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Financial Disclosure:
Internal Medicine Alert's Editor, Stephen Brunton, MD, is a consultant for Sanofi-Aventis, Ortho-McNeil, McNeil, Abbott, Novo Nordisk, Eli Lilly, Endo, EXACT Sciences, and Astra-Zeneca, and serves on the speaker's bureau of McNeil, Sanofi-Aventis, and Ortho-McNeil. Peer reviewer Gerald Roberts, MD, reports no financial relationship to this field of study.

New Hope for Snorers

ABSTRACTS & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips serves on the speaker's bureau of Cephalon, Boehringer Ingelheim, Merck, ResMed, and GlaxoSmithKline, and is a consultant for Boehringer Ingelheim, Wyeth-Ayerst, and ResMed.

Synopsis: *Oral appliances are effective in the treatment of snoring and mild-to-moderate sleep apnea, and are indicated for patients with mild-to-moderate obstructive sleep apnea who prefer oral appliances to CPAP, do not respond to CPAP, are not appropriate candidates for CPAP, or fail treatment attempts with CPAP*

Sources: Kushida CA, et al. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances. *Sleep*. 2006;29:240-243; Ferguson KA, et al. Oral appliances for snoring and obstructive sleep apnea: A review. *Sleep*. 2006;29:244-262.

THIS PAIR OF PAPERS WAS PRODUCED BY THE STANDARDS OF Practice committee of the American Academy of Sleep Medicine (AASM) using their standard procedure of vetting and reviewing the peer-reviewed literature on the topic to produce a review paper, then creating a practice guideline based on that review.

For the review, the task force addressed the following questions:

1. What is the efficacy of oral appliances in the treatment of snoring and obstructive sleep apnea in the short and long term?
2. By what mechanisms do oral appliances improve snoring and obstructive sleep apnea?
3. Do patients use oral appliances in the short and long term?
4. What short and long-term side effects occur with the use of oral appliances?
5. How do oral appliances compare with nasal continuous positive airway pressure (CPAP), surgery, and other treatments for snoring and sleep apnea?
6. What device selection and procedures are best for implementing oral appliances in the treatment of sleep-disordered breathing?

A PubMed search was conducted for peer-reviewed papers in the English language that included original research on oral appliances; task force members contributed relevant articles that did not appear

VOLUME 28 • NUMBER 12 • JUNE 29, 2006 • PAGES 89-96

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in the PubMed search. One hundred thirty-one papers were included in this review. Task force members graded the evidence using a method adapted from Sackett,[1] and extracted data relevant to the questions posed above to produce evidence tables.

The literature assembled demonstrated a 52% chance of control of sleep apnea with an oral appliance. Successful treatment was much more likely in patients with mild-to-moderate sleep apnea (variously defined as an apnea plus hypopnea index [AHI] of less than 30 or 40 events per hour of sleep). Greater degrees of mandibular protrusion were associated with greater likelihood of successful treatment. Several studies suggested that a high body mass index (BMI) was associated with less likelihood of benefit with oral appliance treatment. The data assembled demonstrated that oral appliances are not as effective as CPAP, but are generally better accepted by patients. They appear to work by enlarging the upper airway and reducing its collapsibility. Assessment of compliance with oral appliances is generally by self-report, and is comparable to adherence rates with CPAP. There is a tendency for oral appliance use to decrease over time. Minor side effects include salivation and temporomandibular joint pain; the most significant side effect is bite change, which does not always resolve after cessation of use. Oral appliances are not as effective as CPAP in improving the AHI, but are generally better accepted by patients. Oral appliances outperform uvulopalatopharyngoplasty (UPPP) in both the short and the long term.

Based on this review of the literature, a panel of experts produced the accompanying Practice Parameter paper addressing the use of oral appliances to treat sleep apnea and snoring. This paper states that oral appliances are effective in the treatment of snoring and mild to moderate sleep apnea. They are indicated for patients with mild to moderate obstructive sleep apnea who prefer oral appliances to CPAP, do not respond to CPAP, are not appropriate candidates for CPAP, or fail treatment attempts with CPAP. The panel recommends that the devices be fitted by "dental personnel" and that "dental specialists" see patients who have oral appliances in follow-up. The panel recommended that the diagnosis of sleep apnea (or snoring) be established by polysomnography and that follow-up sleep study be performed to assess the efficacy of the oral appliance or if symptoms persist or recur.

COMMENTARY

This pair of papers is extremely important because of the very high (and increasing!) prevalence of sleep apnea, the severity of its sequelae, and the cumbersome nature of CPAP treatment. Sleep apnea is conservatively estimated to afflict 5% of Americans,[2] but some estimates are much higher.[3]

The findings of these papers are mirrored by the Cochrane Database, which reports, "CPAP is effective in reducing symptoms of sleepiness and improving quality-of-life measures in people with moderate and severe obstructive sleep apnea [OSA]. It is more effective than oral appliances in reducing respiratory disturbances in these people but subjective outcomes are more equivocal. Certain people tend to prefer oral appliances to CPAP where both are effective. This could be because they offer a more convenient way of controlling OSA."[4]

The review published in the Sleep and the Cochrane data base focuses extensively on the effect of oral appliance treatment on the AHI and subjective symptoms (sleepiness, quality of life). Indeed, those are important outcomes. However, the best-proven and most significant consequences of sleep apnea are cardiovascular

Internal Medicine Alert, ISSN 0195-315X, is published twice monthly by American Health Consultants, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to *Internal Medicine Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $21. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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World-Wide Web: www.ahcpub.com

Subscription Prices

United States
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sequelae and automobile crashes. Sleep apnea is now listed first among the treatable causes of hypertension by the Joint National Council on High Blood Pressure.[5] This finding is based on several large, well-done studies demonstrating significantly increased risk of hypertension in those with even mild sleep-disordered breathing as well as improvement of blood pressure with CPAP treatment in the absence of any other treatment.[6,7] There is also evidence strongly linking sleep apnea with ischemic events, arrhythmias, pulmonary artery hypertension, cerebrovascular events, and congestive heart failure; all of the cardiovascular consequences of sleep-disordered breathing have been demonstrated to improve with CPAP treatment.[8] In addition to cardiovascular morbidity and mortality, it is clear that people with untreated sleep apnea are at increased risk for car wrecks, and that effective treatment with CPAP can reduce that risk.[9,10]

There is, in fact, a small amount of evidence that oral appliances can reduce blood pressure in individuals with sleep apnea, though not to the degree that CPAP does.[11,12] As of this writing, data about the effect of oral appliances on other cardiovascular outcomes and on car crashes are lacking.[13] So, despite these very encouraging new recommendations about oral appliance use, it is important to remember that oral appliance therapy is second-line to CPAP treatment, and not appropriate for patients with severe sleep apnea.

On the other hand, this new vetting of oral appliances by both the AASM and the Cochrane Database should reduce substantially the number of hapless patients who are subjected to upper airway surgery, which has also recently been scrutinized by Cochrane, and which concluded, "The studies assembled in the review do not provide evidence to support the use of surgery in sleep apnea/hypopnea syndrome, as overall significant benefit has not been demonstrated."

In the clinical practice of medicine, this means that patients with snoring and mild sleep apnea who do not tolerate CPAP now have a viable, effective treatment option other than CPAP (which works better) or surgery (which doesn't). ■

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MRSA Hits the Streets

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

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Dr. Ferris reports no financial relationship to this field of study.

Synopsis: *Methicillin-resistant* Staphylococcus aureus *(MRSA) in the community was the cause of the majority of skin and soft tissue infections, and was predominantly of one strain different from MRSA of hospital origin.*

Source: King MD, et al. Emergence of community-acquired methicillin-resistant *Staphylococcus aureus* USA 300 clone as the predominant cause of skin and soft-tissue infections. *Ann Intern Med*. 2006;144:309-317.

All staphylococcus isolates from community-acquired skin and soft tissue infections for 3½ months from Grady Memorial Hospital and its affiliated clinics in Atlanta, Georgia, were analyzed, amounting to

389 specimens. Infection in hospitalized patients was considered community-acquired if it occurred within 72 hours of admission. Seventy two percent of all *S. aureus* infections were found to be MRSA, and 87% of those fell into one group (USA300) with a susceptibility profile demonstrating resistance only to beta-lactams and erythromycin and not to clindamycin, levofloxacin, trimethoprim-sulfa or vancomycin.

They also analyzed the initial treatment choices made for these patients and found that only 57% of infections were treated appropriately before sensitivity results were known. Among the MRSA patients, only 18% had been hospitalized during the previous year, suggesting that MRSA acquisition was most likely from the community and not the hospital. More black persons and younger persons had MRSA. Traditional risk factors for MRSA such as previous incarceration or day care attendance were not seen in the available records for the MRSA-infected group.

COMMENTARY

This study in urban Atlanta shows that a particular clone of MRSA has become the most common cause of all community-acquired skin and soft tissue infections, which is clearly increasing based on studies in previous years. This clone remains sensitive to tetracyclines and trimethoprim-sulfa, which is not the case with the classic hospital-acquired MRSA. Other studies have confirmed these trends. Unfortunately, a 4-fold increase in clindamycin resistance, with the most common presentation being abscess and cellulitis, has also been confirmed.[1]

Susceptibility patterns may vary regionally, so this research reminds us of the urgent need to culture community-acquired skin and soft tissue infections whenever possible to guide our treatment decisions. Drainage of abscesses may be the most important intervention,[2] but if there is no fluctuant collection of purulent material to be drained and the clinical setting suggests MRSA, a sulfa drug or tetracycline has been recommended as the best choice for initial empiric therapy.[3] Otherwise, treatment is guided by disease severity, clinical response, culture results and cost, but we should certainly be highly suspicious of MRSA in groups not previously thought to be at high risk. ■

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Walking Ability is an Important Predictor of CV Disease and Mortality in the Elderly

SPECIAL REPORT

By Harold L. Karpman, MD, FACC, FACP

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Dr. Karpman reports no financial relationship to this field of study.

EXERCISE CAPACITY AND FITNESS MEASUREMENTS have been successfully used to predict cardiovascular and total mortality in middle-aged adults.[1-4] Extended walking tests have been of value when assessing exercise capacity in patients with chronic obstructive pulmonary disease, advanced heart failure, respiratory disease and/or osteoarthritis.[5-8] A long-distance corridor walk test which is similar to the 6-minute walk test has previously been used to measure fitness in healthy older adults[9] and has been demonstrated to predict mortality in patients with congestive heart failure.[10]

Newman and her colleagues from the National Institute on Aging hypothesized that analysis of the performance time and determination of the cardiovascular response to the exercise effort in patients who were able to complete the 400-m component of the long-distance corridor or walk test would successfully predict mortality, cardiovascular disease, mobility limitation and disability in a cohort of well-functioning adults in the eighth decade of life.[11] The participants received standard instructions (ie, walk as quickly as you can without running at a pace that you can maintain) to walk 400 meters in a hallway in 20-m segments after a 2-minute warm up. After adjusting for potential confounders, those in the poorest quartile of functional capacity (ie, walk time greater than 362 seconds) had a significantly higher risk of death than those in the best quartile (ie, walk time less than 290 seconds).

COMMENTARY

The use of the timed 400-m walking test to objectively demonstrate the ability to perform a measured amount of exercise in community-dwelling older adults without known difficulty in performing mobility-related tasks

permitted the authors to discriminate mortality and cardiovascular risk and risk for mobility limitation and disability in this group of participants. Among the individuals who completed the walk, those who walked faster were found to be slightly younger, more often were men of the Caucasian race, were less likely to have significant health conditions, subclinical disease or cardiovascular risk factors, had lower body mass indices, and were more physically active. The findings in this extremely objective study[11] involving 3075 adults between the ages of 70-79 confirmed well-established, published evidence that middle-aged men and women adults who are physically fit have a lower incidence of cardiovascular events and total mortality.[1-3]

At least one previous study has demonstrated that poor lower-extremity performance is strongly predictive of future disability, hospitalization and mortality.[12] However, it should be recognized that the impact of any mobility-related deficits is significantly diminished or eliminated if the participant is able to successfully perform the timed 400-m "corridor" walk. The Newman study[11] provides validation of the importance of having the capacity to walk longer distances and shows that there can be a wide range of exercise performance in well-functioning older adults. Therefore, besides being an important objective method for assessing the risk of total mortality, cardiovascular disease, mobility limitation and mobility disability in older individuals, it may be a superb technique which allows easy identification of patients afflicted with an early decline in overall function. In conclusion, this standardized exercise study has once again demonstrated the importance of physical fitness in reducing both mortality and incident cardiovascular disease. ■

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Does Your Cell Phone Give You Headaches? Not Likely

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD

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Dr. Jamieson is a consultant for Boehringer Ingelheim and Merck, and is on the speaker's bureau for Boehringer Ingelheim, Merck, Ortho-McNeil, and Pfizer.

Synopsis: *No evidence was found to indicate that people with self-reported sensitivity to mobile phone signals are able to detect such signals or that they react to them with increased symptom severity.*

Source: Rubin GJ, et al. Are Some People Sensitive to Mobile Phone Signals? Within Participants Double Blind Randomized Provocation Study. *BMJ*. 2006. Epub ahead of print.

THE LABEL OF ELECTROMAGNETIC HYPERSENSITIVITY (EHS) is given to individuals who report non-specific symptoms that are perceived to be related to electrical devices, including cell phones, visual display units, and

power lines. Surveys of susceptible individuals with EHS ascribe a multitude of complaints to electromagnetic field (EMF) exposure, including headaches, sleep disorders, dizziness, fatigue, and tension. (Al-Khlaiwi T, Meo SA. *Saudi Med J*. 2004:25:732-736. Roosli M, et al. *Int J Hyg Environ Health*. 2004;207:141-150). A review of the literature published between 2000 and 2004 evaluated 13 observational or experimental studies of exposure to EMF (Seitz H, et al. *Sci Total Environ*. 2005;349:45-55). Results of randomized cross-over studies were contradictory. No causal relationship was noted in a provocation study of purportedly sensitive individuals. Results of studies of the association between EMF exposure and headache were mixed. Further investigation was suggested.

Rubin and colleagues performed a double-blind, randomized, within-participants provocation study in London to test whether people who reported sensitivity to mobile phone signals had more symptoms when exposed to a pulsing mobile signal than when exposed to a sham signal or non-pulsing signal. Sixty sensitive people who reported headache-like symptoms within 20 minutes of using a 9000 MHz global system for mobile communication (GSM) mobile phone were compared to 60 control participants who denied any symptoms related to mobile phone use. Conditions for 3 exposures, GSM signal, an unpulsed continuous wave signal, and sham without signal, were exactly the same for 50 minutes with an antenna mounted above and behind the left ear. Each participant was randomly administered the exposure in a blinded fashion in 3 separate sessions. Questionnaires about subsequent symptoms, with visual analogue scale measures, were administered at the end of the exposure and 24 hours later. The participants were also asked to state their degree of confidence that a particular exposure had taken place. Statistical calculations including 2-way analysis of variance and generalized estimating equations found no evidence that self-reported sensitivity to the mobile phone signals was correlated to reported symptoms. Headache severity increased during exposure and decreased immediately afterwards without correlation between exposure conditions and symptom severity. The proportion of sensitive participants who believed a signal was present during GSM exposure (60%) was similar to the proportion that believed one was present during sham exposure (63%). Rubin et al note that as sham exposure was sufficient to trigger severe symptoms in sensitive participants, psychological factors may have an important role in purported sensitivity to mobile phones.

COMMENTARY

The psychological factors linked to headaches are notable by the high rate of placebo effects from multiple types of interventions. This scientifically rigorous study debunks the notion that use of a mobile phone might trigger headaches due to EHS exposure. It also illustrates the importance of the nocebo effect on headaches, and requires that epidemiological studies of headache causation be carefully designed to take this factor into consideration. Patients who report sensitivity to mobile telephone use should be encouraged to seek alternative explanations for their headache symptoms. ■

Pharmacology Update

Lubiprostone Capsules (Amitiza™)

By William T. Elliott, MD, FACP, and James Chan, PhD, PharmD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Chan and Elliott report no financial relationships to this field of study.

A NEW AGENT WITH A UNIQUE MECHANISM OF action has been approved for the treatment of chronic constipation. Lubiprostone is an activator of the chloride channels in the apical membrane of the gastrointestinal epithelium. It is marketed by Sucampo Pharmaceuticals and Takeda Pharmaceuticals America as Amitiza™.

Indications

Lubiprostone is indicated for the treatment of chronic idiopathic constipation in adult patients.[1]

Dosage

The recommended dose is 24 µg twice daily with food.[1]

Potential Advantages

Lubiprostone increases the number of spontaneous bowel movements with a different mechanism of action compared to traditional laxatives. No protein binding interactions or drug-drug interactions involving CYP isoenzymes are expected.

Potential Disadvantages

About one third of patients report nausea and 8.7%

discontinue treatment due to nausea. Diarrhea is reported in 13.2% of patients and 3.4% reported severe diarrhea and 2.2% discontinued treatment.[1]

Comments

Lubiprostone is a selective type 2 chloride channel activator. This action on the apical intestinal membrane leads to increased intestinal fluid secretion which softens the stool, promotes spontaneous bowel movement, and reduces abdominal discomfort, pain, and bloating.[2,3] The drug was evaluated in 2 studies (n = 479) in mainly Caucasian female patients with chronic idiopathic constipation defined as < 3 spontaneous bowel movements per week. Lubiprostone administration resulted in a median increase of 3.5-3.8 spontaneous bowel movements at week 1 compared to 1.5 for placebo. The median increase was 3 vs 1.5 at week 4. In open-label studies patients have been treated for 6-12 months, lubiprostone appears to continue to improve symptoms.[1,3] Nausea and diarrhea are the most common adverse events. Nausea appears to be dose-dependent and is reduced with administration with food. The rate is lower in men than in women (13.2% vs 18.6%). Approximately 9% of patients discontinue treatment due to nausea. The rate of lubiprostone-induced diarrhea does not appear to be dose-dependent. Lubiprostone is contraindicated in patients with a history of or presence of mechanical obstruction. The wholesale cost of lubiprostone is about $5 per day.

Clinical Implications

Lubiprostone offers an effective and apparently safe drug for the treatment of chronic idiopathic constipation. There are currently no comparative studies with other drugs such as laxatives or tegaserod. Lubiprostone should be reserved for patients in whom traditional agents have not been effective. ■

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CME Questions

28. Long-distance corridor walk performance in elderly patients is:

a. an excellent and objective measure of aerobic fitness.
b. an important prognostic indicator for total mortality, cardiovascular disease, mobility limitation and mobility disability.
c. often negatively affected by chronic health conditions.
d. All of the above.

29. Which of the following is an increasing cause of community-acquired abscess?

a. Group A Streptococci
b. Group B Streptococci
c. Staphylococcus aureus
d. Methicillin-resistant *S. aureus*
e. None of the above

Answers: 28 (d); 29 (d)

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances; and
- to describe cost-effective treatment regimens.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Telithromycin Impact in Acute Asthma

Most exacerbations of asthma are related to viral infection. Hence, antibiotics are usually not useful unless there is a suspicion of bacterial infection. Indeed, a Cochrane review of antibiotics in asthma identified 2 prior studies in which antibiotics (not telithromycin [TEL]) provided no benefit for acute asthma exacerbations.

TEL is a macrolide antibiotic with effects on atypical bacteria that are sometimes recovered during acute asthma exacerbations, and often colonize patients with asthma, eg, Chlamydia and Mycoplasma. TEL also possesses some immunomodulatory effects. This study compared TEL 800 mg/d with placebo for patients with acute asthma exacerbations (n = 278). The end points were changes in symptoms and peak expiratory flow rate (PEFR).

Although TEL treatment was not superior to placebo for PEFR, there was a statistically significant effect on symptoms favoring TEL. Subgroup analysis of *Chlamydia/Mycoplasma serostatus* indicated that subjects who were bacteria sero-positive *did* enjoy a statistically significant improvement in FEV_1 compared to sero-negative subjects. The role of serostatus is uncertain, since only a very small percentage of subjects were PCR-positive for bacteria, which should be a more sensitive test. Because telithromycin has a potential for severe liver injury, and because the increments of asthma benefit in this study were small, the potential role of TEL in asthma treatment remains to be determined. ■

Johnston SL, et al. N Engl J Med. 2006;354:1589-1600.

Comorbid Hypogonadism in Diabetic Men with Erectile Dysfunction

Erectile dysfunction (ED) most commonly reflects endothelial dysfunction, usually as a consequence of hypertension, dyslipidemia, smoking, or diabetes. Since diabetic men also have a proclivity to neuropathy (motor, sensory, and autonomic), the combination of vasculopathy with neuropathy is particularly burdensome to erectile function.

In non-diabetic men, hypogonadism is responsible for only a small proportion of ED, typically reported as 5-10%. Recently, an association between diabetes and hypogonadotropic hypogonadism—the situation where both pituitary trophic hormones and testosterone are concomitantly low—has been noted.

A study of consecutive patients attending a sexual dysfunction clinic (n = 1,246) was done which included measurement of LH, TSH, and testosterone (total and free testosterone). Eighteen percent of this population had diabetes. Using the threshold criteria adopted by the authors, the prevalence of hypogonadism in diabetic men was much higher than the non-diabetic men: 24.5% vs 12.6%; $P < 0.0001$. These data also confirmed a disproportionate incidence of hypogonadotropic hypogonadism.

This high prevalence of hypogonadism in diabetic men cannot be extrapolated to the general population of diabetic men since these subjects were preselected for suffering sexual dysfunction. PDE5 inhibitors have shown lesser efficacy in diabetics than other populations. Comorbid hypogonadism may explain some of this discrepancy. ■

Corona G, et al. Int J Impot Res. 2006; 18:190-197.

Is Iron Deficiency Related to Alopecia?

The relationship between iron status and hair loss is complex. Most of the data set has evaluated women, who experience iron deficiency anemia 3-5 times more often than men, usually attributable to the combination of lower baseline body stores combined with menstrual blood loss. In trials that have evaluated iron status in women with respect to alopecia, results have been mixed and inconclusive. Some investigators have supplemented iron for women with androgenetic alopecia (in combination with the anti-androgen spironolactone), and found a subgroup of responders.

Despite an the lack of a consensus in the dermatologic literature about the relationship between low iron status and alopecia, these Cleveland Clinic authors screened male and female patients presenting with alopecia with a CBC and serum ferritin, commenting that despite an inconclusive evidence base, their anecdotal experience indicates superior responses in patients with alopecia when depleted iron stores are replenished. When a low ferritin is observed, with or without anemia, the authors provide iron supplementation (dietary or supplement) to maintain a ferritin concentration greater than 70 ng/mL. Their recommendation includes maintenance of iron treatment for 3-6 months, to ensure replenishment of iron stores. ■

Trost LB, et al. J Am Acad Dermatol. 2006;54:824-844.

In Future Issues: COPD, PE, or Both?