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Internal Medicine

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ABSTRACT & COMMENTARY

Drug-resistant Hypertension? Consider Adding a Nonpharmacologic Prescription

By Barbara Phillips, MD, MSPH

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

SYNOPSIS: In patients with obstructive sleep apnea and hypertension, continuous positive airway pressure use was associated with clinically and statistically significant reductions in blood pressure for both resistant and non-resistant hypertension.

SOURCE: Walia HK, Griffith SD, Foldvary-Schaefer N, et al. Longitudinal effect of CPAP on BP in resistant and nonresistant hypertension in a large clinic-based cohort. *Chest* 2016;146:747-755.

Over the past decade, the prevalence of drug-resistant hypertension has risen sharply, while the prevalence of hypertension has remained stable.[1] Drug-resistant hypertension is defined as blood pressure that remains above 140/90 mmHg despite simultaneous use of three classes of antihypertensive agents, or blood pressure that requires at least four medications to control. Walia et al speculated that the increased prevalence of sleep-disordered breathing could be contributing to the rising prevalence of drug-resistant hypertension. The authors decided to leverage their large clinical sleep apnea population and electronic records to test the hypotheses that continuous positive airway pressure (CPAP) use in obstructive sleep apnea (OSA) will reduce blood pressure significantly both in resistant and non-resistant hypertension, but the effect will be more pronounced in resistant hypertension. They also speculated that neck circumference will more accurately predict the risk of resistant hypertension than body mass index (BMI).

Researchers undertook electronic medical record data extraction for adult outpatients in the Cleveland Clinic Sleep center over three and a half-year period. Hypertension and OSA diagnoses were based on physician diagnoses. CPAP use was self-reported. Patients with the most common causes of secondary hypertension (chronic renal disease, primary hyperaldosteronism, Cushing syndrome, renal artery stenosis)

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were excluded. Authors collected baseline demographic and clinical data as well as sleep study data and data on antihypertensive use.

They analyzed data from 894 patients with hypertension and OSA, 15% of whom had resistant hypertension. The mean age and BMI were significantly higher in the resistant hypertension group ($P = 0.02$ and $P = 0.007$, respectively). There were no statistically significant differences between resistant and non-resistant groups in terms of sex or race. The mean arterial pressure and systolic pressure at baseline were higher in the resistant group, but there was no difference in diastolic blood pressure between groups.

In the year following CPAP initiation, there were significant decreases in systolic (3.08 mmHg), diastolic (2.28 mmHg), and mean (2.54 mmHg) arterial pressures. Patients with resistant hypertension exhibited higher blood pressures overall, both before and after CPAP initiation There was no differential effect of CPAP on blood pressure between the resistant and nonresistant groups.

In secondary analyses, Walia et al found that neck circumference predicted blood pressure fall with CPAP better than did BMI, and that Apnea plus Hypopnea Index (AHI) predicted blood pressure; each one-unit increase in AHI was associated with incremental increases in blood pressure. Patients who reported CPAP adherence had greater improvement in blood pressure than the entire cohort.

■ COMMENTARY

This paper should lead to changes in the management of hypertension, especially drug-resistant hypertension, which is notoriously difficult to control. In this large "real-world" clinical sample, Walia et al found statistically and clinically significant improvements in blood pressure within a year of CPAP initiation, regardless of whether the hypertension was resistant, in an intention-to-treat model.

These blood pressure changes are enough to affect important outcomes. Even modest reductions in blood pressure of 2-3 mmHg can reduce coronary artery disease by 4-5% and stroke by 6-8%.[2]

CPAP adherence is somewhat predictable and is actually no worse than adherence to most treatments for chronic diseases. For example, as many as one-third of patients presenting with "drug-resistant hypertension" are actually nonadherent with antihypertensive medications.[3] Sicker, symptomatic (e.g., sleepy) OSA patients are more likely to adhere to CPAP.[4] Additionally, patients suffering from more severe sleep apnea exhibit higher blood pressure. This leads to speculation that patients with drug-resistant hypertension and severe OSA may be more likely to adhere to CPAP than to their medication, since CPAP makes them feel better (CPAP reliably reduces sleepiness) and the medications may not. Consider the possibility of OSA as part of the workup of hypertension, especially drug-resistant hypertension. ■

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ABSTRACT & COMMENTARY

Menopausal Hormone Therapy: Useful and Indicated for Vasomotor Symptoms

By Robert W. Rebar, MD

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

SYNOPSIS: Menopausal hormone therapy is the most effective treatment for symptoms of the menopause, and benefits may exceed risks for most women within 10 years of menopause.

SOURCE: Stuenkel CA, Davis SA, Gompel A, et al. Treatment of symptoms of the menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2015;100:3975-4011.

The Treatment of Symptoms of the Menopause Task Force appointed by the Endocrine Society developed a consensus document on the role of menopausal hormone treatment (MHT). Based on evidence, the task force concluded MHT is the most effective treatment for vasomotor symptoms (VMS) and improves genitourinary symptoms, sleep disturbance, menopause-associated anxiety and depressive symptoms, and arthralgia. It further concluded that the benefits may exceed the risks for the majority of symptomatic postmenopausal women < 60 years of age or within 10 years of the onset of menopause. The task force further emphasized the need for healthcare providers and their patients to use a shared decision-making approach to choose the most appropriate therapy only after a careful assessment of individual risks and benefits.

Use of MHT is not warranted to prevent coronary heart disease, breast cancer, or dementia. The task force noted there are other, albeit less effective, therapies for individuals with VMS who cannot or choose not to use MHT. Similarly, they noted that low-dose vaginal estrogen and ospemifene are effective in treating the genitourinary syndrome of menopause and that various vaginal moisturizers and lubricants are also effective for those who do not choose hormonal therapy. The task force further emphasized that estrogens alone should be prescribed for women without a uterus, and progestogens should be added only for those with a uterus. Starting dosages generally should be lower than those utilized in the Women's Health Initiative (WHI, 0.625 mg conjugated equine estrogens with or without 2.5 mg medroxyprogesterone daily) and should be titrated upward until the appropriate clinical response is achieved. The task force also recommended against the use of custom compounded hormones. Although the use of MHT is recommended for the shortest duration possible, strong evidence to support this conclusion is lacking. Thus, clinicians and patients should reassess MHT continuation yearly and consider the risks and individual benefits beyond five years of use. Continuing therapy can be considered for those who become symptomatic after stopping MHT, those at high risk of osteoporotic fractures, and those for whom alternative therapies are not appropriate and who have no contraindications to continuing therapy. For young women with premature ovarian insufficiency or premature menopause, MHT can be taken until the time of anticipated natural menopause when the use of continued MHT can be reassessed. The task force concluded its recommendations by noting that the most important question for postmenopausal women is how to balance menopausal symptom relief with the prevention of chronic diseases of aging and by emphasizing the need for further research.

■ COMMENTARY

Publication of the initial results of the WHI in 2002 changed the use of hormone therapy for menopausal women dramatically.[1] In some sense, the changes were warranted: Provide no therapy to any individual without a specific indication, as clinicians were administering MHT to women who had no reason to initiate therapy. Simultaneously, the report and ensuing publicity led to a marked reduction in usage of MHT even by symptomatic menopausal women who might well have benefited greatly. That the initial findings of the WHI were misleading and are more complex and difficult to interpret than initially reported was the subject of a recent commentary.[2] In fact, in a recent reanalysis of the data from the WHI for women 50 to 59 years of age, benefits for women using estrogen alone or estrogen and progestin seemed to outweigh the risks.[3] To be sure, the WHI was not powered for age-related subset analyses, and none of the data were significant, but the data indicated that all-cause mortality was favor-

ably influenced in both arms of the study for women initiating MHT close to menopause. When these data are analyzed over a five-year period, there seems to be similarly beneficial effects.[4]

This guideline is a powerful statement recommending consideration of use of MHT — and it has been provided to a group consisting largely of internist-endocrinologists. Moreover, despite the reanalysis of the WHI data, most clinicians remain wary of the use of MHT, and the majority of symptomatic women in the United States who might benefit from MHT are, in fact, not receiving therapy. Women's health-care providers have an obligation to educate other clinicians about the responsible use of MHT and a responsibility to provide accurate and appropriate information to patients.

While this guideline hardly provides all the answers, it does provide a framework for discussing the use of MHT with other clinicians and patients. There is clearly a balance that must be struck between ruling out MHT for all women and providing MHT to all. It is now clear that MHT should not be provided to women to prevent chronic diseases, such as cardiovascular disease, but it continues to play a critical role in treating women with VMS. This is particularly relevant in light of recent data from the Study of Women Across the Nation (SWAN), which noted that frequent VMS, defined as experiencing hot flushes or night sweats for six days in the two weeks before an exam, lasted more than seven years during the menopausal transition and persisted for four and a half years following the final menstrual period in women who exhibited such symptoms.[5] Women who were premenopausal or early postmenopausal when they first reported frequent VMS had the longest total VMS duration (median > 11.8 years) and persistence following the final menstrual period (median 9.4 years). Interestingly, the SWAN noted differences among various ethnic groups, with African-American women experiencing the longest total duration (median 10.1 years). Earlier SWAN data showed that experiencing frequent VMS is highly related to anxiety, depression, sleep disturbances, quality of life, cardiovascular risk, bone health, and how much VMS bother women. Thus, MHT should be of significant benefit to women with frequent VMS, and frequent VMS can be expected to last for several years. However, such therapy should be provided only after appropriate risk assessment and counseling.

Over time, as the information about MHT becomes more widely disseminated, one can only hope MHT will be used more appropriately when it should and avoided when usage is inappropriate. One also should recognize that a single large, randomized trial, which was inappropriately analyzed, deprived an entire generation of women from receiving potential benefits of MHT. Clinicians should remain vigilant to ensure this never happens again. ■

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ABSTRACT & COMMENTARY

Outcome of PCSK9 Inhibitor-treated Patients

By Michael Crawford, MD

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

SYNOPSIS: In a meta-analysis of 17 studies, proprotein convertase subtilisin-kexin type 9 serine protease inhibitors markedly reduced low-density lipoprotein cholesterol levels and all-cause mortality, but was associated with a significant increase in neurocognitive adverse events.

SOURCE: Lipinski MJ, Benedetto U, Escarcega RO, et al. The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolaemia: A network meta-analysis. *Eur Heart J* 2016;37:536-545.

Studies of proprotein convertase subtilisin-kexin type 9 serine protease (PCSK9) inhibitors demonstrate markedly reduced low-density lipoprotein (LDL) cholesterol and possibly improved outcomes. To further investigate potential outcomes, investigators from the United States, United

Kingdom, and Italy performed a network meta-analysis of 17 trials of PCSK9 inhibitors vs. placebo or ezetimibe to assess whether PCSK9 inhibitors reduced all-cause mortality or cardiovascular (CV) events. They excluded studies involving patients homozygous for familial hypercholesterolemia. The outcomes analyzed included all-cause mortality, CV death, CV events, adverse events, and serious adverse events. The 17 randomized, controlled trials included 13,083 patients: 8,250 randomized to PCSK9 inhibitors, 3,957 to placebo, 846 to ezetimibe, and 30 to PCSK9 plus ezetimibe. The subjects' mean age was 59 years and 52% were male, most of the subjects were Caucasian, and many had known coronary artery disease or risk factors for it. PCSK9 inhibitors reduced LDL cholesterol 57% from a mean baseline of 122 to 51 mg/dL, and increased HDL cholesterol 6%. PCSK9 inhibitors significantly reduced all-cause mortality (hazard ratio [HR], 0.43; 95% confidence interval [CI], 0.22-0.82; $P = 0.01$) but not CV death (HR, 0.50; CI, 0.22-1.13; $P = 0.10$) or CV events (HR, 0.67; CI, 0.43-1.04; $P = 0.07$) compared to placebo. PCSK9 inhibitors significantly increased neurocognitive events (HR, 2.31; CI, 1.11-4.93; $P = 0.02$). Other adverse events were not different on PCSK9 inhibitors compared to placebo. The authors concluded that PCSK9 inhibitors significantly improved lipid profiles and reduced all-cause mortality, but were associated with more neurocognitive adverse events than placebo.

■ COMMENTARY

Last year, the FDA approved PCSK9 inhibitors for patients with homozygous familial hypercholesterolemia and those intolerant to statins or statin failures who have compelling reasons to lower cholesterol. These drugs are monoclonal antibodies, which must be administered by subcutaneous injection every two-four weeks. They are very effective at lowering LDL cholesterol, even on top of other therapy, and many trial patients were found to have at least one LDL value below 25mg/dL. Naturally, there has been concern about potential neurocognitive adverse effects. The individual trials did not demonstrate an increase in neurocognitive adverse effects, but they were clearly apparent in this meta-analysis.

The significant reduction in all-cause mortality was mainly due to two large studies (ODYSSEY LONG-TERM and OSLER 2), which had long follow-up periods. Although there was a trend toward reduced CV death and events, it was not statistically significant. Since the individual studies were not powered for outcomes, these results are hypothesis generating, and we must await the results of larger studies to confirm any outcome benefits.

This study fuels the debate about prescribing statins (or other LDL-lowering drugs) based on risk of vascular disease alone or treating to certain targeted LDL values. Proponents of the latter approach espouse that aggregating statin studies shows the lower the LDL, the better the outcomes. This also occurred in the recent IMPROVE IT study of adding ezetimibe to simvastatin. However, prior studies did not achieve the LDL levels that are possible with PCSK9 inhibitors, especially if they are added to statin plus ezetimibe therapy. Thus, many believe there is a lower limit to LDL lowering beyond which neurological adverse effects occur more commonly. The Cholesterol Treatment Trialists' Collaboration has suggested that this may be 50 mg/dL. Since PCSK9 studies often achieved LDL levels below that in many patients, this may explain the meta-analysis results of more neurocognitive adverse events with PCSK9 inhibitors.

At this point, PCSK9 inhibitors are a reasonable alternative or additional therapy for those intolerant to statins or those in whom LDL cholesterol remains elevated despite statins plus ezetimibe. However, perhaps adjusting the dosage to keep the LDL in the 50-70 mg/dL range is prudent until further studies produce more data. ■

PHARMACOLOGY UPDATE

Ixekizumab Injection (Taltz)

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

Dr. Elliott is Medical Director, Pharmacy, Northern California Kaiser Permanente, and Assistant Clinical 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 FDA has approved a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody directed against interleukin-17A (IL-17A). IL-17A has been identified as a key cytokine involved in the pathogenesis of psoriasis and psoriatic arthritis. Ixekizumab is the second IL-17A antagonist to be approved (secukinumab). It is marketed as Taltz.

INDICATIONS

Ixekizumab is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[1]

DOSAGE

The recommended dose is 160 mg initially, followed by 80 mg at week two, four, six, eight, 10, and 12, then every four weeks.[1] The drug can be self-administered by subcutaneous injection. Recommended injection sites are abdomen, thigh, or back of arm. Ixekizumab is available as a 80 mg/mL single-dose prefilled autoinjector or prefilled syringe.

[Ixekizumab is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy; however, clinicians and patients should be mindful of potential disadvantages such as infections.]

POTENTIAL ADVANTAGES

Ixekizumab appears to be more effective than etanercept.[2]

POTENTIAL DISADVANTAGES

The most frequent adverse event is injection site reactions (17%).[1] As with other biologic drugs affecting the immune system, the risk of infections may be increased. Patients should be evaluated for tuberculosis prior to starting treatment.

COMMENTS

The efficacy of ixekizumab was evaluated in three randomized, double-blind, placebo-controlled trials.[1,2] Subjects were ≥ 18 years of age presenting with plaque psoriasis involving a minimum body surface involvement of 10% and a static Physician Global Assessment (sPGA) score of ≥ 3 in overall assessment, and a Psoriasis Area and Severity Index (PASI) score ≥ 12, and were candidates for phototherapy or systemic therapy. Coprimary endpoints were a 75% improvement in PASI (PASI75) and sPGA of "0" (clear) or "1" (minimal) and at least a 2-point improvement from baseline. For those randomized to ixekizumab, the percent achieving sPGA of "0" or "1" ranged from 81-83% across the three studies, with placebo ranging from 2-7%. The percent achieving PASI75 ranged from 87-90%, compared to 2-7% for placebo.

In two studies, subjects were also randomized to etanercept (50 mg twice weekly).[1,2] The response for etanercept response ranged from 36-53% for the coprimary endpoints.[2] For treatment responders on ixekizumab at week 12, 75% of patients randomized to the maintenance dose of 80 mg every four weeks maintained their response compared to 7% randomized to placebo at week 60.[1] For responders randomized to discontinue ixekizumab, the median time to relapse was 164 days. In this population, 66% regained their response within 12 weeks when the drug was restarted. There are no published studies comparing ixekizumab and secukinumab.

When comparing across placebo-controlled studies, the placebo-subtracted response rates for ixekizumab ranged from 80-88% for PASI75. For secukinumab, rates ranged 71-84% for PASI75.[3] The study populations demonstrated similar PASI baseline scores — a median of 20 for secukinumab and 17-18 for ixekizumab. The studies used different five-point physician/investigator scales to assess disease severity.

CLINICAL IMPLICATIONS

Psoriasis is an inherited systemic inflammatory disease related to immune dysfunction. Ixekizumab is the second in the class monoclonal antibody to IL-17A, which is regarded as an important cytokine in the pathogenesis of psoriasis.[4] Ixekizumab appears to be an effective drug, but how it compares to secukinumab in term of efficacy remains to be determined. The cost for ixekizumab is $4,104 for a two-week supply. ■

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Clinical Briefs

By Louis Kuritzky, MD

The Associations of Vitiligo

SOURCE: Gill L, Zarbo A, Isedeh P, et al. Comorbid autoimmune diseases in patients with vitiligo: A cross-sectional study. *J Am Acad Dermatol* 2016;74:295-302.

The cause of vitiligo (VTL) remains obscure, but it is generally recognized to be an autoimmune disorder, with components of genetic predisposition, environmental stressors, and oxidative stress that ultimately influence its presentation.

The most common disorder with which clinicians may associate VTL is hypothyroidism, which is also usually autoimmune (Hashimoto's disease).

Gill et al reviewed autoimmune comorbidities associated with VTL in a large population (n = 1873) of VTL patients observed at the Henry Ford Health System in Detroit between 2002-2012.

A number of comorbid autoimmune disorders were significantly more frequently identified in the VTL population than in the comparator general U.S. population.

Included among these were hypothyroidism, alopecia areata, inflammatory bowel disease, pernicious anemia, lupus, myasthenia gravis, and Sjögren's syndrome.

Overall, approximately 20% of VTL patients had one or more comorbid autoimmune disorders.

The authors suggested vigilance and appropriate screening for comorbid autoimmune disorders when patients present with VTL. ■

A Toast to Not So Fast

SOURCE: Goulden R. Moderate alcohol consumption is not associated with reduced all-cause mortality. *Am J Med* 2016;129:180-186.

Conventional and clinical wisdom says alcohol in moderation benefits one's health.

Plenty of observational data show those who are non-drinkers and those who drink excessively have higher mortality than those who drink in moderation.

But observational studies can only generate hypotheses because such studies cannot prove causation. Have we jumped the gun on causation?

Goulden reported on 206,966 person-years of follow-up from the Health and Retirement Study, a cohort study comprised of a nationally representative sample of adults > 50 years of age (n = 24,029).

When adjusted for sociodemographic variables, health status, and functional status, there was no difference in all-cause mortality associated with moderate alcohol intake compared to other groups.

The relationship between moderate alcohol use and health benefits may have nothing to do with alcohol.

Might those who drink in moderation also practice moderation in other aspects of their lives, such as smoking, exercise, diet, and relationships, which could lead to better outcomes regardless of alcohol intake?

As usual, there are no simple answers. ■

What Should Americans Eat?

SOURCE: DeSalvo K, Olson R, Casavale KO. Dietary guidelines for Americans. *JAMA* 2016;316:457-458.

Since the National Nutrition Monitoring and Related Research Act of 1990, governmental agencies have provided the Dietary Guidelines, now called Dietary Guidelines for Americans (available at: http://1.usa.gov/1unIEvF).

The most recent edition, intended to inform diet for the 2015-2020 interval, contains several pertinent recommendations: 1) Limit added sugars to < 10% of calories/day (currently at 13%); 2) Limit saturated fats to < 10% of calories/day; 3) Limit sodium to < 2,300 mg/day (currently at 3,440 mg/day).

The 2010 Dietary Guidelines suggested limiting dietary cholesterol to 300 mg/day.

Because the guidelines advisory committee felt there was insufficient evidence to provide specific dietary cholesterol targets, comment on cholesterol was omitted from this document.

However, the healthy diet patterns suggested in the guidelines would inherently provide a dietary cholesterol of 100-300 mg/day.

The guidelines' overarching message is consistent with much of current popular diet philosophy — A healthy eating pattern limits saturated fats, trans fats, added sugars, and sodium. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. **In patients with obstructive sleep apnea and hypertension, continuous positive airway pressure treatment is associated with improved blood pressure:**

   a. only in those without drug-resistant hypertension.

   b. only in those with drug-resistant hypertension.

   c. both in those without drug-resistant hypertension and those with drug-resistant hypertension.

   d. None of the above

2. **Menopausal hormone therapy is indicated for the:**

   a. treatment of osteoporotic fractures.

   b. treatment of frequent vasomotor symptoms.

   c. prevention of cardiovascular disease.

   d. prevention of dementia.

   e. prevention of breast cancer.

3. **A meta-analysis of 17 proprotein convertase subtilisin-kexin type 9 serine protease-controlled treatment trials showed:**

   a. a two-fold increase in neurocognitive adverse events.

   b. a 90% decrease in low-density lipoprotein cholesterol.

   c. a 25% increase in high-density lipoprotein cholesterol.

   d. no difference in all-cause mortality.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Trimethoprim-sulfamethoxazole vs. Placebo for Skin Abscesses After Incision and Drainage

Early Chest CT Can Improve Treatment for Community-acquired Pneumonia