INSOMNIA/STATIN MYOPATHIES

Insomnia

Adam J. Sorscher, MD, Assistant Professor of Community and Family Medicine, Geisel School of Medicine at Dartmouth, Hanover, NH

Chronic insomnia: affects ≈25 million adults in United States; risk factors include female sex, advanced age (primarily associated with development of comorbidities [eg, chronic medical conditions, chronic pain, polypharmacy, mental health conditions]), and low socioeconomic status; defined as difficulty initiating or maintaining sleep, or nonrestorative sleep, for >1 mo; must cause distress or impairment in daytime functioning (eg, irritability, cognitive dysfunction); patients often do not feel sleepy (due to physiologic state of hyperarousal) and unable to take naps in daytime (they feel “tired but wired”); associated with reduced quality of life, increased absenteeism at work, increased health care costs, and comorbidities (eg, chronic pain, depression, anxiety, substance abuse)

Sleep log: hour-by-hour account of sleep history spanning 24 hr, with 12 am at midpoint; ask patients in morning to estimate how much they slept day before; studies show process of keeping track of sleep may lead to adoption of better sleep behaviors instinctively; assess log after 3 wk; log provides helpful information about sleep schedule (eg, bedtime), daytime napping, irregular wake times, and excessive time spent in bed

Causes and comorbid conditions: ≈50% of people with chronic insomnia have comorbid mental health disorder; chronic insomnia result of chronic pain or medical conditions (eg, shortness of breath, heart failure, polypharmacy) in 25% of cases; 10% of cases due to sleep disorder (eg, sleep apnea); comorbid condition absent in 15% of cases; insomnia often wrongly attributed to depression or anxiety due to overlap of symptoms (careful diagnosis important); initial evaluation — according to American Academy of Sleep Medicine (AASM), sleep study not warranted for most cases of insomnia unless sleep-disordered breathing (based on snoring, witnessed apneas, obesity, or hypertension) suspected

Cognitive behavioral therapy

Behavioral strategies: sleep hygiene — regularize sleep and wake times, avoid caffeine, create dark and quiet sleep environment, and limit napping; effective for 40% of patients with chronic insomnia; stimulus control — avoid looking at clock at night, do not remain in bed when awake and not drowsy, avoid screen time (eg, television, computer), and read, do craft, or do crossword puzzle until drowsy, then return to bed; associated with highest level of evidence for effectiveness; sleep restriction — recommended for patients who spend >8.5 hr in bed at night but sleep for only 3 to 4 hr; establish 5- to 6-hr window (eg, 12 am to 6 am) for sleep, with no napping during day for 2 wk; based somewhat on deliberate sleep deprivation; after 2 wk, patients struggle to stay awake until bedtime and fall asleep rapidly; add 15 min of sleep time every week

Cognitive strategies: address misconceptions about sleep (eg, some patients feel that <8 hr of sleep per night is damaging to body); address catastrophization (eg, patients convinced that insomnia will lead to job loss or marital problems [ask, “How long have you had insomnia? Are you still at your job? What is the likelihood of losing your job?”]); advise patients (in evening well before bedtime) to make list of top worries and action plan for next day to avoid ruminating if they wake up in middle of night; adjust expectations of sleep quality (eg, plan to increase sleep to 6 hr per night rather than to 8 hr per night); psychologists perform more advanced strategies (eg, imagery, meditation)

Results: cognitive behavioral therapy effective in 70% to 80% of patients

Pharmacologic sleep aids: no guideline from AASM about appropriate use; expert panel concluded that patients with insomnia tend to show therapy-seeking rather than drug-seeking behavior, and patients without history of drug abuse unlikely to self-escalate dose

Educational Objectives

The goal of this program is to improve management of insomnia and statin-induced myopathies. After hearing and assimilating this program, the clinician will be better able to:

1. Identify causes and comorbid conditions of insomnia.
2. Employ cognitive behavioral strategies for treatment of insomnia.
3. Recognize patients who may benefit from pharmacologic sleep aids.
4. Distinguish between statin-induced myalgias and immune-mediated myopathy.
5. Explain the role of 3-hydroxy-3-methyl-glutaryl-CoA reductase in immune-mediated myopathy.

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, members of the faculty and planning committee reported nothing to disclose.
Toxic myopathy related to polypharmacy:

Predictors of myopathy or myopathic events:

Prevalence:

Alcohol: not recommended; may shorten latency to sleep onset at beginning of night, but known to destabilize sleep as it metabolizes; leads to awakenings during night

Statin Myopathies

Chester V. Oddis, MD, Professor of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA

Statin toxicity: ranges from life-threatening rhabdomyolysis to myalgias; 5% to 10% of patients refuse or stop statins due to fear of problems

Statin-induced myalgias: affect 9% to 20% of patients; cross-sectional study of 1000 patients found 1.5-fold increased risk for muscle complaints in statin users compared with nonstatin users; myalgia — pain with no creatine kinase (CK) elevation

Myositis: mild — CK elevation 1 to 3 times upper limit of normal; severe — CK elevation 3 to 10 times upper limit of normal

Rhabdomyolysis: CK elevation 10 times upper limit of normal

Prevalence: study of 10,000 diabetic and 22,000 non-diabetic patients found no difference in prevalence of rhabdomyolysis between statin and nonstatin users; prevalence of myopathy significantly greater in individuals taking statins, and 1.5 times greater in diabetic patients taking statins compared with nondiabetic patients taking statins; 95% of events myalgias and mild myositis

Predictors of myopathy or myopathic events: concurrent medications (eg, fibrates, glucocorticoids, calcium channel blockers); advanced age; hypothyroidism; concurrent metabolic problems; increased body mass index; hepatic dysfunction

Toxic myopathy related to polypharmacy: case presentation — 53-yr-old man with heart transplant and multiple comorbidities presented with muscle stiffness; CK 22,000 IU/L; creatinine 8.2 mg/dL at outside hospital; medications included immunosuppressive agents concomitantly with statin; statin stopped at outside hospital; few days later, patient became progressively weak and unable to walk; CK >50,000 IU/L; treated with steroids and hemodialysis; cyclosporine held; combining cyclosporine with statin leads to increased risk for myopathy or rhabdomyolysis; addition of clarithromycin inhibits cytochrome P450 3A4 (CYP3A4) system and increases levels of cyclosporine (which also inhibits metabolism of CYP3A4); statins metabolized through CYP3A4 system in liver; patient had rhabdomyolysis secondary to myotoxicity from 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase (HMGCR) in form of simvastatin in combination with cyclosporine and clarithromycin; cyclosporine and macrolide synergistically inhibit metabolism, increasing likelihood of statin adversely affecting muscle

Randomized placebo-controlled trial: 5-yr study looked at 20,000 patients on simvastatin (40 mg/day) vs placebo; increased risk for muscle complaints in statin users not found; 6% reported adverse symptoms at 4, 8, and 12 mo during first year, and every 6 mo thereafter for 5 yr; one-third of patients in each group had symptoms on at least one visit; high rate in each group thought to be due to patients being told about muscle-related problems during informed-consent process

Dose dependence: meta-analysis of 4 large trials found nearly 10-fold increased risk for myopathy (CK >10 times normal) in patients on high-dose (80 mg/day) atorvastatin or simvastatin compared with patients on moderate-dose therapy; absolute risk somewhat low (0.7%); number needed to harm 1534; risk for myopathy dose dependent (high-dose statin associated with increased risk for myopathy)

Rechallenge: small study of 51 patients with myalgias and elevated transaminases on statins; 75% of patients able to tolerate mean dose of rosuvastatin of 5.6 mg every other day, and two-thirds reached target goal for low-density lipoprotein cholesterol

Treatment strategy: statin-induced muscle symptoms (eg, myalgias) and/or CK elevation — stop statin; if symptoms normalize, no workup necessary; try another agent or consider using statin every other day; persistent symptoms and/or CK elevation — rule out hypothyroidism or other minor metabolic disturbance and polypharmacy; coenzyme Q10 (CoQ10) — small study of patients with myopathic symptoms randomly assigned to CoQ10 (100 mg/day) vs vitamin E (400 IU/day) for 30 days; in CoQ10 group, pain decreased by 40% (statistically significant) and activities of daily living improved by 38%; no change seen in vitamin E group; CoQ10 supplementation may decrease muscle pain associated with statins

Mitochondrial myopathy: statins inhibit production of CoQ10, which may impair mitochondrial function or production of muscle energy; however, symptoms persist even after stopping statin; rule out underlying metabolic myopathy in patients with persistent symptoms (difficult; may require muscle biopsy)

Immune-mediated necrotizing myopathy: signs — persistent paroxysmal weakness during or after statin use; elevated CK despite stopping statin; improvement with immunosuppressive agents; necrotizing myopathy on muscle biopsy; no inflammation

HMGCR expression: statins lower cholesterol by inhibiting HMGCR; HMGCR identified as autoantigenic
target; HMGCR expressed in regenerating muscle; immune-mediated damage and autoantibody formation (induced by statins) sustained even after statin stopped; during regeneration of injured muscle, persistent HMGCR expression associated with repair perpetuates autoimmune inflammatory process.

**Algorithm:** perform baseline CK before starting statin; if symptoms develop, stop statin; if symptoms persist, consider chronic immune-mediated disorder; HMGCR antibody testing commercially available.

**Summary:** mild muscle symptoms commonly seen with statin use; rhabdomyolysis rarely occurs; look for comorbid factors or polypharmacy in patients with myopathic symptoms; immune-mediated myopathy rarely occurs.

**Acknowledgments**

Dr. Sorscher was recorded at the 2014 American Academy of Family Physicians Scientific Assembly, held October 21-25, 2014, in Washington, DC; sponsored by the American Academy of Family Physicians. To learn about upcoming CME activities from the University of Pittsburgh School of Medicine Center for Continuing Education in the Health Sciences. To learn about upcoming CME activities from the University of Pittsburgh School of Medicine, visit www.upmc.com. The Audio Digest Foundation thanks the speakers and the sponsors for their cooperation in the production of this program.

**Suggested Reading**


**Accreditation:** The Audio Digest Foundation is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

**Designation:** The Audio Digest Foundation designates this enduring material for a maximum of 2 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Academy of Physician Assistants (AAPA) accepts certificates of participation for educational activities designated for AMA PRA Category 1 Credit™ from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 2 AAPA Category 1 CME credits of each Audio Digest activity completed successfully.

This Enduring Material activity, Audio Digest Family Medicine Volume 63, Issues 1-48, has been reviewed and is acceptable for up to 96.00 Prescribed credit(s) by the American Academy of Family Physicians. AAFP certification begins January 1, 2015. Term of approval is for one year from this date. Each issue is approved for 2.00 Prescribed credits. Credit may be claimed for one year from the date of each issue. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Audio Digest Foundation is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s (ANCC’s) Commission on Accreditation. Audio Digest designates each activity for 2.0 CE contact hours.

Audio Digest Foundation is approved as a provider of nurse practitioner continuing education by the American Academy of Nurse Practitioners (AANP Approved Provider number 030064). Audio Digest designates each activity for 2.0 CE contact hours, including 0.5 pharmacology CE contact hours.

The California State Board of Registered Nursing (CA BRN) accepts courses provided for AMA PRA Category 1 Credit™ as meeting the continuing education requirements for license renewal.

**Expiration:** This CME activity qualifies for AMA PRA Category 1 Credit™ for 3 years from the date of publication.

**Cultural and linguistic resources:** In compliance with California Assembly Bill 1195, Audio Digest Foundation offers selected cultural and linguistic resources on its website. Please visit this site: www.audiodigest.org/CLCreources.

**Estimated time to complete the educational process:**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review Educational Objectives on page 1</td>
<td>5 minutes</td>
</tr>
<tr>
<td>Take pretest</td>
<td>10 minutes</td>
</tr>
<tr>
<td>Listen to audio program</td>
<td>60 minutes</td>
</tr>
<tr>
<td>Review written summary and suggested readings</td>
<td>35 minutes</td>
</tr>
<tr>
<td>Take posttest</td>
<td>10 minutes</td>
</tr>
</tbody>
</table>
1. All the following are considered risk factors for insomnia, except:
   (A) Female sex  
   (B) Young age  
   (C) Chronic medical condition  
   (D) Low socioeconomic status

2. Which of the following is most often seen in individuals with insomnia?
   (A) Polypharmacy  
   (B) Chronic pain  
   (C) Sleep apnea  
   (D) Mental health disorder

3. Which of the following strategies for treating insomnia is associated with the highest level of evidence-based effectiveness?
   (A) Sleep log  
   (B) Sleep hygiene  
   (C) Stimulus control  
   (D) Sleep restriction

4. Which of the following statements about sleep aids is correct?
   (A) Diphenhydramine and doxylamine have long half-lives  
   (B) Melatonin is most effective when taken immediately before bedtime  
   (C) Doxepin or melatonin-type products are not appropriate for patients with a history of substance abuse  
   (D) The effectiveness of trazadone is supported by ample scientific data

5. Which of the following is the most likely diagnosis in a patient with creatine kinase (CK) elevation 5 times the upper limit of normal?
   (A) Mild myositis  
   (B) Severe myositis  
   (C) Myalgia  
   (D) Rhabdomyolysis

6. Patients who are taking statins are least likely to develop myopathy if they are:
   (A) Also taking glucocorticoids  
   (B) Also taking calcium channel blockers  
   (C) Young  
   (D) Overweight

7. The concomitant use of cyclosporine and clarithromycin increases risk for statin-induced myopathy.
   (A) True  
   (B) False

8. A small study found that ______ of patients with statin-induced myalgias and elevated transaminases were able to tolerate rosvastatin every other day on rechallenge.
   (A) 10%  
   (B) 25%  
   (C) 50%  
   (D) 75%

9. A small study of patients with myopathic symptoms found that:
   (A) Vitamin E improved activities of daily living  
   (B) Vitamin E decreased pain  
   (C) Coenzyme Q10 decreased pain  
   (D) All the above

10. All the following are signs of immune-mediated necrotizing myopathy, except:
    (A) Persistent paroxysmal weakness  
    (B) Improvement with immunosuppressive agents  
    (C) Elevated CK despite stopping statin  
    (D) Inflammation

Answers to Audio Digest Family Medicine Volume 63, Issue 04: 1-C, 2-D, 3-A, 4-A, 5-D, 6-A, 7-B, 8-C, 9-A, 10-B