibromyalgia management, whereas nonsteroidal anti-inflammatory drugs and opioids have limited proven benefit. Fibromyalgia can cause significant disability and loss of function. Family physicians are well equipped to direct the multimodal care of patients with fibromyalgia.

Case 1. Eva is a 34-year-old woman who has experienced depression, body aches, and fatigue for 13 months. She reports no fever, cough, abdominal pain, or irregular menses. She has no history of tick bites or recent international travel. She does not use alcohol or illicit drugs. Physical examination reveals bilateral muscle tenderness above and below the waist. Her joints are not inflamed.

Overview

Fibromyalgia is a syndrome of chronic widespread pain typically accompanied by fatigue, nonrestorative sleep, cognitive dysfunction, and mood disorders. Up to 75% of patients with fibromyalgia have depression, anxiety, or both, and migraines, dysmenorrhea, temporomandibular joint disorder, chronic fatigue, irritable bowel syndrome, interstitial cystitis, and endometriosis are common. Fibromyalgia, as defined by the 2010 American College of Rheumatology (ACR) criteria, affects approximately 5% of the population and is the second most common disorder, after osteoarthritis, for which patients are referred to rheumatology subspecialists. Fibromyalgia occurs more frequently among women than among men, with a 2.3:1 prevalence ratio.

Pathophysiology

Fibromyalgia is not understood completely, but recognition of its characteristics has progressed to the point where it is now a condition known to be characterized by abnormal central and peripheral pain processing. Functional magnetic resonance imaging studies show greater response to nonpainful and painful stimuli among patients with fibromyalgia than among controls. Magnetic resonance spectroscopy studies of women with fibromyalgia show dysfunction in regions of the brain integral to cognition, memory, sleep, and pain. Genes that likely contribute to the pathophysiology of fibromyalgia have been identified, and a family history of fibromyalgia is known to increase risk.

Diagnosis

Fibromyalgia is diagnosed based on a history of chronic widespread pain with associated fatigue, cognitive dysfunction, mood disorders, and sleep disturbance. The ACR criteria are used widely to aid in diagnosis. The original 1990 ACR criteria included widespread pain above and below the waist on the sides of the body and tenderness on pressure in at least 11 of 18 specific anatomic sites. Applying these criteria was challenging because the clinician needed to locate the correct sites, standardize the pressure to 4 kg/cm², and rely on the patient’s response.

The 2010 ACR diagnostic criteria for fibromyalgia focus on a Widespread Pain Index (WPI) and Symptom Severity (SS) scale. The newer criteria do not require analysis of tender points but instead...
Myalgias and Myopathies

acknowledge the polysymptomatic nature of fibromyalgia. Fibromyalgia may be diagnosed if the following conditions are met: 1) symptom duration of at least 3 months; 2) WPI score of at least 7 and SS scale score of at least 5 or WPI score between 3 and 6 and SS scale score of at least 9; 3) lack of another disorder to explain the patient’s pain. The SS scale includes other facets of the syndrome, including fatigue, cognitive disorders, and sleep disturbance.

The differential diagnosis of fibromyalgia is broad and includes anemia, rheumatoid arthritis, systemic lupus erythematosus, spondyloarthropathy, osteoarthritis, hypothyroidism, polymyalgia rheumatica, inflammatory myopathy, vitamin D deficiency, and systemic autoimmune disorders. Infectious diseases, such as Lyme disease, Rocky Mountain spotted fever, malaria, dengue fever, chikungunya, and others, can cause similar symptoms. Depression, anxiety, and other psychiatric conditions should be considered.

Laboratory Testing

In the absence of joint or muscle inflammation, only a limited number of laboratory tests are necessary to evaluate patients with suspected fibromyalgia. For most patients, a complete blood count, erythrocyte sedimentation rate, C-reactive protein, thyroid function tests, creatine kinase, and vitamin D levels are sufficient. Imaging typically is not necessary.

Case 1, cont’d. Eva scores a 10 on the Widespread Pain Index and a 5 on the Symptom Severity scale. Her history and physical examination are consistent with a diagnosis of fibromyalgia. She returns to discuss treatment options.

Management

Nonpharmacologic Management

A multimodal approach to fibromyalgia management should be encouraged, with evidence-based nonpharmacologic therapies serving as the cornerstone. Education, cognitive behavioral therapy (CBT), and exercise are well-studied and effective forms of management. Patients should be informed that meaningful, sustainable improvement in function can be obtained with self-management strategies. Integrative medicine treatments have less evidence but can play a role in fibromyalgia treatment.

Education should focus on methods to maintain functionality despite persistent pain, and patients should be reassured that fibromyalgia does not cause inflammation or damage tissue. Educational handouts, small group sessions, and Internet resources can provide reassurance for patients and validate their symptoms. Patients must recognize that symptoms will fluctuate over time and that becoming pain free is unlikely. Although some clinicians have voiced concern about labeling patients with the disease, patients who receive a new diagnosis of fibromyalgia eventually report less dissatisfaction with health; report fewer symptoms at 36 months; and require less testing, drug therapy, and imaging.

A Cochrane review showed that CBT slightly reduces fibromyalgia pain, improves mood, and decreases self-reported disability for up to 6 months after treatment. CBT also improves pain-related behaviors, self-efficacy, and physical function. A meta-analysis showed that psychological treatments improve pain, sleep, and functional status, and reduce depression and catastrophizing. Benefits are greater with early initiation of CBT and more hours spent in therapy. Mindfulness-based stress reduction can provide significantly reduced pain, anxiety, depression and somatic symptoms and improved quality of life and coping skills compared with controls. Relaxation therapy and biofeedback also are useful.

Prescribed exercise therapy for fibromyalgia should be started at a mild to moderate intensity and be increased gradually to avoid exacerbating symptoms. Patients should be counseled that the benefits of exercise outweigh the risk of a temporary increase in pain. There is good evidence that aerobic exercise improves well-being and physical function, may improve pain and pressure thresholds, and is superior to resistance training for pain reduction in fibromyalgia. Aquatic physical therapy enhances quality of life, reduces stiffness, and improves physical function as measured by a 6-minute walk test.

Although evidence is limited, acupuncture reduces pain and stiffness in patients with fibromyalgia.
and a small trial of electrical acupuncture showed significant improvement in fatigue and anxiety. The practice of tai chi showed a slight benefit in a small trial, improving Fibromyalgia Impact Questionnaire (FIQ) scores, pain, quality of life, and sleep, with some benefits lasting up to 24 weeks. Yoga and similar exercises can benefit patients, with minimal adverse events.

**Pharmacotherapy**

Only duloxetine, milnacipran (Savella), and pregabalin (Lyrica) currently are approved by the Food and Drug Administration for the management of fibromyalgia; however, this should not preclude the use of older, well-studied generic drugs. Table 1 lists the most common drugs used in fibromyalgia. When nonpharmacologic treatments are not sufficient for pain management, these drugs should be considered. Drugs should be selected with consideration of the patient’s most prominent symptoms and comorbid conditions as well as of cost and adverse effect profiles.

The muscle relaxant cyclobenzaprine can produce global improvement, reduce pain, and improve sleep. (This is an off-label use of cyclobenzaprine.) In two small randomized trials, cyclobenzaprine in dosages from 10 to 40 mg/day decreased stiffness, aches, and sleep disturbances. Somnolence can be mitigated by reducing the dose and recommending evening administration.

### Table 1

**Drugs to Manage Fibromyalgia**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugsa</th>
<th>Benefits</th>
<th>Adverse effects</th>
<th>Costb</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs</td>
<td>Amitriptyline/Nortriptyline</td>
<td>Reduce pain, may improve sleep</td>
<td>Arrhythmias, constipation, drowsiness, dry mouth, falls, hypertension, weight gain</td>
<td>$5</td>
</tr>
<tr>
<td>Skeletal muscle relaxant</td>
<td>Cyclobenzaprine</td>
<td>Reduces pain, may improve sleep</td>
<td>Dry mouth, sedation, serotonin syndrome, somnolence</td>
<td>$10</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Duloxetine/Milnacipran</td>
<td>Reduce pain, reduce depression/anxiety, may help with fatigue</td>
<td>Elevated transaminase levels, headache, hypertension, increased heart rate, nausea, palpitations</td>
<td>$30</td>
</tr>
<tr>
<td>Other analgesics</td>
<td>Tramadol</td>
<td>Reduce pain</td>
<td>Addiction, constipation, nausea, sedation, seizures, serotonin syndrome</td>
<td>$10</td>
</tr>
<tr>
<td>Opioid antagonist</td>
<td>Naltrexone</td>
<td>Reduces pain</td>
<td>Headache, insomnia, nausea, nightmares, vivid dreams</td>
<td>$40</td>
</tr>
<tr>
<td>Neurologics</td>
<td>Gabapentin/Pregabalin</td>
<td>Reduce pain, may improve sleep, may help with anxiety (pregabalin)</td>
<td>Cognitive impairment, dizziness, somnolence, weight gain</td>
<td>$10</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Fluoxetine/Paroxetine/Sertraline</td>
<td>Reduce pain, reduce depression/anxiety</td>
<td>Agitation, anxiety, discontinuation syndrome, headache, nausea, serotonin syndrome, sexual side effects, sleep difficulties, suicidal ideation, weight gain</td>
<td>$5</td>
</tr>
</tbody>
</table>

*aOnly duloxetine, milnacipran, and pregabalin currently are approved by the Food and Drug Administration for the treatment of fibromyalgia.

*bEstimated retail price for one month’s therapy based on author research.

NSAID = nonsteroidal anti-inflammatory drug; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.
Tricyclic antidepressants (TCAs) can reduce pain and morning stiffness and improve sleep quality. In one study, amitriptyline, started at dosages of 10 mg/day and increased to 50 mg/day, effectively relieved fibromyalgia symptoms. (This is an off-label use of TCAs.) In another study, amitriptyline 25 mg/night reduced pain, sleep difficulties, fatigue, and tender points. The addition of naproxen to amitriptyline did not add significant benefit. A more recent meta-analysis found amitriptyline provided better reduction in pain, sleep disturbances, and fatigue compared to duloxetine or milnacipran. Because arrhythmias are a potential adverse effect of TCAs, an electrocardiogram evaluating for blocks or QT prolongation should be considered for patients older than 50 years or with cardiac risk factors.

There is inconsistent evidence for selective serotonin reuptake inhibitors (SSRIs) in the management of fibromyalgia. Escalating doses of fluoxetine reduced pain, fatigue, and depression scores and improved overall FIQ scores compared with placebo during a 12-week trial. Patients without depression or anxiety who took paroxetine for 12 weeks had improved FIQ scores, decreased fatigue and anxiety, and more days on which they felt good. Adverse effects were more prevalent in the SSRI groups than in the placebo groups. (Fibromyalgia is an off-label use of SSRIs.) Serotonin-norepinephrine reuptake inhibitors (SNRIs), including duloxetine and milnacipran, reduce pain and slightly improve fatigue and quality of life for patients with fibromyalgia. (This is an off-label use of some SNRIs.) In one study, duloxetine 60 or 120 mg/day significantly reduced pain, global severity scores, and mental fatigue for up to 6 months. Duloxetine may be particularly beneficial for patients with prominent fatigue, depression, or anxiety. Milnacipran 100 or 200 mg/day improves pain, global status, and function compared with placebo, with some benefits lasting 1 to 3 years. However, nausea is common, and patients should be monitored for increases in heart rate and blood pressure.

A meta-analysis of randomized controlled trials showed that gabapentin and pregabalin significantly reduce pain and sleep disturbances and improve quality of life for patients with fibromyalgia. (Fibromyalgia is an off-label use of gabapentin.) The rate of treatment-related adverse events (ie, pain, dizziness, somnolence, and weight gain) was significantly lower with gabapentin. In a Cochrane review, there was insufficient evidence to determine the efficacy or safety of gabapentin for fibromyalgia, but pregabalin reduced pain and sleep disturbance compared with placebo. In a study of 124 patients taking pregabalin, the most common adverse events were dizziness, somnolence, and weight gain; approximately 33% of patients discontinued taking the drug because of adverse effects. Pregabalin at 150 mg 2 times/day or 300 mg/night significantly reduced pain and fatigue and improved sleep. Antiepileptic drugs, including carbamazepine, clonazepam, valproic acid, topiramate, and lamotrigine, did not show adequate evidence of significant benefit in fibromyalgia. (This is an off-label use of these drugs.)

Tramadol with or without acetaminophen improves pain in patients with fibromyalgia. Because tramadol works as a weak opioid agonist and along a serotonin-norepinephrine pathway, regular scheduled dosing may be more effective than as-needed dosing.

There is little to no evidence that opioids or nonsteroidal anti-inflammatory drugs are useful for managing fibromyalgia, and they should be avoided if possible because risks likely outweigh benefits. A 2014 Cochrane review showed no benefit of oxycodone in the management of fibromyalgia. The American Academy of Neurology recommends against the use of opioids in fibromyalgia. However, the opioid antagonist naltrexone 4.5 mg/day reduced pain and improved mood in patients with fibromyalgia. (These are off-label uses of naltrexone.)

The majority of patients with fibromyalgia requires at least two drugs for management. In one study, a combination of fluoxetine in the morning and amitriptyline in the evening significantly reduced pain and improved sense of well-being, sleep, and overall function. Pregabalin can be used in combination with SSRIs and SNRIs. Pregabalin in combination

A multimodal approach to pain management is beneficial. Fibromyalgia can result in loss of function and disability, but many patients can continue working, and those who remain in the workforce have better symptom control and quality of life.
with milnacipran improved pain and global status. If multiple serotonergic drugs are combined, patients should be educated on the risks of serotonin syndrome and its signs and symptoms.

A multimodal approach to pain management is beneficial. Fibromyalgia can result in loss of function and disability, but many patients can continue working, and those who remain in the workforce have better symptom control and quality of life. Although symptoms fluctuate, patients may note improvement over time. Family physicians have the tools necessary to care for most patients with fibromyalgia. Referral to a rheumatology subspecialist should be considered when the diagnosis is unclear or when the patient’s pain, depression, or other symptoms are not reduced with current management.

Case 1, cont’d. Eva enrolls in a fibromyalgia education program and begins a graded aerobic exercise program. She reports pain with exercise and difficulty sleeping. You advise her to continue the exercise program, and you prescribe amitriptyline 12.5 mg at bedtime with a plan to adjust the dosage if needed.
Polymyalgia Rheumatica and Giant Cell Arteritis

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are related inflammatory disorders that often coexist. Both are most common among women, whites, and older individuals. PMR is characterized by morning stiffness, pain, and decreased range of motion in the shoulders, neck, and pelvis. Diagnosing PMR can be challenging because no standard set of criteria or single diagnostic test exists. Patients with PMR benefit rapidly from treatment with oral glucocorticoids, and full recovery is likely, although adverse effects of treatment contribute to morbidity. GCA is a subacute vasculitis in which focal, segmental inflammatory infiltrates primarily affect cranial arteries. Diagnosis of GCA is based on clinical features, such as headache, jaw pain, vision changes, and temporal artery tenderness, along with an elevated erythrocyte sedimentation rate and inflammation seen on temporal artery biopsy. Permanent vision loss can occur, so patients who may have temporal arteritis should be started on glucocorticoids promptly. If treatment for GCA is started before visual symptoms progress, the prognosis for a full recovery is good. In PMR and GCA, relapses or exacerbations necessitating changes in therapy occur in up to 60% of patients.

Case 2. Mrs Roberts is a healthy 72-year-old woman who has had pain and stiffness in her neck, shoulders, and hips for 2 months. She reports fatigue but no visual disturbances or fever. Her symptoms are worse in the morning. She has a stiff, antalgic gait. Physical examination reveals no joint swelling, but does show decreased range of motion due to pain in her shoulders and hips. There is no tenderness to palpation of the temporal scalp.

Overview

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are closely related inflammatory disorders that often coexist. Approximately half of patients with GCA have features of PMR, and approximately one-fifth of patients with PMR have clinical features of GCA.59 Both diseases are most common among women, whites, and older individuals, with a peak incidence between ages 70 and 80 years.59,60 PMR and GCA do not increase mortality risk except in a subgroup of patients with GCA who develop thoracic aortic aneurysms and dissection.59,60

Polymyalgia rheumatica is the most common inflammatory rheumatic disease among elderly patients and is responsible for the greatest long-term use of glucocorticoids in this population.61,62 The syndrome is characterized by morning stiffness, pain, and decreased range of motion in the muscles and joints of the shoulders and pelvis.63 Patients with PMR benefit rapidly from treatment with oral glucocorticoids and have a good prognosis for full recovery.60 Patients with isolated PMR tend to be younger than those with coexisting GCA.64

Giant cell arteritis is a chronic systemic vasculitis of medium and large arteries, primarily affecting the cranial branches originating from the aortic arch.60,65 It is the most common vasculitis among adults.66 Approximately one-third of patients with GCA experience complications, including aortic aneurysms, dissection, or large vessel stenosis.67 In one cohort study of patients with GCA, 23% had vision changes and 4.4% experienced blindness.68 Stroke also can occur in GCA; approximately 2.8% of patients in another study had stroke at the time of diagnosis.69

Pathophysiology

The pathophysiology of PMR and GCA is based on antigen-mediated inflammation.59,63,70 Although myalgias are the presenting symptoms, true muscle inflammation is absent.63 Because seasonal and geographic variations in incidence have been found in several observational studies, an environmental or infectious etiology has been postulated, but no specific pathogens have been defined.59,63 A genetic predisposition is evidenced by the increased prevalence of PMR and GCA among individuals of Scandinavian and Northern European descent. Two genes in the HLA complex are associated with susceptibility to these syndromes.59,60,63
gest that an impaired hypothalamic-pituitary-adrenal axis may play a role,\textsuperscript{63,71}

In GCA, medium and large arteries originating from the aortic arch are affected by a focal, segmental inflammatory infiltrate,\textsuperscript{72,73} and this inflammation is responsible for the clinical symptoms. In advanced disease, tissue necrosis can occur as a result of vessel stenosis and occlusion.\textsuperscript{72}

**Clinical Presentation**

Patients with PMR typically present with bilateral, aching pain in the shoulders, neck, and pelvis, with morning stiffness lasting at least 1 hour.\textsuperscript{59,63,70} Symptoms typically are present for 2 to 3 months before diagnosis.\textsuperscript{60} Shoulder pain is the most common presenting symptom, occurring in more than 50% of patients.\textsuperscript{59,63} Musculoskeletal pain typically is worsened with movement and affects the ability to perform daily activities. Pain may radiate to the neck, buttocks, knees, and elbows.\textsuperscript{61,63}

Approximately 25% to 50% of patients report distal musculoskeletal manifestations, including carpal tunnel syndrome, peripheral arthritis, and hand swelling.\textsuperscript{59,63} Approximately 40% of patients have constitutional symptoms such as fatigue, fever, and malaise. Physical examination should not reveal swelling consistent with synovitis or joint effusion, but limitation because of pain often is present at the shoulder and hip. Trochanteric bursitis is the most common symptom of PMR to manifest in the hip.\textsuperscript{61} True muscle weakness should be absent but may be difficult to assess because of pain.\textsuperscript{59,63,67} Patients with PMR also may experience lower extremity claudication symptoms and peripheral arterial disease.\textsuperscript{63}

Giant cell arteritis tends to follow a subacute course; the most common presenting symptom is a temporal headache resistant to standard analgesics.\textsuperscript{59,60} Jaw pain due to claudication is present in approximately 50% of patients with GCA, and tongue claudication can be present as well.\textsuperscript{59} Permanent vision changes occur in up to 20% of patients and can progress from affecting one eye to affecting both in 1 to 2 weeks.\textsuperscript{60} Amaurosis fugax, a transient monocular visual loss, manifests in 10% to 15% of patients and can progress to total blindness in up to 20% to 60% of untreated patients.\textsuperscript{60,65,74} Neurologic manifestations of GCA include peripheral polyneuropathies, transient ischemic attacks, or cerebrovascular attacks in the vertebrobasilar or carotid arteries.\textsuperscript{59,60}

Systemic manifestations of GCA may include fever, fatigue, and weight loss. The prevalence of large vessel involvement is not well understood and ranges reported in the literature vary based on the technique used, areas of the vessels studied, and definitions of active disease.\textsuperscript{75} Symptoms of this may not become apparent until years after the onset of typical GCA symptoms.\textsuperscript{59} Large vessel involvement can be verified by findings on fluorodeoxyglucose-positron emission tomography, color Doppler ultrasonography, magnetic resonance angiography, or computed tomographic angiography of the aortic arch.\textsuperscript{65,67,75} Less common presenting signs and symptoms of GCA are peripheral neuropathy; diplopia; tongue, lip, or scalp necrosis; facial and submandibular swelling; and audiovestibular disturbances.\textsuperscript{60} Physical examination should focus on evaluation of visual acuity and extraocular movements, funduscopic evaluation, and evaluation of the temporal artery.\textsuperscript{60,65} The temporal arteries of patients with GCA may exhibit tenderness, palpable nodules, bruits, or decreased pulses. The funduscopic examination may reveal a swollen optic disc, which foreshadows vision loss if present at the time of diagnosis.\textsuperscript{66}

The gold standard for diagnosing GCA is temporal artery biopsy, although this is not necessary for all patients.\textsuperscript{60,67} A known subset of patients will experience silent (ie, temporal artery biopsy-negative) GCA.\textsuperscript{65} The presence of jaw claudication and diplopia strongly predicts a finding of GCA on temporal artery biopsy.\textsuperscript{67}

**Diagnosis**

The diagnosis of PMR is a subject of debate in the literature. There are numerous sets of criteria (Table 2), but none is considered the standard.\textsuperscript{59,76} Diagnosis is based on common clinical features, elevated inflammatory markers, benefit from treatment with glucocorticoids, and the absence of other syndromes.\textsuperscript{59,60,63,67,77} No specific laboratory test or gold standard for diagnosing PMR exists, and clinicians

Patients with polymyalgia rheumatica typically present with bilateral, aching pain in the shoulders, neck, and pelvis, with morning stiffness lasting at least 1 hour.
often consider treatment response as verification of the diagnosis.\textsuperscript{60,63,64,78} This can lead to potentially unnecessary long-term treatment with oral steroids.

The differential diagnosis of PMR is broad (Table 3). An alternative diagnosis should be considered for patients younger than 60 years with prominent systemic features (eg, weight loss, fever, night sweats), normal or high acute phase reactants, or lack of shoulder involvement.\textsuperscript{62,77} A lack of benefit from treatment also should prompt the search for an alternate diagnosis.\textsuperscript{61,62,78}

The high prevalence (approximately 39\% of peripheral synovitis among patients presenting with PMR symptoms makes distinguishing between late-onset rheumatoid arthritis (RA) and PMR difficult.\textsuperscript{63} However, the synovitis in pure PMR typically is asymmetric and nonerosive, in contrast to the synovitis in RA.\textsuperscript{61,63} In addition, cyclic citrullinated peptide antibodies typically are not present in PMR but present in RA.\textsuperscript{61} In a retrospective analysis, the symptoms of 13\% of 135 patients treated for pure PMR eventually were attributed to seronegative RA.\textsuperscript{79}

### Table 2

#### Diagnostic Criteria for Polymyalgia Rheumatica

<table>
<thead>
<tr>
<th>System</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healey</td>
<td>Age ≥50 years plus 3 of the following: Pain in neck, shoulders, or pelvic joints; Morning stiffness ≥1 hour; Elevated ESR; Rapid relief with low-dosage (≤20 mg/day) prednisone; RF and antinuclear antibody results must be negative</td>
</tr>
<tr>
<td>European League Against Rheumatism/American College of Rheumatology</td>
<td>In patients ≥50 years with elevated ESR and bilateral shoulder pain, a score of 4 without ultrasound or 5 with ultrasound meets criteria</td>
</tr>
<tr>
<td>Clinical criteria:</td>
<td>Morning stiffness ≥45 minutes = 2 points; Hip pain or reduced range of motion = 1 point; Absence of RF or anti-CCP = 2 points; Absence of other joint involvement = 1 point</td>
</tr>
<tr>
<td>Ultrasound criteria:</td>
<td>At least one hip and one shoulder with evidence of inflammation = 1 point; Both shoulders with evidence of inflammation = 1 point</td>
</tr>
<tr>
<td>The British Society of Rheumatology/the British Health Professionals in Rheumatology</td>
<td>Inclusion criteria: Age ≥50 years; Duration ≥2 weeks; Bilateral shoulder and/or pelvic joint pain; Elevated ESR, CRP, or both; Morning stiffness ≥45 minutes</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>Active infection; Active cancer; Active GCA</td>
</tr>
</tbody>
</table>

\textsuperscript{Anti-CCP = antibody to cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; GCA = giant cell arteritis; RF = rheumatoid factor.}

\textsuperscript{Information from various sources.}

Diagnosis of GCA requires the presence of three of the five criteria from the American College of Rheumatology (ACR)\textsuperscript{73,74} (Table 4). The presence of three criteria has a sensitivity of 93.5\% and a specificity of 91.2\%.\textsuperscript{74}

Case 2, cont’d. Laboratory test results show Mrs Roberts has an elevated erythrocyte sedimentation rate of 45 mm/hour. The rheumatoid factor, creatine kinase, complete blood count, thyroid function, urinalysis, liver function, and metabolic panel test results are normal. Symptoms have not improved.

#### Laboratory Testing

Initial laboratory investigation of patients with suspected PMR or GCA should include a complete blood count; metabolic panel; erythrocyte sedimentation rate (ESR); and levels of creatine kinase, rheumatoid factor, and antinuclear antibody.\textsuperscript{63,66,72} Although an ESR greater than 40 mm/hour is considered suggestive of a PMR diagnosis (normal is less than 20 mm/hour), 7\% to 20\% of patients with PMR have normal ESRs at diagnosis.\textsuperscript{60} An ESR of 50 mm/hour or higher is cited by the ACR as one criterion for the diagnosis of GCA, but
patients with normal ESRs at diagnosis have been described.\textsuperscript{59,73} Rheumatoid factor and antinuclear antibody test results typically are negative. Mild anemia of chronic disease and slightly elevated liver enzyme levels may be present.\textsuperscript{63,67} Elevated creatine kinase or persistent transaminitis (ie, elevated aspartate transaminase and alanine transaminase levels) should prompt consideration of an alternate diagnosis.\textsuperscript{63}

**Imaging**

Imaging can be helpful in the evaluation of patients with PMR, but more research is needed to determine the best modality.\textsuperscript{67} Plain x-rays of the chest can be considered to rule out paraneoplastic syndrome from lung cancer in high-risk patients.\textsuperscript{72} Radiosotopic and magnetic resonance imaging (MRI) study as well as arthroscopy have shown mild synovitis in the proximal joints of patients with PMR.\textsuperscript{64,70,80,81} Subacromial and subdeltoid bursitis are the most common lesions identified with MRI study and ultrasound, although the severity of bursitis does not correlate with the ESR.\textsuperscript{61,64,70,81} Musculoskeletal ultrasound of the shoulders and pelvic joints can help diagnose PMR in atypical presentations, because patients with PMR are more likely to have inflammatory changes in these joints than patients without PMR.\textsuperscript{63,77} In the assessment of hip and pelvic symptoms, physical examination is equivalent to ultrasound or MRI study for detecting trochanteric bursitis, hip synovitis, ischial-gluuteal bursitis, and iliopsoas bursitis.\textsuperscript{81}

In the diagnosis of GCA, ultrasound is not more accurate than physical examination and is not used routinely. If extracranial GCA is suspected, imaging with fluorodeoxyglucose-positron emission tomography, computed tomography scan, magnetic resonance studies, or arteriography is recommended.\textsuperscript{65,75}

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**Table 3**

**Differential Diagnosis of Polymyalgia Rheumatica**

<table>
<thead>
<tr>
<th>Rheumatic conditions</th>
<th>Drug-induced myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibromyalgia</td>
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<tr>
<td>Other connective tissue diseases</td>
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<tr>
<td>Polymyositis</td>
<td></td>
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<tr>
<td>Remitting seronegative symmetrical synovitis with pitting edema (RS3PE)</td>
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<tr>
<td>Seronegative rheumatoid arthritis</td>
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<tr>
<td>Spondyloarthropathy</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<td>Vasculitis</td>
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<td><strong>Malignancies</strong></td>
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<tr>
<td>Leukemia</td>
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<tr>
<td>Metastatic disease with bony metastases</td>
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<td>Multiple myeloma</td>
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<tr>
<td><strong>Infections</strong></td>
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<tr>
<td>Bacterial endocarditis</td>
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<tr>
<td>Cytomegalovirus</td>
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<tr>
<td>Epstein-Barr virus</td>
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<td>Lyme disease</td>
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<tr>
<td><strong>Musculoskeletal conditions</strong></td>
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<tr>
<td>Adhesive capsulitis</td>
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<tr>
<td>Osteoarthritis</td>
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<td>Rotator cuff tendinopathy</td>
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<tr>
<td>Trochanteric bursitis</td>
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<tr>
<td><strong>Other conditions</strong></td>
<td></td>
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<tr>
<td>Amyloidosis</td>
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<td>Depression</td>
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<td>Hypercalcemia</td>
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<td>Hypothyroidism</td>
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<td>Parkinsonism</td>
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<td>Posttraumatic stress disorder</td>
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<tr>
<td>Vitamin D deficiency</td>
<td></td>
</tr>
</tbody>
</table>


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**Table 4**

**American College of Rheumatology Diagnostic Criteria for Giant Cell Arteritis**

- At least 3 of the following:
  - Age at onset ≥50 years
  - New headache: new onset or new type
  - Temporal artery abnormality
  - Tenderness to palpation
  - Decreased pulsation
  - Erythrocyte sedimentation rate ≥50 mm/hour
  - Abnormal temporal artery biopsy

Myalgias and Myopathies

Temporal Artery Biopsy

Temporal artery biopsy is recommended for patients with suspected GCA who have visual symptoms or signs, and a prebiopsy score of 2 or 3 using the ACR criteria from Table 4.\(^6,7,4\) Some experts also have recommended temporal artery biopsy for all patients with PMR and significant constitutional symptoms or with physical examination evidence of temporal artery inflammation.\(^7,2\) The sensitivity of temporal artery biopsy is low and is affected by the specimen length (skip lesions are common in GCA) and prebiopsy steroid use.\(^7,4\) There is evidence that biopsy results do not change initial treatment for patients with strong clinical evidence of GCA, so therapy should be initiated for these patients before results are available.\(^7,2,4\) However, because there are significant comorbidities associated with long-term steroid use, it may be useful to confirm the diagnosis before committing a patient to the risks associated with prolonged steroid exposure. A retrospective review of 186 patients who underwent biopsy for presumed GCA confirmed the utility of the ACR criteria, which provide a sensitive (93.5% sensitivity) and specific (91.2% specificity) method to diagnose GCA without performing temporal artery biopsy.\(^7,4\) Patients with prebiopsy ACR scores of 1 or lower should not undergo temporal artery biopsy.

Case 2, cont’d. After you discuss the potential adverse effects of oral steroid therapy with Mrs Roberts, you prescribe prednisone 15 mg/day for polymyalgia rheumatica. A bone density study is scheduled, and you recommend Mrs Roberts start taking omeprazole, calcium, and vitamin D.

Management

Polyarticular rheumatism management decisions can be challenging because of the lack of standard regimens and firm endpoints. Glucocorticoids are considered first-line treatment for PMR and GCA because of rapid response and efficacy.\(^6,1,3,7,2\) (This is an off-label use of some glucocorticoids.) Patients who do not benefit should be evaluated for alternative diagnoses.\(^6,3,7,0,4\) Therapy duration typically is 1 to 2 years, and the need for longer courses to control symptoms should prompt reconsideration of the diagnosis.\(^6,0,3,7,2\) Low-dose aspirin should be considered to prevent cerebrovascular events in patients with GCA.\(^6,6\) Proposed treatment and follow-up schedules for PMR and GCA are shown in Table 5.

Because of the complications associated with long-term glucocorticoid use, incorporating other drugs in PMR and GCA management is an area of ongoing study. The discovery of high levels of tumor necrosis factor and interleukin 6 in the serum of patients with PMR has sparked interest in immune-modulating treatments, such as etanercept (Enbrel) and tocilizumab (Actemra).\(^6,0,7,8\) These appear to be safe and effective for patients with PMR, especially those who cannot tolerate prolonged glucocorticoid therapy, but long-term follow-up studies are lacking.\(^6,4\)

Methotrexate has been investigated as a steroid-sparing alternative to treat PMR and GCA, mainly for patients with adverse effects from steroids or those who need high doses to control active disease.\(^6,3\) (These are off-label uses of methotrexate.) One randomized, double blind, placebo-controlled trial showed that adding methotrexate to steroids decreased the total steroid dose, but the rate of adverse effects from steroids was not reduced.\(^7,2\)

Nonsteroidal anti-inflammatory drugs typically are not recommended; their use neither lowers the total prednisone dose needed to control symptoms nor changes therapy duration, but it does increase the rate of adverse events.\(^6,2\) (These are off-label uses of nonsteroidal anti-inflammatory drugs.)

Case 2, cont’d. Two weeks after Mrs Roberts starts taking prednisone, the morning stiffness has resolved, her energy level has improved, and the erythrocyte sedimentation rate is normal. She notes moodiness and poor sleep. You initiate a long steroid taper.

Relapse

Although most patients with PMR or GCA benefit initially from therapy, relapses or exacerbations necessitating reinitiation or increases in glucocorticoid therapy occur in up to 60% of patients, typically within the first year of therapy.\(^6,3,6,4,7,6\) Women and patients with higher initial inflammatory markers are more likely to experience relapse, and some studies indicate female patients require a longer therapy duration.\(^7,5,8,0\) However, an increased ESR in the absence of clinical signs does not indicate relapse.\(^6,1,4,7,6\)

Approximately 30% to 50% of patients with PMR have relapsing and remitting courses and require low-dose steroids for much longer than the typical 1 to 2 years, with C-reactive protein and interleukin 6 levels remaining elevated throughout treatment.\(^8,3\) Multiple relapses should prompt a change in management and consideration of other diagnoses.\(^7,6\) Options for managing relapses include increasing prednisone...
to the previous higher dose, administering a single intramuscular methylprednisolone injection, or adding a disease-modifying antirheumatic drug such as methotrexate.\(^a\) When GCA relapse is suspected based on changes in visual acuity, visual fields, or funduscopic examination results, prednisone 60 mg/day or intravenous methylprednisolone can be used.\(^{66,75}\) The presence of jaw claudication requires the use

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Management and Follow-Up Recommendations for PMR and GCA</th>
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<tbody>
<tr>
<td><strong>PMR</strong></td>
<td>GCA</td>
</tr>
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</table>
| Initial management | Oral prednisone 15 to 20 mg/day for 1 to 2 months or until remission of myalgias  
OR  
IM methylprednisolone 120 mg every 3 to 4 weeks for mild cases  
Calcium and vitamin D  
Bone-sparing drugs if indicated\(^a\)  
Gastroprotective drugs if indicated\(^b\) | Uncomplicated GCA: oral prednisone 40 to 60 mg/day for 2 to 4 weeks  
Complicated GCA (visual loss): 500 mg to 1 g IV methylprednisolone for 3 days, then transition to oral regimen  
Calcium and vitamin D  
Bone-sparing drugs if indicated\(^a\)  
Gastroprotective drugs if indicated\(^b\)  
Aspirin if indicated\(^c\) |
| Tapering schedule | Taper prednisone dose by 20% per month with frequent follow-up visits and monitoring for signs of clinical relapse  
Monitor ESR and CRP monthly  
Example management regimen (using prednisone):  
15 mg/day for 3 weeks  
12.5 mg/day for 3 weeks  
10 mg/day for 4 to 6 weeks  
Reduction by 1 mg/day every 4 to 8 weeks or alternate day reductions (10/7.5 mg on alternate days) | Start taper after all clinical symptoms have resolved AND inflammatory markers are normal  
Taper prednisone dose by 10 mg every 2 weeks to 20 mg/day. Then by 2.5 mg every 2 to 4 weeks to 10 mg/day, then by 1 mg every 1 to 2 months if no flare occurs  
Monitor ESR and CRP monthly  
Example management regimen (using prednisone):  
40 to 60 mg prednisone continued until symptoms and laboratory result abnormalities resolve (≥3 to 4 weeks)  
Reduce dose by 10 mg every 2 weeks to 20 mg  
Reduce dose by 2.5 mg every 2 to 4 weeks to 10 mg  
Reduce dose by 1 mg every 1 to 2 months |
| Follow-up interval | Weeks 0, 1 to 3, 6  
Months 3, 6, 9, 12 | Weeks 0, 1, 3, 6  
Months 3, 6, 9, 12 |
| Follow-up laboratory tests and imaging | CBC, ESR/CRP, BMP | CBC, ESR/CRP, BMP  
Every 2 years: chest x-ray to monitor for aortic aneurysm |
| Management duration | 1 to 3 years, based on clinical response | Based on clinical response |
| Management of relapse | Increase prednisone to previous dose  
Revisit diagnosis  
Consider temporal artery biopsy | Repeat initial management dose and schedule  
Repeated relapses may require adjuvant therapies, such as methotrexate |

\(^a\)Indicated based on results from screening bone density examination and World Health Organization criteria.

\(^b\)Indicated for all patients taking high-dose regimens for GCA. Indicated for patients at risk of peptic ulcer disease or gastrointestinal bleeding at lower doses.

\(^c\)Indicated for stroke prevention in the absence of contraindications.

**BMP** = basic metabolic panel; **CBC** = complete blood count; **CRP** = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **GCA** = giant cell arteritis; **IM** = intramuscular; **IV** = intravenous; **PMR** = polymyalgia rheumatica.

of oral prednisone 60 mg/day, but in patients who experience the return of only headache symptoms, the previously used higher dose of glucocorticoid may be used. Recurrent relapses should prompt investigation into other diagnoses, referral to a subspecialist, or use of steroid-sparing drugs to manage symptoms.

The PMR Disease Activity Score (Table 6) is a validated tool for assessing treatment response and defining relapse. Scores less than 7 indicate inactive disease; scores of 7 to 17 indicate moderately active disease; and scores greater than 17 indicate highly active disease. A score greater than 9.35 after treatment, or an increase of at least 6.6 between two visits, indicates relapse, whereas a score between 0 and 1.5 indicates disease remission.

Managing Adverse Effects of Steroids

In a 1997 study, 65% of patients with PMR treated with steroids experienced at least one adverse effect, including diabetes, vertebral fractures, femoral neck fractures, hip fractures, and cardiovascular disease. Screening for diabetes, hypertension, osteoporosis, gastric or peptic ulcer disease, and psychiatric disorder should be considered. Individuals with known high risk of fracture (eg, age at least 65 years, prior fragility fracture, or T-score of -1.5 or less on dual-energy x-ray absorptiometry) may need treatment with bisphosphonates, calcium, and vitamin D while undergoing steroid therapy. For other patients, screening with dual-energy x-ray absorptiometry can help assess risk. Gastroprotective therapy with a histamine2 blocker or a proton pump inhibitor may be helpful for older patients or those with other risk factors for gastroesophageal reflux disease or peptic ulcer disease.

Case 2, cont’d. Mrs Roberts’ prednisone dose is tapered slowly over the next 2 years, and she is eventually able to discontinue it without a return of symptoms.

### Table 6

**Polymyalgia Rheumatica Disease Activity Score**

<table>
<thead>
<tr>
<th>Components</th>
<th>To Score, Add the Following</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of morning stiffness</td>
<td>Minutes, multiplied by 0.1</td>
</tr>
<tr>
<td>Ability to elevate the upper limbs</td>
<td>Scale of 0 to 3, where 0 = normal and 3 = cannot lift the arms</td>
</tr>
<tr>
<td>Physician’s global assessment of disease activity</td>
<td>10-point visual analog scale</td>
</tr>
<tr>
<td>Patient’s report of disease activity</td>
<td>10-point visual analog scale</td>
</tr>
<tr>
<td>C-reactive protein level</td>
<td>In mg/dL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>&lt;7</td>
<td>Inactive disease/remission</td>
</tr>
<tr>
<td>7 to 17</td>
<td>Moderately active disease</td>
</tr>
<tr>
<td>&gt;17</td>
<td>Highly active disease</td>
</tr>
</tbody>
</table>

Drugs can cause myalgias and myopathies through a variety of mechanisms. Most drug-induced myopathies are potentially reversible if recognized early. Prescribers should be familiar with common drug-induced myopathies and drug-drug interactions. Clinical presentations can be subacute or acute, ranging from benign muscle pain with mild elevations of serum creatine kinase to fulminant rhabdomyolysis with high creatine kinase levels and potentially life-threatening acute kidney injury. Myalgias and proximal muscle weakness are typical symptoms; onset can be weeks to months after drug exposure. Endocrine disorders and inflammatory etiologies should be excluded because their management may differ from that of drug-induced myopathies. Statin drugs are prescribed widely, and statin-induced myopathy is one of the most commonly recognized and studied myopathies. Risk factors include dose and type of statin prescribed, older age, female sex, genetic predisposition, and concomitant use of other drugs metabolized by the cytochrome P450 system. Glucocorticoids, immunologic drugs, and antimicrobials, as well as other drugs and alcohol, can cause myopathies. Management typically involves discontinuing the drug and switching to an alternative drug or considering an alternative dosing schedule. Referral to a neuromuscular subspecialist is warranted if symptoms persist.

**Case 3. Samuel, 55 years, recently started a moderate-dose statin based on his score on a standardized cardiovascular risk stratification tool. He returns 6 weeks later with muscle aches and weakness in his upper arms and thighs. The physical examination reveals bilateral and symmetric muscle tenderness to palpation of his upper arms and thighs. There is no evidence of inflamed joints. He has difficulty climbing stairs and rising from a seated position.**

**Overview**

When recognized early, most drug-induced myopathies are potentially reversible, and awareness of drug-drug interactions may make them preventable. Although statin-induced myopathies have received much attention in the medical literature, prescribers should be aware of the many other drug-induced myopathies. The wide range of definitions used to describe muscle-related symptoms makes it difficult to standardize reporting of adverse events, and the true incidence is unknown. This edition of *FP Essentials* uses the following definitions: A *myopathy* is any disease involving the muscle. A *myalgia* is a muscle ache or pain. *Myositis* refers to muscle inflammation, typically with an elevated serum creatine kinase (CK) level. *Rhabdomyolysis* is a necrotizing myopathy that can cause severe muscle symptoms accompanied by CK elevations of at least 10 times the upper limit of normal (and up to 2,000 times the upper limit of normal), typically with an elevated serum creatinine level and myoglobinuria.

**Etiology**

Drugs can cause myalgias and myopathies through a variety of mechanisms affecting muscle fiber metabolism. They may alter mitochondria; affect muscle antigens, generating an immunologic or inflammatory response; or change the electrolyte balance of the muscle cell. Statin-associated myopathy appears to have a genetic component involving the gene responsible for regulating hepatic uptake of statins.

**Clinical Presentation and Evaluation**

Drug-induced muscle symptoms are variable and can present acutely or subacutely. Drug-induced myalgias are benign muscle cramps with normal to mildly elevated CK levels, whereas drug-induced myopathies exhibit more severe degrees of muscle weakness and significantly elevated CK levels. Severe drug-induced myopathies can result in rhabdomyolysis. Myalgias and proximal muscle weakness, often accompanied by cramps and fatigue, can occur weeks to months after drug exposure.

A thorough history should be obtained, including a close review of the patient’s drugs as well as present and
past use of alcohol and illicit drugs. The physical examination should focus on identifying objective muscle weakness. Weakness in a proximal distribution is consistent with myopathy. Both proximal and distal weakness is of concern, suggesting uncommon neuromyopathy, as can be seen with colchicine in high doses. Initial laboratory tests may include serum CK, thyroid-stimulating hormone, creatinine, and urinalysis. Thyroid disease should be treated if identified. The suspected drug should be discontinued, or the dose should be reduced. Consultation with a neuromuscular subspecialist for muscle biopsy and electromyography may be indicated if symptoms are marked or if they fail to resolve with discontinuation of the suspect drug. A muscle biopsy may be needed to help define the etiology and guide treatment.

The differential diagnosis of muscle symptoms is vast. Endocrine disorders and inflammatory etiologies should be excluded because their management may differ from that of drug-induced myopathies (Table 7). Metabolic disorders and muscular dystrophies may be revealed by or may mimic drug-induced myopathies. 

### Statin-Induced Myopathy

Statin (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors)-induced myopathy is one of the most commonly recognized and studied drug-induced myopathies, primarily because statins are prescribed frequently. Thirty million individuals worldwide have received prescriptions for statins to manage cardiovascular risk reduction in the primary and secondary care settings. In the Prediction of Muscular Risk in Observational conditions (PRIMO) study of 7,924 patients taking a moderate- to high-dose statin, more than 10% of patients had muscle symptoms within 1 month of drug initiation. An estimated 5% to 10% of patients discontinue statin therapy because of muscle symptoms. A common definition of statin-induced myopathy is muscle pain, tenderness, and weakness, with CK levels at least 10 times the upper limit of normal. Using this definition, the incidence of myopathy is 11 per 100,000 individuals per year, so the risk of developing a statin-induced myopathy is low. The 2013 American College of Cardiology/American Heart Association cholesterol guidelines recommend statins as first-line drugs to reduce atherosclerotic cardiovascular disease risk in adults. Although many patients may benefit from treatment with statins, not all may tolerate them. The risk of statin-induced myopathy varies with the dose and type of statin prescribed and is increased by older age, age-associated diseases, female sex, polypharmacy, concomitant use of certain drugs metabolized by the cytochrome P450 (CYP) system, genetic predisposition, and possibly deficiencies of vitamin D and coenzyme Q10 (Table 8).

The mechanism by which statin-induced myopathy develops is not fully understood. Statins inhibit HMG-CoA reductase, an enzyme essential for the biosynthesis of cholesterol. One proposed etiology is a deficiency of coenzyme Q10, which plays an important role in the mitochondrial process of adenosine triphosphate production and muscle metabolism. Supplementation with coenzyme Q10 for the management and prevention of statin-induced myopathy has shown variable results and needs further evaluation. An immune-mediated etiology has been proposed, and autoantibodies against HMG-CoA reductase have been identified in some patients with necrotizing autoimmune myopathy.

<table>
<thead>
<tr>
<th>Differential Diagnosis for Drug-Induced Myalgias and Myopathies</th>
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<tbody>
<tr>
<td><strong>Endocrine disorders</strong></td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
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<td>Hyperthyroidism</td>
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<tr>
<td>Hypothyroidism</td>
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<tr>
<td><strong>Inflammatory disorders</strong></td>
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<tr>
<td>Dermatomyositis</td>
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<tr>
<td>Polymyositis</td>
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<tr>
<td><strong>Metabolic disorders</strong></td>
</tr>
<tr>
<td>Glycogen storage diseases</td>
</tr>
<tr>
<td>Lipid storage diseases</td>
</tr>
<tr>
<td>Mitochondrial myopathy</td>
</tr>
<tr>
<td><strong>Muscular dystrophies</strong></td>
</tr>
<tr>
<td>Becker muscular dystrophy</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
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</table>

The 2008 Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) study helped identify a genetic susceptibility for statin-induced myopathy caused by high-dose simvastatin. Individuals with a dysfunctional polymorphic variant of SLCO1B1, a gene that encodes the enzyme responsible for facilitating hepatic uptake of statins, have impaired simvastatin transport to the liver. This variant may explain up to 60% of simvastatin-associated cases of myopathy. Clinicians are likely to increase the dose when expected lipid goals are not reached, further exacerbating the risk of myopathy. The 2014 update from the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for SLCO1B1 warn against initiating simvastatin therapy at 80 mg/day for all patients. The guidelines also offer recommendations for initiating and escalating doses of simvastatin. Testing for variant SLCO1B1 is available commercially.

Vitamin D deficiency often causes myalgias and muscle weakness. Low 25-hydroxyvitamin D (less than 30 ng/mL) has been proposed as a potential risk factor for statin-induced myopathy. A small observational study showed improvement in symptoms with administration of vitamin D. The evidence regarding vitamin D supplementation for the prevention or treatment of statin-induced myopathy is limited, and further investigation is needed.

Many statins, including simvastatin, fluvastatin, atorvastatin, and lovastatin, are metabolized by the microsomal hepatic CYP system. Concomitant use of another drug metabolized by the CYP system can lead to drug-drug interactions and increase the risk of statin-induced myopathy. However, pitavastatin (Livalo), pravastatin, and rosuvastatin (Crestor) are metabolized independently of the CYP system and have a lower risk of statin-induced myopathy.

In vitro data support pravastatin as having the lowest cytotoxicity of statins currently available in the United States, with simvastatin having the highest (Table 9). The clinical scenario of statin-induced myopathy is similar to those of other drug-induced myopathies.
Myalgias and Myopathies

The muscle pain is described as aching and cramping in the proximal limbs and trunk, often with nocturnal leg cramps.\(^{108}\) Weakness typically is proximal but occasionally involves distal muscles and commonly manifests as difficulty rising from a chair, climbing stairs, or reaching overhead. The average onset of symptoms ranges from weeks to 6 months after statin initiation.\(^{109}\) Vigorous exercise can aggravate statin-induced myopathies.\(^{110}\)

Diagnosing statin-induced myopathy requires a high index of suspicion and an awareness of drug-drug interactions and risk factors. It is reasonable to inquire at each visit if a statin user is experiencing symptoms.\(^{87}\) A muscle biopsy is indicated rarely for drug-induced myopathy;\(^{111}\) however, referral to a neuromuscular subspecialist for biopsy would be prudent if symptoms or elevated CK levels do not resolve with drug discontinuation or if a previously unrecognized neuromuscular disorder is suspected.\(^{112}\) Obtaining a baseline CK level before initiation of statin therapy is not routinely recommended. A prudent option would be to consider a baseline CK if a patient is at high risk or is taking another drug dependent on the CYP system.\(^{88}\)

**Case 3, cont’d.** Results of serum creatinine, thyroid-stimulating hormone, and urinalysis are normal, but the serum creatine kinase level is more than 10 times the upper limit of normal. You diagnose a statin-induced myopathy and instruct Samuel to discontinue the statin until symptoms resolve.

**Management Options**

Alternative dosing schedules, such as administering a statin 2 to 3 times/week or even once weekly, can result in favorable lipid outcomes and improvement of myopathic symptoms.\(^{113}\) Switching to another cholesterol-lowering nonstatin class, such as ezetimibe (Setia) or a bile acid sequestrant, is a reasonable option,\(^{96}\) but these drugs do not have the same proven benefits as statins. Red yeast rice is an over-the-counter supplement that contains a naturally occurring statin bioidentical to lovastatin.\(^{90,114}\) A small randomized controlled trial of red yeast rice 2,400 mg 2 times/day compared with pravastatin 20 mg/day showed similar decreases in low-density lipoprotein levels and similar levels of muscle pain but lower rates of discontinuation of red yeast rice.\(^{114}\) Referral to a neuromuscular subspecialist is warranted if symptoms persist.

**Glucocorticoid-Induced Myopathies**

Glucocorticoids decrease the rate of protein synthesis, leading to protein catabolism and muscle atrophy,\(^{115}\) and myopathy has been reported in up to 50% of patients taking prolonged high doses.\(^{90}\) Fluorinated glucocorticoids such as dexamethasone, betamethasone, and triamcinolone have a higher incidence of myopathy.\(^{116}\) Women are affected more commonly than men.\(^{117}\) The typical scenario is insidious onset of proximal muscle weakness after 2 to 4 weeks of daily high-dose glucocorticoid use, typically prednisone at dosages of more than 30 mg/day. Respiratory muscles can be affected as well.\(^{118}\) Muscle biopsy results are normal or show nonspecific type 2 atrophy, and electromyography and CK levels often are normal.\(^{88,92,115}\) Management involves discontinuing or reducing the steroid dose, using alternating treatment day regimens, or switching to a nonfluorinated steroid.\(^{115}\) Recovery typically is seen within 24 hours but may take longer if the patient has been taking glucocorticoids long term or at high doses.\(^{88}\) Exercise has been shown to be potentially helpful in the recovery phase.\(^{119}\) Inhaled corticosteroids are rarely associated with myopathy.\(^{115}\)

**Other Myopathy-Inducing Drugs**

**Immunologic Drugs**

Rheumatologic and antimalarial drugs, such as hydroxychloroquine and chloroquine, can cause a painless, slowly progressive weakness of the proximal muscles, which tends to be more severe in the lower extremities.\(^{88,116}\) Symptoms can be delayed, occurring months to years after the drug is started. Improvement typically is seen within 6 months of discontinuation.\(^{120}\) Cyclosporine and tacrolimus can cause a similar clinical picture. Because they are metabolized by the CYP system, they have a higher incidence of rhabdomyolysis and drug-drug interactions if used with statins or fibrates (Table 8).\(^{88}\)
Antiviral Drugs
Several of the antiviral drugs used in HIV treatment, especially zidovudine, can cause myopathy. The diagnosis may be difficult to ascertain because of the simultaneous presence of HIV-related myopathies. Rhabdomyolysis is rare, but the risk is increased when the antiviral is used in combination with a macrolide antibiotic or statin.

Antibacterial and Antifungal Drugs
The fluoroquinolone antibiotics have been associated with myopathies, tendinopathies, and, rarely, malignant hyperthermia. There is a considerable risk of rhabdomyolysis when a statin is prescribed concomitantly with ketoconazole or itraconazole.

Cardiovascular Drugs
Labetalol, amiodarone, and procainamide have been associated with myopathies. Procainamide-induced myopathy often is accompanied by a drug-induced lupus syndrome. Calcium channel blockers that are metabolized by the CYP system, such as diltiazem, nifedipine, and verapamil, when used in combination with statins, increase the risk of myopathy.

Gastrointestinal Drugs
Omeprazole can cause classic proximal myopathic weakness but is unique in its potential to cause neuropathic parasthesias involving a stocking distribution of the lower extremities.

Neurologic Drugs
Phenytoin can cause a hypersensitivity reaction in which weakness and myalgias are accompanied by fever, rash, and lymphadenopathy. Colchicine
Colchicine is toxic to muscles and nerves. The risk of generalized myopathies, painful neuropathies, and rhabdomyolysis increases when colchicine is used by patients with chronic kidney disease or who are taking diuretics. Addition of a statin significantly increases this risk. Resolution of symptoms occurs often but not always.

Drugs Affecting Electrolyte Balance
Drugs that change electrolyte concentrations can cause myalgias, cramps, and weakness. Classically, this form of myopathy occurs with drugs that cause hypokalemia. Alcohol can cause an acute hypokalemic myopathy accompanied by painless flaccid paralysis. Binge drinking may result in acute necrotizing myopathy involving significant muscle pain and swelling, with muscle fiber necrosis on biopsy. Chronic alcoholic myopathy can cause painless proximal muscle weakness and wasting.

Case 3, cont’d. Samuel’s symptoms and elevated creatine kinase level resolve several weeks after he discontinued the statin. You prescribe a low dose of a different statin, which he tolerates well.
Rhabdomyolysis is the rapid breakdown of skeletal muscle with release of electrolytes, myoglobin, and other proteins into the circulation. The clinical presentation encompasses a spectrum of patients ranging from those with asymptomatic increases in creatine kinase (CK) levels to those with fulminant disease complicated by acute kidney injury (AKI), severe electrolyte abnormalities, compartment syndrome, and disseminated intravascular coagulation. A CK level at least 10 times the upper limit of normal typically is considered diagnostic, as is myoglobinuria. AKI is the most significant complication. Prompt recognition and management of rhabdomyolysis is crucial to preserving renal function. Management consists of rapidly initiating aggressive intravenous saline resuscitation to maintain a urine output of at least 300 mL/hour. Sodium bicarbonate can be used for patients who are acidic, and mannitol can be used for those whose urine output is not at goal. Significant electrolyte abnormalities may be present and must be managed to avoid cardiac arrhythmias and arrest. Compartment syndrome can develop as an early or late finding and requires decompressive fasciotomy for definitive management. Intravenous fluids typically are continued until CK levels are lower than 1,000 U/L.

**Overview and Prevalence**

Rhabdomyolysis is the rapid breakdown of skeletal muscle with release of electrolytes, myoglobin, and such proteins as creatine kinase (CK) into the circulation. The clinical presentation ranges from a benign asymptomatic elevation of CK levels to life-threatening acute kidney injury (AKI), cardiac arrhythmias, and disseminated intravascular coagulation (DIC). An estimated 26,000 cases occur annually in the United States. There is no consensus or standard definition of rhabdomyolysis; however, a CK level at least 10 times the upper limit of normal is used widely to define statin-induced rhabdomyolysis. Myoglobinuria and elevated creatinine levels are common features. AKI is the most important and serious complication, occurring in 10% to 40% of adult patients with rhabdomyolysis.

**Pathophysiology**

Rhabdomyolysis causes muscle destruction and injury. This leads to imbalances of sodium, calcium, and potassium, resulting in faulty adenosine triphosphate and energy production, which in turn causes increased cellular permeability. Calcium-dependent proteases and phospholipases are released, contributing to muscle destruction. Muscle injury releases myoglobin into the circulation; this can physically obstruct the renal tubules, leading to AKI. The effects of muscle damage and loss of fluid into the interstitial space stimulate the sympathetic nervous system, renin-angiotensin-aldosterone system, and vasopressin system, resulting in intrarenal vasoconstriction.

**Etiology and Risk Factors**

Rhabdomyolysis can be acquired or inherited. Acquired rhabdomyolysis is the most common, accounting for 75% of first-time episodes, and it can be subclassified further as traumatic or nontraumatic. Among adults, the most common risk factors are trauma, substance abuse, drugs, exercise, seizures, and infections. Viral infections are an important etiology of rhabdomyolysis in children. Recurrent rhabdo-
myolysis typically is due to inherited muscle enzyme deficiencies, often first noted in childhood. Trauma-associated rhabdomyolysis often involves crush injuries or burns. Trauma patients have a high risk of AKI and rhabdomyolysis.\textsuperscript{125,136} Crush injuries resulting in rhabdomyolysis cause AKI in 4\% to 33\% of patients, with a mortality rate of approximately 14\%.\textsuperscript{137} In the initial stages of evaluation and management of trauma patients, imaging with contrast-enhanced computed tomography scan often is required to help direct therapy. Although the use of intravenous iodinated contrast is an independent risk factor for AKI, trauma patients who are young and otherwise healthy do not appear to have an increased rate of AKI after receiving intravenous contrast.\textsuperscript{136} In a retrospective review of 525 burn patients, for each 10-fold increase in peak CK levels, there was a 70\% increase in the risk of AKI and a 50\% increase in the risk of mortality.\textsuperscript{134}

Exertional heat stroke is a preventable etiology of exertion-related mortality that has been studied in the military and in sports medicine literature.\textsuperscript{138} It often is associated with multiorgan failure, including kidney failure due to rhabdomyolysis. In a study of military trainees, the average incidence of exertional rhabdomyolysis over a 6-year period was 22 cases per 100,000 recruits per year.\textsuperscript{139} Renal failure associated with exertional heat stroke may require weeks for recovery and can be associated with long-term morbidity.\textsuperscript{129}

Individual risk factors for exertional heat stroke and resulting rhabdomyolysis include age older than 40 years; dehydration; poor conditioning; and the use of drugs such as stimulants, angiotensin-converting enzyme inhibitors, diuretics, and antihistamines.\textsuperscript{138}

Rhabdomyolysis can be a complication of bariatric surgery, likely related to pressure exerted on the body by the surgical table intraoperatively. Patients with a body mass index of at least 55 kg/m\textsuperscript{2} were shown to have an increased risk of rhabdomyolysis after undergoing bariatric surgery.\textsuperscript{140} Additional risk factors include male sex, a longer duration of surgery, hypertension, and diabetes.

Illicit drug use, especially use of sympathomimetic drugs such as cocaine and amphetamines, can cause rhabdomyolysis, primarily because of vasoconstriction. Abuse of the dissociative anesthetic phencyclidine, as well as serotonin syndrome, anesthesia-related neuroleptic malignant syndrome, and seizures, can cause muscle damage that increases the risk of rhabdomyolysis.\textsuperscript{141} Some drugs are directly toxic to muscle tissue, the most common ones being statins, fibrates, antimalarial drugs, and alcohol. Multiple bee or wasp stings, as well as some snake and other animal venoms, can have a similar toxic effect. Statins have been studied extensively and are most likely to cause rhabdomyolysis when taken in combination with fibrates.\textsuperscript{128} Some anticancer drugs, such as the tyrosine kinase inhibitors and the DNA-binding drug trabectedin (Yondelis), have been associated with rhabdomyolysis. High doses of propofol, used to sedate critically ill patients, and daptomycin, a gram-positive bactericidal drug, have been linked to rhabdomyolysis.

Inherited metabolic defects that potentiate the risk of rhabdomyolysis typically become apparent in childhood.\textsuperscript{127} These include mutations in the glycolysis and glycogenolysis pathways, defective protein synthesis involved in muscle excitation-contraction, and skeletal muscle dystrophies.\textsuperscript{126} Hereditary or metabolic disorders may be unmasked when rhabdomyolysis is precipitated by drugs, infections, or exertion.

Rhabdomyolysis in the pediatric population has several etiologies distinct from those in the adult population. Viral infections (eg, influenza viruses, Coxsackie virus, HIV, enteroviruses, Epstein-Barr virus, cytomegaloviruses) are the primary etiologies in pediatric rhabdomyolysis, followed by trauma, exercise, and inflammatory disorders.\textsuperscript{142} Boys have a higher predilection for developing rhabdomyolysis than girls.

**Clinical Presentation**

Rhabdomyolysis has a wide range of clinical presentations. In up to 50\% of patients there are no symptoms at onset, necessitating a high index of suspicion and close monitoring of patients at risk.\textsuperscript{126} The classic triad of myalgias, weakness, and dark-colored urine is present in less than 10\% of patients. Localized symptoms may include muscle weakness, swelling, and tenderness.\textsuperscript{143} Symptoms can be nonspecific and systemic in nature, including fever, nausea, emesis, confusion, agitation, delirium, and anuria.\textsuperscript{126}

Patients with severe rhabdomyolysis have significant muscle soreness and pain with any activity. These patients have tight muscles that are tender to palpation, with limited passive stretch. Patients also may present when they collapse or become obtunded. Their symptoms can progress to life-threatening electrolyte disturbances, cardiac arrhythmias, AKI, compartment syndrome, and DIC.
Myalgias and Myopathies

The clinical signs and symptoms of rhabdomyolysis in children are similar to those in adults, with muscle pain and weakness being the most commonly encountered symptoms; dark-colored urine is less likely in children than in adults.\(^{142}\) Awareness of the most common etiologies of rhabdomyolysis among children helps guide the evaluation of those who may not have classic signs and symptoms.

**Diagnosis**

Evaluation for rhabdomyolysis is indicated when a patient presents with myalgias and dark-colored urine or when these symptoms are present along with weakness in a clinical setting that predisposes a patient to developing rhabdomyolysis. When possible, the initial laboratory evaluation should include CK. The CK level ultimately corresponds with the degree of muscle breakdown, and a CK level more than 10 times the upper limit of normal typically is considered diagnostic of rhabdomyolysis.\(^{126}\) The initial increase in CK level typically occurs 2 to 12 hours after insult and typically peaks at 24 to 72 hours. CK levels typically return to baseline after 3 to 5 days. Urinalysis with microscopy also is indicated.\(^{144}\) Myoglobinuria is likely if the urinalysis result is positive for hemoglobin but few or no red blood cells are seen on microscopy. Serum myoglobin typically is not available rapidly enough to help guide therapy. Myoglobin has a shorter half-life than CK and is, therefore, a less sensitive test; a high serum myoglobin level is observed in only half of patients with rhabdomyolysis.

In settings such as natural disasters, when CK cannot be obtained quickly, myoglobinuria can be identified using dipstick urinalysis, with sensitivity and specificity as high as 83.3% and 56.6%, respectively.\(^{145}\) If rhabdomyolysis is diagnosed in a patient with potentially nonspecific findings, treatment that might prevent complications, such as AKI, can be started. Other settings in which a urine dipstick can help establish the diagnosis of rhabdomyolysis quickly include heat injury, physical abuse, seizure, near-drowning, and exertional rhabdomyolysis.\(^ {137}\)

Other useful laboratory tests include a basic metabolic panel with creatinine and potassium, liver function tests (ie, transaminases, albumin, bilirubin, lactate dehydrogenase), a complete blood count, and uric acid.\(^ {128}\) Muscle breakdown and decreased renal function typically explain the abnormalities in some but not all of these test results. When electrolyte abnormalities are detected, an electrocardiogram should be obtained.

In patients with more severe rhabdomyolysis, calcium, phosphate, prothrombin time, partial thromboplastin time, fibrinogen, and fibrin split products should be evaluated. An arterial blood gas test is indicated if there is suspicion of an acid-base imbalance.

**Case 4, cont’d.** During the first 24 hours of Tony's hospital stay, he is given intravenous normal saline at a high rate to maintain a urine output of more than 300 mL/hour. Electrolyte abnormalities are managed. There is no concern regarding compartment syndrome. By hospital day 2, the creatine kinase level is 102,000 U/L. The creatinine level peaks at 4.4 mg/dL.

**Complications**

The mortality rate in rhabdomyolysis is approximately 8% to 10%, which increases approximately fourfold when AKI develops.\(^ {126}\) AKI is the most serious complication of rhabdomyolysis; therefore, attempts to prevent and recognize AKI are critical.\(^ {147}\) The RIFLE (Risk, Injury, Failure, Loss of function, End-stage renal disease) classification system is a useful tool for assessing the risk of kidney damage in patients with rhabdomyolysis.\(^ {146}\) The increase in CK correlates with an increased incidence of AKI, and patients with significantly elevated CK levels need careful monitoring of their renal function.\(^ {147}\) However, if patients present with normal CK levels, the likelihood is low that they will develop AKI.\(^ {144}\) Clinical factors in rhabdomyolysis that increase the risk of AKI and the risk of needing renal replacement therapy are listed in Table 10.\(^ {129}\) Among children, AKI is also a significant complication of rhabdomyolysis.\(^ {148}\) A study of pediatric trauma patients showed that CK levels of more than 3,000 U/L were associated with a higher risk of AKI, indicating a need for aggressive monitoring of CK in those patients.

Hypovolemia is another significant complication of rhabdomyolysis.\(^ {149}\) Damaged tissue can sequester large amounts of fluid in the interstitial space, up to 12 L, leading to hypovolemia. Patients also can be dehydrated or hypovolemic because of other etiologies, increasing their risk of AKI. Hypovolemia is difficult to manage in patients with medical conditions that preclude aggressive fluid resuscitation.

Direct muscle injury causes breakdown of muscle cells, leading to potassium and phosphate release.\(^ {149}\) Hyperkalemia, when severe, can cause cardiac arrhythmias and cardiac arrest. In cases of severe hyper-
Section Four

Management

The initial goals of rhabdomyolysis management are to preserve renal function and address electrolyte abnormalities. Initiating intravenous fluids with normal saline (avoiding potassium- or lactate-containing solutions) as soon as possible, preferably within the first 6 hours, can help prevent AKI. Fluids should be administered at a rate that maintains a urine output of at least 300 mL/hour for at least 24 hours unless the patient has a medical condition that would be worsened by such a fluid load. Intravenous fluids should be continued until the CK has declined to less than 1,000 U/L. Intravenous sodium bicarbonate may benefit patients who are acidic. Mannitol can help maintain the desired urine output of 300 mL/hour or more when adequate fluid administration is not achieving this goal. No other diuretics are recommended during initial treatment. Dialysis may be indicated for patients with severe rhabdomyolysis with life-threatening electrolyte abnormalities or renal failure. Underlying etiologies must be addressed, such as removal of toxins or drugs and management of infections. Patients with recurrent rhabdomyolysis need expanded evaluation for possible predisposing genetic conditions.

Case 4, cont’d. Aggressive hydration is maintained until Tony’s creatine kinase level is below 1,000 U/L and electrolyte levels remain normal. He is discharged after an 11-day hospital stay. Over the next several months, renal function normalizes, and he has no further episodes of rhabdomyolysis. He undergoes a gradual return-to-play process, and during follow-up visits he reveals that he had been taking several performance-enhancing drugs, which he has subsequently discontinued. Further evaluation would be indicated if there were suspected underlying genetic or metabolic abnormalities.

Table 10
Clinical Factors That Increase the Risk of Renal Complications in Rhabdomyolysis

<table>
<thead>
<tr>
<th>Increased Risk of Acute Kidney Injury</th>
<th>Increased Risk of Needing Renal Replacement Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Drugs, toxins, or muscle hypoxia as the etiology of rhabdomyolysis</td>
</tr>
<tr>
<td>Dark urine</td>
<td>Peak serum blood urea nitrogen level</td>
</tr>
<tr>
<td>Increased body temperature as the etiology of rhabdomyolysis</td>
<td>Peak serum creatinine level</td>
</tr>
<tr>
<td>Increased serum level of Blood urea nitrogen</td>
<td>Serum creatine kinase level on the third day</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
</tr>
<tr>
<td>Initial serum myoglobin ≥600 ng/mL</td>
<td></td>
</tr>
<tr>
<td>Peak serum myoglobin level</td>
<td></td>
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</tbody>
</table>


kalemia, hypocalcemia also should be managed. Proteases released by the breakdown of muscle cells can cause hepatic inflammation, and approximately 25% of patients with rhabdomyolysis develop hepatic dysfunction. As hepatic function declines, DIC, which can be life-threatening, can occur.

When fluid is sequestered in damaged muscles and edema increases because of fluid resuscitation, compartment pressures may rise, causing acute compartment syndrome. Data on the incidence of compartment syndrome are lacking. Classic symptoms include pain out of proportion to the apparent injury, deep aching or persistent burning pain, and paresthesias. Persistently elevated CK levels also can be suggestive of compartment syndrome. There is overlap between the clinical presentations of rhabdomyolysis and compartment syndrome, so serial examinations may be necessary, and physicians should not hesitate to measure compartment pressures. For patients with compartment syndrome, surgical consultation is indicated for consideration of early decompressive fasciotomy.
References


Myalgias and Myopathies


Myalgias and Myopathies


Suggested Reading


1. Using the 2010 American College of Rheumatology criteria, which one of the following is true of fibromyalgia?
   - A. It affects approximately 10% of the population.
   - B. It is more common in women than in men.
   - C. It is the most common disorder for which patients are referred to rheumatology subspecialists.

2. Using the 2010 American College of Rheumatology criteria, which one of the following is consistent with a diagnosis of fibromyalgia?
   - A. Symptom duration of 2 months.
   - B. Symptom Severity scale score of 4.
   - C. Tenderness on pressure in 12 of 18 specific anatomic sites.
   - D. Widespread Pain Index of 8.

3. Which one of the following statements is true of fibromyalgia?
   - A. Becoming pain-free is likely.
   - B. Exercise is an effective form of treatment.
   - C. Symptom fluctuation is rare.
   - D. Tissue damage due to inflammation is common.

4. Which one of the following drugs is Food and Drug Administration-approved for management of fibromyalgia?
   - A. Amitriptyline (tricyclic antidepressant).
   - B. Cyclobenzaprine (muscle relaxant).
   - C. Duloxetine (serotonin-norepinephrine reuptake inhibitor).
   - D. Fluoxetine (selective serotonin reuptake inhibitor).
   - E. Gabapentin (neurologic).

5. Which one of the following drugs should be avoided in fibromyalgia management?
   - A. Amitriptyline (tricyclic antidepressant).
   - B. Gabapentin (neurologic).
   - C. Naltrexone (opioid antagonist).
   - D. Oxycodone (opioid analgesic).
   - E. Tramadol (analgesic).

6. Which one of the following statements is true of polymyalgia rheumatica?
   - A. Finger and toe joints are affected.
   - B. Morning stiffness is common.
   - C. Patients have a poor prognosis.

7. For the past week, a patient has had a temporal headache that is resistant to standard analgesics. Amaurosis fugax then develops. A swollen optic disc is present on funduscopic examination. Which one of the following conditions is most likely?
   - A. Fibromyalgia.
   - B. Giant cell arteritis.
   - C. Polymyalgia rheumatica.
   - D. Rhabdomyolysis.

8. Which one of the following is unusual for a patient with polymyalgia rheumatica and would lead to consideration of a different diagnosis?
   - A. Age 75 years.
   - B. Asymmetric nonerosive synovitis.
   - C. Elevated erythrocyte sedimentation rate.
   - D. Morning stiffness.
   - E. Presence of cyclic citrullinated peptide antibodies.

9. Imaging with ultrasound is most useful in identifying which one of the following?
   - B. Rhabdomyolysis in statin-induced myopathy.
   - C. Subacromial bursitis in polymyalgia rheumatica.
   - D. Temporal arteritis in giant cell arteritis.

10. Which one of the following drugs is a first-line treatment for polymyalgia rheumatica and giant cell arteritis?
    - A. Alendronate (bisphosphonate).
    - B. Etanercept (Enbrel) (tumor necrosis factor inhibitor).
    - C. Methotrexate (immunosuppressive).
    - D. Naproxen (nonsteroidal anti-inflammatory drug).
    - E. Prednisone (glucocorticoid).

Complete the online quiz at http://www.aafp.org/fpequiz.
11. When the creatine kinase level is at least 10 times the upper limit of normal and myoglobinuria is present, which one of the following is the most likely diagnosis?
   - A. Myalgia.
   - B. Myopathy.
   - C. Myositis.
   - D. Rhabdomyolysis.

12. Concomitant use of a statin with which one of the following drugs is the most likely etiology of statin-induced myopathy?
   - A. Amlodipine (dihydropyridine calcium channel blocker).
   - B. Cephalexin (cephalosporin antibiotic).
   - C. Gemfibrozil (fibrate).

13. Which one of the following statins is contraindicated at an initial dosage of 80 mg/day in all patients because of its higher risk of statin-induced myopathy?
   - A. Atorvastatin.
   - B. Fluvastatin.
   - C. Lovastatin.
   - D. Simvastatin.

14. Which one of the following statins is least likely to cause a statin-induced myopathy?
   - A. Atorvastatin.
   - B. Fluvastatin.
   - C. Lovastatin.
   - D. Pravastatin.

15. Which one of the following statements about drug-induced myopathies is true?
   - A. Colchicine is toxic to muscles and nerves.
   - B. Inhaled corticosteroids commonly cause myopathy.
   - C. Omeprazole causes a hypersensitivity reaction in which weakness and myalgias are accompanied by fever, rash, and lymphadenopathy.
   - D. Procainamide causes neuropathic paresthesias involving a stocking distribution of the lower extremities.

16. Recurrent rhabdomyolysis typically is due to inherited muscle enzyme deficiencies.
   - A. True.
   - B. False.

17. Which one of the following causes rhabdomyolysis primarily by vasoconstriction, rather than by direct muscle toxicity?
   - A. Amphetamines.
   - B. Alcohol.
   - C. Fibrates.
   - D. Multiple bee or wasp stings.
   - E. Statins.

18. Less than 10% of adults presenting with rhabdomyolysis have the classic triad of signs and symptoms: dark-colored urine, myalgias, and weakness. Which one of these symptoms is less likely to manifest in children with rhabdomyolysis?
   - A. Dark-colored urine.
   - B. Myalgias.
   - C. Weakness.

19. In a patient with rhabdomyolysis, which one of the following conditions can lead to cardiac arrhythmias and cardiac arrest?
   - A. Compartment syndrome.
   - B. Elevated creatine kinase level.
   - C. Hyperkalemia.
   - D. Myoglobinuria.

20. To help prevent acute kidney injury during the initial management of rhabdomyolysis, intravenous saline typically is started as soon as possible with a goal of maintaining a urine output of at least which one of the following rates?
   - A. 75 mL/hour.
   - B. 150 mL/hour.
   - C. 300 mL/hour.
   - D. 600 mL/hour.
Question 1: The correct answer is B. Fibromyalgia, as defined by the 2010 American College of Rheumatology criteria, affects approximately 5% of the population and is the second most common disorder, after osteoarthritis, for which patients are referred to rheumatology subspecialists. Fibromyalgia occurs more frequently among women than among men, with a 2.3:1 prevalence ratio. See page 11.

Question 2: The correct answer is D. The 2010 American College of Rheumatology diagnostic criteria for fibromyalgia focus on a Widespread Pain Index (WPI) and Symptom Severity (SS) scale. The newer criteria do not require analysis of tender points but instead acknowledge the polysymptomatic nature of fibromyalgia. Fibromyalgia may be diagnosed if the following conditions are met: 1) symptom duration of at least 3 months; 2) WPI score of at least 7 and SS scale score of at least 5 or WPI score between 3 and 6 and SS scale score of at least 9; 3) lack of another disorder to explain the patient’s pain. See pages 11-12.

Question 3: The correct answer is B. Education, cognitive behavioral therapy, and exercise are well-studied and effective forms of management for fibromyalgia. See page 12.

Question 4: The correct answer is C. Only duloxetine, milnacipran (Savella), and pregabalin (Lyrica) currently are approved by the Food and Drug Administration for the management of fibromyalgia. See pages 12-13.

Question 5: The correct answer is D. There is little to no evidence that opioids or nonsteroidal anti-inflammatory drugs are useful for managing fibromyalgia, and they should be avoided if possible because risks likely outweigh benefits. A 2014 Cochrane review showed no benefit of oxycodone in the management of fibromyalgia. The American Academy of Neurology recommends against the use of opioids in fibromyalgia. See page 14.

Question 6: The correct answer is B. Patients with polymyalgia rheumatica typically present with bilateral, aching pain in the shoulders, neck, and pelvis, with morning stiffness lasting at least 1 hour. See page 17.

Question 7: The correct answer is B. Giant cell arteritis tends to follow a subacute course; the most common presenting symptom is a temporal headache resistant to standard analgesics. Amaurosis fugax, a transient monocular visual loss, manifests in 10% to 15% of patients and can progress to total blindness in up to 20% to 60% of untreated patients. The funduscopic examination may reveal a swollen optic disc, which foreshadows vision loss if present at the time of diagnosis. See page 17.

Question 8: The correct answer is E. Cyclic citrullinated peptide antibodies typically are not present in polymyalgia rheumatica but present in rheumatoid arthritis. See page 18.

Question 9: The correct answer is C. In patients with polymyalgia rheumatica, subacromial and subdeltoid bursitis are the most common lesions identified with magnetic resonance imaging study and ultrasound, although the severity of bursitis does not correlate with the erythrocyte sedimentation rate. See page 19.

Question 10: The correct answer is E. Glucocorticoids are considered first-line treatment for polymyalgia rheumatica and giant cell arteritis because of rapid response and efficacy. See page 20.

Question 11: The correct answer is D. Rhabdomyolysis is a necrotizing myopathy that can cause severe muscle symptoms accompanied by creatine kinase elevations of at least 10 times the upper limit of normal (and up to 2,000 times the upper limit of normal), typically with an elevated serum creatinine level and myoglobinuria. See page 23.

Question 12: The correct answer is C. Risk factors for statin-induced myopathy include concomitant use with drugs metabolized by the cytochrome P450 3A4 systems, which include fibrates (especially gemfibrozil). See Table 8.

Question 13. The correct answer is D. The 2014 update from the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for \textit{SLCO1B1} warn against initiating simvastatin therapy at 80 mg/day for all patients. See page 25.

Question 14: The correct answer is D. Many statins, including simvastatin, fluvastatin, atorvastatin, and lovastatin, are metabolized by the microsomal hepatic cytochrome P450 (CYP) system. Concomitant use of another drug metabolized by the CYP system can lead to drug-drug interactions and increase the risk of statin-induced myopathy. However, pitavastatin (Livalo),...
pravastatin, and rosuvastatin (Crestor) are metabolized independently of the CYP system and have a lower risk of statin-induced myopathy. In vitro data support pravastatin as having the lowest cytotoxicity of statins currently available in the United States, with simvastatin having the highest. See page 25 and Table 9.

Question 15: The correct answer is A.
Colchicine is toxic to muscles and nerves. See page 27.

Question 16: The correct answer is A.
Recurrent rhabdomyolysis typically is due to inherited muscle enzyme deficiencies, often first noted in childhood. See pages 28-29.

Question 17: The correct answer is A.
Illicit drug use, especially use of sympathomimetic drugs such as cocaine and amphetamines, can cause rhabdomyolysis, primarily because of vasoconstriction. See page 29.

Question 18: The correct answer is A.
The clinical signs and symptoms of rhabdomyolysis in children are similar to those in adults, with muscle pain and weakness being the most commonly encountered symptoms; dark-colored urine is less likely in children than in adults. See page 30.

Question 19: The correct answer is C.
In patients with rhabdomyolysis, direct muscle injury causes breakdown of muscle cells, leading to potassium and phosphate release. Hyperkalemia, when severe, can cause cardiac arrhythmias and cardiac arrest. See page 30.

Question 20: The correct answer is C.
The initial goals of rhabdomyolysis management are to preserve renal function and address electrolyte abnormalities. Initiating intravenous fluids with normal saline (avoiding potassium- or lactate-containing solutions) as soon as possible, preferably within the first 6 hours, can help prevent acute kidney injury. Fluids should be administered at a rate that maintains a urine output of at least 300 mL/hour for at least 24 hours unless the patient has a medical condition that would be worsened by such a fluid load. See page 31.
The following topics appear in this month’s edition of the AAFP FP Audio™ program:

Clinical Topic: Risk Stratification

Clinical Topic: U.S. Preventive Services Task Force Recommendations on Vitamin D and Calcium Supplementation

Journal Notes: Appendectomy vs Antibiotics for Acute Appendicitis

Editor’s Q&A: Epididymo-Orchitis

The next edition of AAFP FP Essentials™ will be:

The Changing Drug Culture