CONTINUUM CME

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Relationship Disclosure:

Dr Thorpy serves on the speakers bureaus and consults for Jazz Pharmaceuticals and Teva Pharmaceuticals and has provided expert witness testimony for a legal case on a sleepiness motor vehicle accident.

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Patient Management Problem—Preferred Responses

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Following are the preferred responses for the Patient Management Problem in this **CONTINUUM** issue. The case, questions, and answer options are repeated, and the preferred response is followed by an explanation and a reference with which you may seek more specific information. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the material. The comment and references included with each question are intended to encourage independent study.

Learning Objective

Upon completion of this activity, the participant will be able to:

• Describe an approach to the differential diagnosis, clinical evaluation, and management of a patient presenting with excessive daytime sleepiness.

Case

A 20-year-old female college student presents with lethargy and daytime sleepiness that interfere with her ability to study and have occurred for the past 4 years. She states that she falls asleep whenever she is inactive, especially during lectures, when watching television, or when reading. In addition she has difficulty sleeping at night. She lives in rural Connecticut with her parents and 18-year-old brother. At the age of 13, she was diagnosed with attention deficit hyperactivity disorder and was placed on methylphenidate; at age 16, she was placed on an antidepressant because of depression. The depression at times was severe, and she even received electroconvulsive therapy, which was temporarily effective. Because of her lethargy she has been seen by an endocrinologist and was found to have a hypothyroid condition; levothyroxine was prescribed. The only other medication she is taking is an oral contraceptive.

Further questioning reveals that the patient usually goes to bed between 2:00 AM and 3:00 AM, takes about 1 hour to fall asleep, and gets out of bed in the morning between 10:00 AM and 2:00 PM. On days when she has morning classes, she is either unable to get out of bed to get to school or she is very fatigued and easily falls asleep while at school. The patient does not have cataplexy or hallucinations, but she does have rare episodes of sleep paralysis. She dreams a lot at night and occasionally dreams during naps.

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- ▶ 1. Considering the above patient history, which of the following is the most likely initial working diagnosis?
 - A. circadian rhythm sleep disorder
 - B. hypersomnia caused by a medical disorder
 - C. hypersomnia caused by a psychiatric disorder
 - D. hypersomnia caused by drugs or medications
 - E. hypersomnia of central origin

The preferred response is A (circadian rhythm sleep disorder). Delayed sleep-phase syndrome is a circadian rhythm disorder that most typically occurs in young adults and is characterized by difficulties in falling asleep at an appropriate time and in awakening in the morning.¹ This patient's sleep pattern best fits this description; however, additional features of her history, such as depression, hypothyroidism, and a long use of stimulant medications, could be responsible for her symptoms. She also has features of REM sleep that might suggest narcolepsy.

- 1. American Academy of Sleep Medicine. International classifications of sleep disorders, second edition: diagnostic and coding manual. Westchester, IL; American Academy of Sleep Medicine, 2005.
- ▶ 2. What is the next most useful information to obtain regarding the patient's symptoms?
 - A. actigraphy
 - B. Epworth Sleepiness Scale
 - C. polysomnogram
 - D. psychiatric evaluation
 - E. sleep log or diary

The preferred response is B (Epworth Sleepiness Scale). The Epworth Sleepiness Scale (ESS) is an easy-to-complete questionnaire that assesses the patient's likelihood of dozing in eight everyday situations and can provide a score that allows the clinician to determine the severity of sleepiness.¹ Out of a maximum of 24, a score higher than 10 indicates significant sleepiness and higher than 15 indicates severe sleepiness. An ESS score will help to differentiate fatigue from sleepiness, because fatigued patients who are not sleepy will score low on the ESS. A psychiatric evaluation would provide useful information if a psychiatric rather than a physical cause for the sleepiness were suspected; however, the first step is to determine whether clinically significant sleepiness is present, because it may take time to get a psychiatric evaluation. Sleep studies, including polysomnography, may be helpful, as may actigraphy, but the primary complaint must first be understood and a differential diagnosis developed.

1. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14(6):540-545.

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The patient completes an ESS in the office. The result is 16 out of 24, indicating severe daytime sleepiness. This result helps to differentiate fatigue from sleepiness. Fatigue, which is not associated with excessive sleepiness, is more likely to be a feature of a medical or psychiatric disorder rather than a specific sleep disorder. The patient then undergoes a physical examination.

- ► 3. Which of the following aspects of the physical examination is most likely to be of help in the evaluation of this patient?
 - A. abdominal examination
 - B. cardiovascular examination
 - C. head and neck examination
 - D. neurologic examination
 - E. pulmonary examination

The preferred response is C (head and neck examination). A major cause of daytime sleepiness is obstructive sleep apnea (OSA) syndrome caused by upper airway obstruction.¹ Examination of the head and neck can suggest whether narrowing of the upper airway might be a factor. However, OSA is less common in females and usually presents with a primary complaint of snoring, gasping, choking, or witnessed apneas during sleep. The cardiopulmonary examination would be helpful in a patient with relevant symptoms, such as congestive heart failure or a cardiac arrhythmia, which could be associated with OSA. A neurologic examination can be helpful if a specific neurologic deficit is suspected as a cause of the patient's sleepiness. The age of the patient and the lack of specific neurologic symptoms other than sleepiness suggest that a primary neurologic lesion is less likely to be the cause of the sleepiness, although a specific sleep disorder such as one of the hypersomnias of central origin, including narcolepsy or idiopathic hypersomnia, may be still be considered. An endocrine examination will also be helpful for two reasons: (1) to look for features of hypothyroidism that might imply that the patient has inadequate thyroid replacement therapy, and (2) to look for features that might suggest polycystic ovarian disease, such as hirsutism and acne, which is often associated with OSA.²

- 1. Bagai K. Obstructive sleep apnea, stroke, and cardiovascular diseases. Neurologist 2010;16(6):329–339.
- 2. Attal P, Chanson P. Endocrine aspects of obstructive sleep apnea. J Clin Endocrinol Metab 2010;95(2):483–495.

On physical examination the patient is 168 cm (66 in) tall and weighs 90.7 kg (200 lbs); her body mass index is 32.3 kg/m². Her neurologic examination is normal. Head and neck examination show a Mallampati class of II and the presence of small tonsils. Her neck size is 16 inches in circumference. She has a mild degree of nasal congestion in the right nostril. There is no hirsutism or acne.

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- ▶ 4. Which of the following diagnoses does the physical examination suggest?
 - A. hypothyroidism
 - B. intracerebral tumor
 - C. Kleine-Levin syndrome
 - D. narcolepsy
 - E. obstructive sleep apnea syndrome

The preferred response is E (obstructive sleep apnea syndrome). OSA syndrome is a likely diagnosis because the patient is overweight and has a neck circumference of 16 inches. A female neck circumference greater than 15 inches is compatible with OSA. The Mallampati classification is a 4-point score that assesses the ability to see the posterior pharvnx based on the visibility of the base of the uvula, faucial pillars, and soft palate.¹ The odds of having OSA increase more than twofold for every point increase on the Mallampati classification. Other than the presence of sleepiness and cataplexy, no clinical signs compatible with narcolepsy are present; however, cataplexy is rarely seen in the office. Hypothyroidism would be suggested by a slow pulse, loss of the outer third of the eyebrows, dry itchy skin, and thin brittle fingernails. Kleine-Levin syndrome is one of the recurrent forms of hypersomnia, but this syndrome has no physical findings other than sleepiness when a patient is in a sleepy phase of the disorder. An intracerebral tumor would usually be associated with clinical neurologic signs; however, a subtle hypothalamic tumor could be present without neurologic features. Despite the mild features of OSA, the patient's symptoms still require consideration of a full differential diagnosis.

1. Nuckton TJ, Glidden DV, Browner WS, Claman DM. Physical examination: Mallampati score as an independent predictor of obstructive sleep apnea. Sleep 2006;29(7):903–908.

Sleep studies are required to determine whether a specific sleep disorder, such as OSA or a hypersomnia of central origin, is present. Because of the circadian rhythm features, an actigraphic recording is ordered for 2 weeks, to be followed by an overnight polysomnogram and multiple sleep latency test. Blood work is arranged.

- ▶ 5. Which of the following laboratory tests is most useful and practical for determining a possible cause of this patient's symptoms?
 - A. CSF hypocretin level
 - B. human leukocyte antigen testing
 - C. routine blood CBC and chemistry
 - D. serum Lyme antibody test
 - E. thyroid function tests

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Continuum (Minneap Minn) 2013;19(1):274-283



1. Nishino S, Mignot E. Narcolepsy and cataplexy. Handb Clin Neurol 2011;99:783-814.

The patient has 2 weeks of actigraphy that shows a pattern of variable sleep-onset times between 11:00 PM and 2:00 AM and variable wake-up times between 7:00 AM and 10:00 AM. She then undergoes a polysomnogram followed by a multiple sleep latency test (MSLT). The patient's bedtime was 10:23 PM. The following results were obtained: sleep latency, 5 minutes and 34 seconds; total sleep time, 7 hours and 35 minutes; sleep efficiency, 92%; REM latency, 11 minutes; REM sleep percentage, 37%; apnea-hypopnea index, 3.4 events/h; lowest oxygen saturation, 95%; and MSLT with mean sleep latency of 1 minute and 5 seconds and five sleep-onset REM periods (SOREMPs). Routine laboratory studies, thyroid function tests, and Lyme antibody screening are negative.

- ► 6. Based on these test results, which of the following is the most likely diagnosis?
- A. depression
- B. idiopathic hypersomnia
- C. narcolepsy
- D. obstructive sleep apnea syndrome
- E. recurrent hypersomnia

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The preferred response is C (narcolepsy). Actigraphy showed a sleep pattern that was not consistent with delayed sleep-phase syndrome in that the patient was able to fall asleep as early as 11:00 PM. The pattern was not unusual for a young adult. The sleep studies confirmed that she could fall asleep before 11:00 PM and showed a very rapid sleep latency with an early REM sleep onset consistent with narcolepsy. She had a very small amount of sleep apnea but not enough to account for her symptoms. Her MSLT was consistent with narcolepsy with a short mean sleep latency of less than 8 minutes and five SOREMPs that occurred after sleeping for 7.5 hours the night before.¹ The presence of the SOREMPs excludes a diagnosis of idiopathic hypersomnia. Although the results could be associated with recurrent hypersomnia, the consistent with recurrent hypersomnia.² The severity of the sleepiness and the presence of the SOREMPs exclude a psychiatric cause for her symptoms.

- 1. Ahmed I, Thorpy M. Clinical features, diagnosis and treatment of narcolepsy. Clin Chest Med 2010;31(2):371–381.
- 2. Arnulf I, Lin L, Gadoth N, et al. Kleine-Levin syndrome a systematic study of 108 patients. Ann Neurol 2008;63(4):482–493.

A diagnosis of narcolepsy is made, and the patient is educated about the disorder. She is advised to keep a more stable sleep-wake pattern with a regular bedtime of going to bed and a regular wake-up time ensuring that she gets no less than 8 hours of sleep a night. She is advised to use naps as necessary, up to two per day, but to limit them to less than 20 minutes in duration.

- ▶ 7. Which of the following medications should be considered?
 - A. amphetamines
 - B. methylphenidate
 - C. modafinil
 - D. selegiline
 - E. sodium oxybate

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The preferred response is C (modafinil). The most widely used medication in the United States for the treatment of excessive sleepiness in narcolepsy is modafinil.¹ Modafinil comes in two forms: (1) the racemic mixture that has a half-life of approximately 15 hours but contains the s-isomeric form that has a shorter half-life of 3 to 4 hours, and (2) armodafinil, which is the r-isomeric form and has a similar half-life but lasts longer. Sodium oxybate is approved by the US Food and Drug Administration (FDA) for treating the sleepiness of narcolepsy and is an alternative to modafinil, but it has the slight disadvantage of having to be given in the middle of the night. Methylphenidate and amphetamines are regarded as second-line therapy for sleepiness because of their potential for abuse and cardiovascular side effects. Selegiline, a monoamine oxidase B inhibitor, is not FDA-approved for sleepiness but has been used, mainly in Europe, because of its alerting side effects caused by its metabolism to amphetamine derivatives.

1. Thorpy M. Therapeutic advances in narcolepsy. Sleep Med 2007;8(4):427-440.

The patient is started on armodafinil 150 mg per day.

- ▶ 8. Which of the following potential side effects of armodafinil is the most important to note to this particular patient?
 - A. cardiac arrhythmias
 - B. changes in psychiatric state
 - C. headaches
 - D. reduced efficacy of oral contraceptives
 - E. rashes

The preferred response is D (reduced efficacy of oral contraceptives). Modafinil or amodafinil will reduce the efficacy of oral contraceptive agents because of increased metabolism of ethinylestradiol.¹ The patient should be warned to use another form of contraception during the time that she uses armodafinil and for 1 month after stopping armodafinil. Serious skin rashes can occur with modafinil or amodafinil, and the patient should be warned to stop the medication if a rash develops until it is clear whether the rash is caused by the medication. Psychiatric changes may occur, and in view of the patient's history of depression any change in mood should be reported to the physician. Serious cardiac arrhythmias are rare, but an increase in heart rate may occur more commonly. Headaches are a common side effect when starting the medication but will usually subside with continued use of the medication.

1. Thorpy M. Therapeutic advances in narcolepsy. Sleep Med 2007;8(4):427-440.

Armodafinil is helpful in improving the patient's sleepiness, but approximately 1 week after starting the medication she develops a rash on her arms and legs that appears to be related to the armodafinil.

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- ▶ 9. Because of the rash, which of the following treatments is a viable alternative for this patient?
 - A. amphetamine salts
 - B. dextroamphetamine
 - C. methylphenidate
 - D. selegiline
 - E. sodium oxybate

The preferred response is C (methylphenidate). Methylphenidate is approved for the treatment of narcolepsy.¹ A starting dose of 10 mg 3 times a day before meals would be appropriate. Longer-acting forms are available that can be given once a day, but many patients prefer the flexibility of the shorter-acting form. Sodium oxybate is FDA-approved for sleepiness caused by narcolepsy, but because the patient has a variable sleep pattern and a history of depression it is best avoided unless cataplexy develops. Amphetamines such as dextroamphetamine or amphetamine salts are an alternative, but they have a higher side-effect risk than methylphenidate. Selegiline, a monoamine oxidase B inhibitor, is best avoided because of the increased risk of side effects compared with the alternative medications.

1. Thorpy M. Therapeutic advances in narcolepsy. Sleep Med 2007;8(4):427-440.

After 1 year of therapy, the patient has established a more stable sleep pattern and is emotionally more stable but she reports muscle weakness with emotion. She notices a sensation of needing to reach for a chair when she gets excited to avoid slumping to the ground. The episodes occur approximately 2 times per week and greatly concern her.

- ▶ 10. Which of the following medications should be prescribed?
 - A. amphetamines
 - B. atomoxetine
 - C. clomipramine
 - D. sodium oxybate
 - E. venlafaxine

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The preferred response is D (sodium oxybate). This patient's new episodes are classic for cataplexy. Sodium oxybate is effective in improving both cataplexy and excessive sleepiness.¹ It can also help stabilize nocturnal sleep. The patient would be asked to maintain a more stable sleep-wake pattern. The medication is given in divided doses at bedtime and again 2 to 4 hours after sleep onset. Antidepressant medications can be effective but are not FDA-approved for this indication and have a risk of either sleep disturbance or sexual difficulties, such as reduced libido. The norepinephrine reuptake inhibitors appear to be the most effective antidepressant agents for this symptom. Amphetamines, although largely ineffective, may help cataplexy slightly by reducing attacks precipitated by sleepiness.

1. Thorpy MJ. Cataplexy associated with narcolepsy: epidemiology, pathophysiology and management. CNS Drugs 2006;20(1):43–50.

The sodium oxybate is effective at controlling her cataplexy, but the patient continues to have some school and relationship concerns related to her illness and requests advice on where to turn for additional help with her condition.

- ▶ 11. Referral of the patient to which of the following services is most appropriate at this time?
 - A. Narcolepsy Network
 - B. nutritional consultation
 - C. occupational therapy
 - D. physical therapy
 - E. social work consultation

The preferred response is A (Narcolepsy Network). The Narcolepsy Network is a nonprofit organization dedicated to people with narcolepsy and related sleep disorders.¹ Their mission is to provide services to educate, advocate, support, and improve awareness of this neurologic sleep disorder. The Network holds an annual educational meeting for patients with narcolepsy and issues a regular newsletter with current information about narcolepsy and narcolepsy research. In addition, the American Academy of Sleep Medicine can help patients find a sleep specialist in their area and provides resources about narcolepsy for physicians.² The other listed options would not be specifically indicated in this patient at this time.

Narcolepsy Network. www.narcolepsynetwork.org/. Accessed January 18, 2013.
American Academy of Sleep Medicine. www.aasmnet.org/. Accessed January 18, 2013.

Two years later, the patient has married and wishes to start a family. She is concerned about the medications she is taking and how they might affect a pregnancy.

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- ▶ 12. Which of the following represents the most appropriate next step in managing this patient, given her desire to start a family?
 - A. change to different medications
 - B. continue the medications through pregnancy
 - C. discuss therapeutic options with the patient
 - D. reduce the dosage of the medications
 - E. stop all medications immediately

The preferred response is C (discuss therapeutic options with the patient). There is no easy answer to the question of whether to use medications during pregnancy. Most of the medications used for narcolepsy fall in Category C of the FDA's five-category classification of fetal risk from pharmaceuticals. Category C means that animal studies have shown teratogenic or embryocidal effects, but no controlled studies have been conducted in humans. The only exception is sodium oxybate, which is a Category B medication, meaning that animal studies indicate no risk, but no controlled studies in humans have been conducted. In clinical practice there is little evidence that therapeutic doses of Category B medications adversely affect a healthy pregnancy. The greatest risk to the developing fetus is in the first 60 days after conception, so it is preferable that patients avoid use of medications during that time; however, if a patient is at risk from the narcolepsy symptoms, then continuing the medications, perhaps at lower doses, should be discussed with informed patients. If the patient can avoid medications completely during pregnancy without increased risk to herself or the fetus, that would be the preferable course of action. Antidepressants in therapeutic doses pose little problem during breast-feeding, but sedative medications such as sodium oxybate are probably best avoided during this time.^{1,2}

- 1. Hoover-Stevens S, Kovacevic-Ristanovic R. Management of narcolepsy in pregnancy. Clin Neuropharmacol 2000;23(4):175–181.
- 2. Hoque R, Chesson AL Jr. Conception, pregnancy, delivery, and breastfeeding in a narcoleptic patient with cataplexy. J Clin Sleep Med 2008;4(6):601–603.

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