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INSIDE

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When Two is Better Than One

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

Clinical Assistant Professor, West Virginia University School of Medicine, Charleston, WV

Dr. Gupta reports no financial relationships relevant to this field of study.

Synopsis: *A community-based cohort study finds that systolic blood pressure difference between both arms is common and associated with a significant increased risk for future cardiovascular events.*

Source: Weinberg I, et al. The systolic blood pressure difference between arms and cardiovascular disease in the Framingham Heart Study. *Am J Med* 2014;127:209-215.

BLOOD PRESSURE (BP) RECORDINGS OFTEN DIFFER BETWEEN ARMS, BUT THE extent to which these differences exist is significant. Generally, an increased interarm systolic BP difference is usually defined as 10 mmHg or greater, and evidence suggests that 20% of people may have this finding.[1] Some experts suggest that bilateral BP measurements should become a routine part of cardiovascular assessment in primary care since significant differences in systolic BP between arms may be able to predict an increased risk of cardiovascular events and all-cause mortality over time in people with hypertension.[2] Therefore, this difference could be a valuable indicator of increased cardiovascular risk and may become central to appropriate identification and treatment of hypertension. While an association between the interarm systolic BP differences in individuals and mortality has been noted in some studies, the direct association with cardiovascular disease remains to be better defined.

In their research, Weinberg et al describe the distribution of interarm systolic BP difference and risk factor correlates as well as examine the association between interarm systolic BP difference and incident cardiovascular disease and all-cause mortality.

Using data from the Framingham Heart Study cohorts, the researchers evaluated interarm systolic BPs of 3390 patients (56.3% fe-

VOLUME 36 • NUMBER 8 • APRIL 29, 2014 • PAGES 57-64

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male) aged ≥ 40 years (mean age 61.1 years) who had no history of cardiovascular disease and who were examined as part of the original study cohort (between 1991 and 1994) and an offspring cohort (between 1995 and 1998). An increased interarm pressure difference was defined as ≥ 10 mmHg. The maximal difference between arms was used and patients were followed through 2010.

Researchers found that the mean absolute interarm systolic BP difference was 4.6 mmHg. During the follow-up period, a first cardiovascular event occurred in 598 (17.6%) study subjects. Of these subjects, 26.2% had an interarm systolic BP difference of > 10 mmHg. Researchers also found that compared with participants who had a normal interarm pressure difference, those with elevated differences tended to be older (63 years vs 60.9 years), and to have higher rates of diabetes mellitus (13.3% vs 7.5%), higher systolic BP (136.3 mmHg vs 129.3 mmHg), and higher total cholesterol levels (212.1 mg/dL vs 206.5 mg/dL).

After adjusting for cardiovascular risk factors, an interarm BP difference was associated with a significantly higher risk of first-time cardiovascular events (hazard ratio [HR] 1.38; 95% confidence interval [CI], 1.09-1.75). For every standard deviation increase in interarm systolic BP difference, the HR was 1.07 (95% CI, 1.00-1.14). An association between interarm pressure difference and mortality risk was not found.

Weinberg et al conclude that the increased interarm systolic BP difference that was found to be present in nearly 10% of individuals in the study is not only associated with increased levels of traditional cardiovascular risk factors but also an increased risk for incident cardiovascular events, independent of traditional cardiovascular risk factors.

■ COMMENTARY

Accurate measurement of BP is important for detection, evaluation, and treatment of hypertension. With heart disease continuing to be one of the leading causes of death in the United States, there is a constant search for simple and practical tools physicians can use in practice to identify those at higher risk for adverse events within a cohort of hypertensive patients. While accurate measurement and interpretation is essential for proper diagnosis and management of hypertension, current guidelines recommend that BP should be assessed in both arms at the initial visit and the arm with the higher value should be used for assessment at subsequent visits.[3] However, the current study reaffirms that interarm systolic BP differences are fairly common. Moreover, the research finds that such individuals are at an increased risk for incident cardiovascular events, independent of traditional risk factors. These findings are consistent with previous evidence that has found a relationship between interarm systolic BP difference and subclavian artery stenosis, which has been linked to an increased risk of cardiovascular events. According to these findings, it probably makes sense for physicians to consider including BP readings in both arms to get the most accurate readings possible and detect any differences in BP at each visit. The interarm systolic BP difference can easily serve as a simple clinical indicator of increased cardiovascular risk, and the ensuing treatment and monitoring of those patients may be followed more closely. The best part is that this clinical practice tool is not only useful but also inexpensive. ■

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Internal Medicine Alert, ISSN 0195-315X, is published monthly by AHC Media, LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

EXECUTIVE EDITOR: Leslie Coplin.
MANAGING EDITOR: Neill L. Kimball.
EDITORIAL DIRECTOR: Lee Landenberger.

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 550669, Atlanta, GA 30355.

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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A New, Effective Treatment for Obstructive Sleep Apnea: Hypoglossal Nerve Stimulation

ABSTRACT & COMMENTARY

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Segal reports no financial relationships relevant to this field of study. This article originally appeared in the March 2014 issue of Neurology Alert.

Synopsis: *Tongue protrusion, via hypoglossal nerve stimulation, appears to have great efficacy in the treatment of obstructive sleep apnea in this uncontrolled, large case series.*

Source: Strollo PJ Jr, et al. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 2014;370:139-149.

Obstructive sleep apnea (OSA) is a known risk factor for stroke, myocardial infarction, and overall mortality. Continuous positive airway pressure (CPAP) continues to be the mainstay therapy for this disorder, but is plagued by adherence rates as low as 30%. CPAP is better tolerated with optimization of mask fitting, strategies such as daytime adaptation, and close follow-up and monitoring. Even with these maneuvers, however, a large proportion of patients cannot tolerate CPAP. There are alternative therapies to CPAP, including oral appliances to advance the mandible and surgeries such as uvulopalatopharyngoplasty (UPPP), but these are of modest benefit, particularly in cases of moderate-to-severe OSA. Due to these limitations and the overall prevalence and dangers of OSA, the potential benefits for upper airway (tongue) stimulation shown here are particularly exciting.

In OSA, there is excessive relaxation of pharyngeal musculature leading to airway collapse. The genioglossus muscle, responsible for tongue protrusion, is a major contributor to this loss of airway patency as the base of the tongue falls backwards into the airway. This phenomenon is frequently observed in patients with "positional apnea," who snore or obstruct when on their back but improve when turned sideways. In these patients, genioglossus function may be sufficient to push the tongue out of the airway when positioned laterally, but too weak to do so when supine. Devices designed to pull the tongue forward are uncomfortable and ineffective. Hypoglossal nerve stimulation is a more effective strategy, facilitating genioglossus activity and tongue protrusion. This device includes an excitatory electrode placed unilaterally on the hypoglossal nerve and a sensing electrode in the chest, which monitors intercostal muscle activity and allows stimulation timed to the inspiratory phase of ventilation.

The present multicenter study included 126 patients with a history of OSA who were non-adherent to CPAP therapy. More than 900 patients were screened for the study using the apnea-hypopnea index (AHI), with the majority of exclusions due to OSA that was too mild (AHI < 20; n = 324) or too severe (AHI > 50; n = 87). The AHI scores apneas (reductions in airflow > 90%) and hypopneas (reductions in airflow > 30% accompanied by a 4% drop in oxygen saturation) throughout the duration of sleep, with the total number of events converted into an hourly rate index. In addition to requiring an AHI range of 20-50, the study excluded patients with central or mixed obstructive-central events, as well as those with positional apnea (non-supine AHI < 10). Also excluded were patients with markedly enlarged tonsils or with total airway collapse on endoscopic examination. Additionally, patients with significant comorbidities or with a body mass index (BMI) > 32 kg/m^2 were excluded.

After 1 year of stimulator therapy, the AHI in study participants decreased from 29 to 9, a 68% reduction that was highly statistically significant ($P < 0.001$). The Oxygen Desaturation Index, defined as the number of times per hour that oxygen saturation dropped by more than 4%, decreased from 25 to 7, a 70% reduction that was also highly statistically significant. The time spent with O_2 saturations < 90% was also significantly reduced. Dramatic benefits were also seen on the Epworth Sleepiness Scale and the Functional Outcome of Sleep Questionnaire, confirming that the improvements in OSA were robust and directly improved daytime alertness and cognitive function. Of note, participants did not lose weight over the course of the study (which might have been an alternative explanation for their improvement), showing a mean BMI of 28 kg/m^2 at baseline and at 12 months. Following the 12-month study, a consecutive subset of patients who benefitted from the stimulator (n = 46) were randomized to an additional week with or without the device turned on. In the withdrawal group, the AHI increased from 7 to 26 in one week, compared to essentially no change in the patients continued on stimulator therapy. Serious adverse events (n = 2) requiring lead repositioning due to discomfort were rare. Nine patients required a tooth guard due to tongue abrasion.

■ COMMENTARY

This study represents a possible paradigm shift in the management of OSA, providing convincing evidence of the efficacy of stimulator therapy. There do remain limitations in its overall conclusions. The investigators chose

patients in the "sweet spot" of OSA severity, AHI 20-50, having moderate-to-severe, but not very severe disease. Patients with milder OSA (AHI < 20) have significant OSA-associated morbidity that cannot be ignored. Patients in the very severe category (AHI > 50), not included in this study, might not be helped by hypoglossal nerve stimulation but perhaps could be treated with lower CPAP pressures, which would promote adherence.

Patients with BMI > 32 kg/m^2 were excluded. This would include a subset of patients with mild-moderate obesity (BMI 30-35 kg/m^2) and eliminate anyone with severe (BMI 35-40 kg/m^2) or morbid (BMI > 45 kg/m^2) obesity. With increasing weight, excessive neck soft tissue in obese patients contributes to airway collapse even in the presence of optimal tongue positioning. It is not clear, however, if the cutoff point used in this study represents the upper limit of efficacy for this therapy.

The study used a "permissive" definition of a positive response to therapy, using criteria of AHI < 20 and overall AHI reduction by 50%, as evidence of benefit. Patients with AHI values in the 5-20 range are treated with CPAP by many practitioners. Furthermore, successful CPAP therapy is typically considered to be "curative" when AHI is reduced into the normal range (< 5). Even with the liberal definition of treatment effect used in this study, 34% of study subjects did not achieve benefit. Given the profound reductions in mean AHI, there may have been significant inter-subject variability in treatment response.

There is a significant cost differential between CPAP therapy ($1500 for a state-of-the-art machine) and hypoglossal nerve stimulation (approximately $30,000 for the device alone, excluding surgical costs). This may be cost efficient, however, given the major expenses associated with OSA-associated morbidity and mortality, especially in patients who would not otherwise use CPAP.

Hypoglossal nerve stimulation represents a potentially exciting advance in the management of OSA. If a randomized, controlled trial confirms its efficacy, it may become the mainstay of OSA treatment. ■

Red+Blue for Heart Protection

ABSTRACT & COMMENTARY

By Howell Sasser, PhD

Associate, Performance Measurement, American College of Physicians, Philadelphia, PA

Dr. Sasser reports no financial relationships relevant to this field of study.
This article originally appeared in the March 2014 issue of Integrative Medicine Alert.

Synopsis: *In a study of 93,600 women conducted over 18 years, those with the highest levels of anthocyanins in their diets had a risk of myocardial infarction 32% lower than those with the lowest levels, even after adjusting for other risk and protective factors.*

Source: Cassidy A, et al. High anthocyanin intake is associated with a reduced risk of myocardial infarction in young and middle-aged women. *Circulation* 2013;127:188-196.

Researchers analyzed data from the Nurses' Health Study II (NHSII), which began in 1989 with the enrollment of women between the ages of 25 and 42. Each participant completed a questionnaire about health events every 2 years and a questionnaire about dietary patterns every 4 years. Follow-up continued for a maximum of 18 years.

Participants who reported having had a myocardial infarction (MI), stroke, other kinds of cardiovascular disease, or cancer before the study period began were excluded. The outcomes of interest were nonfatal MI and fatal coronary heart disease. Reported events were confirmed with medical records whenever possible.

Intake of a number of subclasses of dietary flavonoids, including anthocyanins, flavanones, flavan-3-ols, flavones, flavonols, and polymers, was estimated mathematically from reported consumption of relevant foods. Supplement use was not reported. Intake levels for each 4-year interval were included in the study's statistical models to allow for dietary changes over time. Other factors collected and used in the analysis to control for possible confounding included body mass index, physical activity, total energy intake, dietary fats, menopausal status, smoking, hormone use, and family history of MI. Secondary statistical models controlled for additional factors related to diet (potassium, folate, and fruit and vegetable intake) and health (hypertension, diabetes, angina, and hypercholesterolemia).

There were 405 cardiac events among 93,600 participants over 18 years of follow-up. There was a trend toward lower risk of MI with rising anthocyanin intake (P < 0.047), even after adjusting for potentially confounding factors. Those in the highest quintile of consumption had a risk 32% lower than those in the lowest quintile (hazard ratio, 0.68; 95% confidence interval, 0.49-0.96). For each 15 mg increase in consumption, the relative risk of MI declined by 17%. There also was evidence of some benefit with higher consumption of flavonols and flavonoid polymers, and with higher intake of flavonoid-containing foods, but these effects did not reach statistical significance.

■ COMMENTARY

The potential health benefit of foods, over and above their nutritional value, has been of interest since ancient times — Hippocrates said "Let your food be your medi-

cine." The modern public is bombarded with advice about "superfoods" and advertisements promising miraculous results ("Eat this and never diet again!"). For a time, dietary supplements containing the active agents of various foods in concentrated form seemed promising, but careful research found little clinical benefit.[1] What appears to remain is the observation that some constituent(s) of foods, perhaps even combinations of foods, have healthful properties when consumed in their original forms. Table 1 lists some common sources of the flavonoid subclasses that showed positive results in the present study.

Anthocyanins, a flavonoid subclass and one group of the phytochemicals responsible for the red and blue coloring of many fruits and vegetables, have strong antioxidant properties in vitro.[2] However, this has not been found to correspond to strong antioxidant effects in vivo. Researchers speculate that anthocyanins and other flavonoids are too degraded by digestion to make their way into body tissue where they might scavenge free radicals. Instead, their effect may be achieved by stimulating other processes. In the case of the cardiovascular system, one theory is that anthocyanins increase the activation of nitric oxide synthase, which in turn affects vascular tone and inflammation.[2] Alternatively, they may inhibit cell growth factors in the vascular endothelium.[3] It should be noted that the present study did not have access to detailed medical information, and so could not shed any light on whether anthocyanin intake correlated with a reduced risk of atherosclerosis, or vascular spasm, or some other mechanism.

Table 1. Common Sources of Anthocyanins, Flavonols, and Flavonoid Polymers.

Flavonoid Subclass	Common Sources in Food or Beverages
Anthocyanins	Blackberries
	Blueberries
	Cabbage, Red
	Cherries
	Concord Grapes
	Radishes, Red
	Raspberries, Black
	Raspberries, Red
Flavonols	Capers
	Chocolate, Dark
	Fennel
	Tea, Black
	Tea, Green
	Hot Peppers
Flavonoid Polymers	Chocolate, Dark
	Grapes, Red
	Tea, Black
	Wine, Red

Regardless of this, if the mechanistic hypotheses are correct, relatively small quantities of anthocyanins may be needed to realize the potential benefit. This is significant because the typical American diet contains only small amounts — far less than in some dietary supplements.[4] A study by Wu and colleagues found that while some foods contain large amounts of anthocyanins per unit of volume, data from the National Health and Nutrition Examination Survey showed that most Americans do not consume significant quantities of those foods. In the present study, the average anthocyanin intake was 2.5 mg/day in the lowest quintile of consumption and 25.1 mg/day in the highest. By comparison, some dietary supplements contain as much as 600 mg per dose.

This is important for the advice that clinicians might wish to give their patients. The present study demonstrated that measurable changes in risk could be achieved with relatively small dietary differences. Drawing on Wu et al's data, the difference between the low and high anthocyanin intake quintile averages is equivalent to two plums, one serving of black beans, or half a serving of red grapes. Changes in eating patterns on this scale should seem manageable to many if not most patients. Choosing to increase one's intake of anthocyanins in this way also has side benefits, such as increased consumption of dietary fiber, vitamins, and other phytochemicals, as well as perhaps crowding out some less healthy foods — in other words changing eating patterns.

Physicians and patients should bear in mind that it is these changes in patterns, rather than rigid adherence, that matter, as well as a consistent and long-term focus on a rainbow of colors in food. No one could — or should — eat an identical diet every day. Nor do foods contain precise and constant levels of any compound. Wu et al found anthocyanin levels in strawberries that varied from 35-69 mg per serving, and Table 2 gives examples of foods that contain several flavonoid subclasses in varying amounts.[5-7] Dietary variety, including multiple sources of the same desirable substances, offers the best chance to maintain appropriate consumption through seasonal fluctuations in availability and phytochemical composition. While this method requires more planning and thought than simply taking a pill, it yields benefits that likely extend beyond what we yet understand. ■

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Table 2. Comparative Flavonoid Content of Several Common Foods

Food/Beverage Source	Anthocyanins (mg/100 g)	Flavonols (mg/100 g)	Proanthocyanins* (mg/100 g)
Blackberries	89-211	13-19	6-47
Blueberries	67-183	1	88-261
Grapes, Red	25-92	2	44-76
Plums	2-25	1-6	106-334
Strawberries	15-75	-	97-183
Wine, Red	1-35	1-55	24-70

*Proanthocyanins are a major class of flavonoid polymers, a group which also includes thearubigins and theaflavins.

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Pharmacology Update

Apremilast Tablets (Otezla)

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

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

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

THE FIRST ORAL DRUG FOR THE TREATMENT OF PSORIATIC arthritis has been approved by the FDA. Apremilast is a selective phosphodiesterase 4 (PDE4) inhibitor. It is marketed by the Celgene Corporation as Otezla.

Indication

Apremilast is indicated for the treatment of adults with active psoriatic arthritis.[1]

Dosage

Due to gastrointestinal symptoms, titration to the recommended dose of 30 mg twice daily is recommended.[1] The titration schedule is as follows: 10 mg in the morning on day 1, 10 mg in the morning and in the evening on day 2, 10 mg in the morning and 20 mg in the evening on day 3, 20 mg in the morning and evening on day 4, 20 mg in the morning and 30 mg in the evening on day 5, and 30 mg twice daily thereafter. Apremilast is available as 10 mg, 20 mg, and 30 mg tablets.

Potential Advantages

Apremilast provides an orally active drug with a different mechanism of action.

Potential Disadvantages

The most common side effects are diarrhea, nausea, and headache (frequency of 5-9% in the first 5 days and 7-9% after day 6 to day 112).[1] Between 5-10% loss of body weight has been reported in 10% of patients. Patients should have their weight monitored during therapy. A numerically higher frequency of depression has been reported compared to placebo (1% vs 0.8%).[1] Risk vs benefit should be weighed before initiating treatment in patients with a history of depression or suicidal thoughts or behavior. If treatment is started, patients and family should be alerted to emergence or worsening of depression or development of mood changes or suicidal thoughts.[1]

Comments

PDE4, a dominant phosphodiesterase expressed in immune cells, is an enzyme responsible for the hydrolysis

of cyclic adenosine monophosphate (cAMP).[2] This is an important messenger that controls a network of pro-inflammatory and anti-inflammatory mediators. Apremilast affects the synthesis of various pro-inflammatory cytokines and chemokines.[3] The safety and efficacy of apremilast were evaluated in three randomized, double-blind, placebo-controlled trials.[1,4] Subjects were adults with active disease (≥ 3 swollen joints and ≥ 3 tender joints) despite prior treatment with a disease-modifying antirheumatic drug therapy (DMARD; e.g., methotrexate, leflunomide, sulfasalazine) and/or biologic treatment or current DMARDs. Subjects were allowed to be on a stable dose of DMARD, low-dose oral steroid, and/or an NSAID during the trial. Subjects who failed more than three agents or more than one biologic were excluded. Subjects were randomized to apremilast 30 mg twice daily, 20 mg twice daily, or placebo. The primary endpoint was ACR20 response at week 16. This represents a 20% improvement in swollen and tender joint counts as well as other improvements such as in pain, disease activity, and disability index. The 30 mg dose (recommended dose) showed higher and more consistent response than the 20 mg dose.[4] ACR20 were 38%, 32%, and 41% for the 30 mg dose for the three studies compared to 19%, 19%, and 18% for placebo, respectively. Subjects who were biologic-naïve generally had a better response than biologic-experienced and biologic failures.[4]

Clinical Implications

Psoriatic arthritis is a chronic systemic inflammatory disease characterized by joint pain, swelling, and stiffness. Psoriatic arthritis is associated with psoriasis, with 14-30% of patients with psoriasis eventually developing psoriatic arthritis. The diagnosis is based on clinical and radiological findings as the vast majority of patients are sero-negative. Currently approved treatment includes corticosteroids, tumor necrosis factor blockers (e.g., etanercept), and interleukin12/interleukin-23 inhibitors (e.g., ustekinumab).[5] There are currently no studies directly comparing apremilast to other agents. The results from placebo-controlled studies with etanercept (25 mg subcutaneously twice a week) showed ACR20 of 50% compared to 13% for placebo. This is an absolute percent difference of 37% for etanercept compared to 19% for apremilast suggesting a potential advantage for etanercept. The latter, however, does provide an orally effective treatment with a different adverse reaction profile. The wholesale cost for a 30-day supply of apremilast (30 mg twice daily) is $1875. ■

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CME Questions

1. **In the study by Weinberg et al, researchers found that the systolic blood pressure difference between both arms is associated with all *except*:**
   a. higher rates of diabetes mellitus.
   b. higher total cholesterol levels.
   c. increased risk for incident cardiovascular events.
   d. increased mortality.

2. **Hypoglossal nerve stimulation helps to correct obstructive sleep apnea by which of the following mechanisms?**
   a. It increases the rate of breathing.
   b. It reduces airway obstruction by initiating tongue protrusion.
   c. It has no effect on the apnea-hypopnea index.
   d. It causes frequent awakenings and therefore stimulates breathing.

3. **Anthocyanins are hypothesized to reduce the risk of myocardial infarction by:**
   a. free radical scavenging.
   b. promotion of nitric oxide synthase production.
   c. endothelial cell growth factor inhibition.
   d. B or C, but likely not A

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is a retained consultant for Boehringer Ingelheim, Daiichi Sankyo, Forest Pharmaceuticals, Janssen, Lilly, Novo Nordisk, Pfizer, and Sanofi.

Is There a Difference Between Dutasteride and Finasteride for Male Pattern Baldness?

Source: Harcha WG, et al. *J Am Acad Dermatol* 2014;70:489-498.

In the United States, the two approved pharmacologic agents for treatment of male pattern hair loss are topical minoxidil (Rogaine) and systemic finasteride 1 mg/d (Propecia). The mechanism by which finasteride enhances hair growth is related to its activity as a 5-alpha-reductase inhibitor (5-ARI), which prevents the conversion of testosterone in the skin to its active derivative dihydrotestosterone (DHT). Since DHT is believed to be the primary culprit inducing male pattern hair loss, diminution of its activity results in reduced hair loss and allows better unrestrained hair regrowth.

The 5-ARI activity of finasteride is designated as type 2. Because there are multiple 5-ARI isoenzymes (types 1, 2, and 3), the potential role of dutasteride — which is active at both type 1 and type 2 tissue sites — is of interest. Indeed, dutasteride is already approved in Korea for treatment of male pattern baldness.

A placebo-controlled, randomized, head-to-head (no pun intended, honest) trial compared hair growth in men with male pattern baldness treated with finasteride 1 mg/d vs dutasteride 0.02-0.5 mg/d for 6 months (n = 917).

At the end of the trial, although both active agents were superior to placebo, there was a significant difference favoring dutasteride for both absolute hair count as well as hair width compared to finasteride. Dutasteride may become a viable alternative to finasteride for male pattern hair loss. ■

Best Management of Superficial Thrombophlebitis in the Lower Extremities

Source: Di Nisio M, et al. *JAMA* 2014;311:729-730.

The consequences of superficial thrombophlebitis (STBP) of the lower extremities are not as well recognized as those of deep venous thrombosis (DVT). Similarly, there is some uncertainty among clinicians about best management. Choosing treatment wisely is important because untreated STBP can extend to DVT; indeed, even treated STBP can progress or recur in as many as 10% of patients.

Although other consequences are important (extension of STBP, recurrence), the most concerning sequel of STBP is DVT. Although trials of fondaparinux found a significant reduction in risk for DVT when administered for 45 days (an 85% risk reduction), data from studies with low-molecular-weight heparin (LMWH) and nonsteroidal anti-inflammatory drugs (NSAIDs) did not confirm venous thromboembolism risk reduction.

LMWH and NSAIDs provided lower rates of STBP recurrence than placebo, but based on equivocal results for VTE reduction, fondaparinux should be the preferred treatment. ■

Is There a Role for Pregabalin in Restless Legs Syndrome?

Source: Allen RP, et al. *N Engl J Med* 2014;370:621-631.

The impact of restless legs syndrome (RLS) can range from nuisance symptomatology requiring modest interruption of sleep to major decrements in quality of life for the patient and/or bed partner. Although dopaminergic medications have become the mainstay of therapy, they are sometimes associated with "augmentation;" a worsening of symptom intensity, symptom frequency, or increase in areas of the body involved with symptoms, over long-term treatment. Since there is no known cure for RLS, many patients require lifelong treatment, necessitating alternatives in the event that RLS augmentation occurs. To complicate the picture further, not everyone agrees that augmentation is a pharmacologically related issue; instead, the worsening of symptoms over time may simply reflect disease progression in susceptible individuals.

Allen et al performed a randomized, double-blind trial to compare the initial success rate for RLS symptoms (over 12 weeks) as well as frequency of augmentation over an additional 40 weeks of treatment with either pregabalin (300 mg/d), pramipexole (0.25 or 0.5 mg/d), or placebo (n = 719).

Both active treatments were effective in reducing RLS symptoms, although only higher dose pramipexole (0.5 mg) and pregabalin were statistically significantly superior to placebo. For the endpoint of augmentation, pregabalin was superior to both placebo and pramipexole 0.5 mg.

The underlying assumptions prompting treatment choices for RLS presume dopaminergic deficits. Since pregabalin has no known dopaminergic activity, and was found to be as effective as the dopaminergic treatment (pramipexole), the current understanding of the pathophysiologic basis for RLS has been challenged. ■

In Future Issues: **Prescription Opioid Analgesics Increase the Risk of Depression**