PHARMACIST'S LETTER

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PRESCRIBER'S LETTER

Statin Muscle Symptoms: Managing Statin Intolerance

Muscle symptoms are commonly reported by statin users; however, over 70% of these patients end up tolerating a statin.[3,5,8] Statin-associated muscle symptoms are usually not serious. Although rhabdomyolysis has a mortality rate of almost 8%, it is rare.[3] The chart below provides information to help clinicians prevent and manage statin-associated muscle symptoms. Also download the ACC Statin Intolerance App at http://www.acc.org/StatinIntoleranceApp.

Abbreviations: ACC = American College of Cardiology; AHA = American Heart Association; BMI = body mass index; CK = creatine kinase; CoQ10 (coenzyme Q10; ubiquinol); CV = cardiovascular; NLA = National Lipid Association; SCr = serum creatinine; ULN = upper limit of normal

Clinical Question	**Suggested Approach/Pertinent Information**

What adverse muscle effects can statins cause?	• Patients may complain of pain, tenderness, stiffness, cramps, weakness, or fatigue.[1]
	• Symptoms usually involve large, proximal muscle groups (e.g., legs, back) symmetrically.[4]
	• Symptoms usually occur within 4 to 6 weeks after starting the statin, but can occur after years of treatment.[4]
	• Examples of terminology commonly used in the context of statin muscle symptoms (definitions used in literature/guidelines vary):
	  • Myopathy: general term for muscle disease (Canada),[3] or used to denote muscle weakness not due to pain, and which may or may not be associated with elevated CK (NLA)[8]
	  • Myalgia: muscle symptoms with CK ≤ULN[3,8]
	  • Myositis: muscle symptoms with CK >ULN (Canada);[3] muscle inflammation (NLA)[8]
	  • Myonecrosis: CK >3 times baseline or ULN adjusted for age, sex, and race (NLA).[8] Further divided into mild, moderate, and severe.
	  • Rhabdomyolysis: muscle symptoms plus myoglobinuria and CK >10 x ULN (CK >10,000 units/L; Canada);[3] myonecrosis with myoglobinuria or acute renal failure (increase in SCr ≥0.5 mg/dL; NLA)[8]

How common are statin-associated muscle symptoms?	• In clinical trials, low- or moderate-intensity statins[a] did not increase the risk of muscle symptoms.[1] However, in practice, up to about 30% of patients complain of muscle symptoms.[4]
	• Cumulative data from patients hospitalized for rhabdomyolysis indicate that rhabdomyolysis may occur in fewer than one patient for every 23,000 patients treated with a statin.[11]
	  • Represents risk associated with monotherapy with a statin, excluding cerivastatin.
	  • Risk of rhabdomyolysis may be higher, especially in patients that are elderly, have impaired renal function, or those taking interacting meds.

More. . .

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Clinical Question	Suggested Approach/Pertinent Information
What are some risk factors for statin-associated muscle adverse effects?	• Multiple disease states (e.g., renal or hepatic insufficiency) or polypharmacy[1,4] • History of musculoskeletal symptoms or CK elevation, neuromuscular disease, or personal or family history of statin or other myopathy[1,3] • Use of medications or foods (e.g., grapefruit) that increase statin levels[1] • Age over 75 to 80 years[1,3] • Asian ancestry[1,3] • Being female[3] • Low BMI or small frame[3] • Frailty[3] • Physical activity[4] • Alcohol or drug abuse[3]
Are certain statins more commonly associated with muscle symptoms?	• The vast majority of patients who do not tolerate one statin can tolerate the same or a different statin.[3,5] • Almost half can tolerate the same statin upon rechallenge, usually at the same or higher dose.[3] • When choosing a different statin, consider one with fewer drug interactions (e.g., rosuvastatin, pravastatin, fluvastatin), or one that a family member can tolerate.[8] Evidence that lipophilicity/hydrophilicity directly affects muscle symptoms is lacking in humans.[8]

What can be done to prevent statin-associated muscle symptoms?	• Before starting a statin, document current or previous muscle symptoms.[1]
	  • This information may help prevent unnecessary statin discontinuation in the future.[1]
	• Do not use gemfibrozil with a statin.[1]
	• Screen for drug interactions.[1] Adjust dose or use a different statin accordingly.[1]
	• Ensure dose is appropriate for renal function.
	• Our *PL Chart*, *Characteristics of the Various Statins*, has information on drug interactions and renal dosing.
	• Ensure the statin dose is appropriate based on cardiovascular risk.[1]
	  • Consider a moderate-intensity statin[a] instead of a high-intensity statin[a] for patients with risk factors for statin muscle symptoms.[1]
	• Avoid simvastatin 80 mg daily.[1,3]
	• Before starting, set patient expectations that side effects can be managed if they occur.[4]

Clinical Question	**Suggested Approach/Pertinent Information**

When should a creatine kinase be checked?	• Consider baseline measurement in patients with risk factors.[1]
	• Do not check routinely.[1]
	  • Elevations ≥3x the ULN occur in patients with heart disease at a similar rate regardless of statin treatment.[1]
	  • The clinical importance of an elevated CK without symptoms is unclear.[4] Exercise can also cause increased CK.[4]
	• Check in the event of muscle symptoms.[1]

What is the general approach to take when a patient complains of muscle symptoms?	Example approach based on ACC/AHA guidelines, NLA panel, and European consensus panel:
	• Hold statin for 2 to 4 weeks in the event of intolerable symptoms, weakness, or CK >3 times ULN. If patient reports weakness, evaluate muscle strength by physical exam, and consider additional testing (e.g., biopsy) if weakness persists despite statin discontinuation.[8]
	• Consider rhabdomyolysis in the event of severe muscle pain or fatigue, generalized weakness, or dark urine.[1,4] Check CK, urine for myoglobin, and SCr.[1]
	  • If rhabdomyolysis is confirmed, treat and do not restart statin at any point in the future.[4]
	• Look for other causes of muscle symptoms (e.g., hypothyroidism, vitamin D deficiency, rheumatologic or musculoskeletal disease, exercise, steroid myopathy, antipsychotics, immunosuppressants, bisphosphonates, alcohol or drug abuse, drug or food interactions [e.g., fibrates, macrolides, immunosuppressives, protease inhibitors]).[1,3,4,9] Also consider alternate causes of leg cramps.
	• Check renal and hepatic function.[1]
	• Assuming no contraindications:[1]
	  • rechallenge with same statin at the same or lower dose once symptoms resolve to establish a causal relationship. If symptoms return, discontinue statin. Once symptoms resolve, start a different statin at a lower dose, then increase as tolerated.[1]
	OR
	  • start a low or target dose of a different statin once symptoms improve.[8] Increase as tolerated.[8] If not tolerated, try extending the dosing frequency, such as every other day or twice a week.[3,6,8] (See more about alternate dosing options in the next sections.)
	OR
	  • for patients at low CV risk, consider lifestyle interventions in lieu of a statin[4]
	• Consider adding ezetimibe for certain high-risk patients who can't tolerate a high-intensity statin, such as those with a prior cardiovascular event. Ezetimibe is the only non-statin with evidence of improving cardiovascular outcomes when added to a statin. See our *PL Chart*, *Non-Statin Lipid-Lowering Agents*, for considerations when deciding to start a non-statin, and a comparison of their lipid effects, outcomes, and cost.
	• Save PCSK9 inhibitors (*Praluent*, *Repatha*) as an add-on to statins for familial hypercholesterolemia. Do not routinely use these agents in other high-risk patients with or without a statin, due to high cost and lack of long-

Continued…

Clinical Question	Suggested Approach/Pertinent Information
General approach, continued	term outcome and safety data. • If symptoms/CK elevation does not improve in 2 to 4 weeks, or do not normalize after two months, evaluate for non-statin cause.[1,8] • If non-statin cause is found, or predisposing condition has been treated, restart original statin at original dose.[1] • Use a "take your time" approach and be persistent. Help patients understand the benefits and risks of continued statin therapy. See our *PL Patient Education Handout, What You Should Know About Statins*.
When should I stop a statin due to muscle symptoms?	• In the event of symptoms, hold statin temporarily pending evaluation.[1] (See General Approach section above for more information.) • European guidelines recommend permanent discontinuation in patients who experience rhabomyolysis.[4]
Can I give statins less often than once daily to reduce symptoms?	• Rosuvastatin is most often used in this strategy because of its long-half life, high potency, and favorable drug interaction profile.[5] • Intermittent dosing of rosuvastatin (i.e., 5 mg 2 to 3 times weekly) can reduce LDL by over 30%.[3] Rosuvastatin 5 to 10 mg weekly may reduce LDL by 10%.[10] • Atorvastatin also has a long half-life.[8] Atorvastatin 20 mg every other day may be as effective as 20 mg daily in regard to LDL reduction.[6] • Intermittent dosing has not been prospectively studied in regard to cardiovascular morbidity or mortality.[5]
What is the role of coenzyme Q10 (ubiquinol)?	• In patients with a history of statin muscle symptoms, confirmed by placebo-controlled crossover rechallenge, CoQ10 600 mg daily did not affect pain, muscle strength, or aerobic performance vs placebo in patients taking simvastatin 20 mg daily [Evidence level B; lower-quality RCT].[2] • Canadian and European consensus panels advise against use of dietary supplements (including vitamin D) for statin muscle symptoms.[3,10] • Coenzyme Q10 is well-tolerated if patients insist on trying it.[7] However, it can be expensive. The suggested dose for statin muscle pain is 100 to 200 mg daily (in divided doses if >100 mg/day).

a. See our *PL Chart, 2013 ACC/AHA Cholesterol Guidelines*, for a list of high- and moderate-intensity statins.

Users of this PL Detail-Document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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