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INSIDE

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Antibiotic Use: Still Room for Improvement

ABSTRACT & COMMENTARY

By Martin S. Lipsky, MD

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Dr. Lipsky is a retained consultant for Health Solutions & Strategies.

Synopsis: *Broad-spectrum antibiotics constitute the majority of antibiotic use in ambulatory care. Despite multiple guidelines promoting more judicious use of antibiotics, about one in four prescriptions were for conditions in which antibiotics are rarely indicated.*

Source: Shapiro DJ, et. al. Antibiotic prescribing for adults in ambulatory care in the USA, 2007-2009. *J Antimicrob Chemother* 2013; Jul 25. doi:10.1093/jac/dkt301. [Epub ahead of print.]

Antibiotics are one of the most commonly prescribed medications in the United States. About 10% of office visits result in an antibiotic prescription. Historically, many of these scripts were used for viral illnesses, a condition for which antibiotics are not indicated. To address antibiotic overuse, several professional organizations have published guidelines promoting judicious use of antibiotics. Many of these address the use of antibiotics for acute respiratory infection, which has traditionally been an illness that often triggers inappropriate prescribing. While there may be some modest decline in overall antibiotic use,[1] there still appears to be persistent prescribing for conditions like bronchitis where antibiotics offer little benefit.

In this study, Shapiro and colleagues sought to determine the current pattern of antibiotic use and describe conditions for which antibiotics are prescribed. They also sought to identify factors associated with broad-spectrum antibiotic use.

The authors used 2007-2009 data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Care Sur-

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vey to examine prescribing patterns for patients over 18 years of age visiting an ambulatory care setting. Visits were grouped into the following categories: respiratory conditions, skin/mucosal conditions, including soft tissue infections, genitourinary (GU) conditions, gastrointestinal (GI) conditions, miscellaneous infections, surgical/post-surgical visits, and all other conditions and diagnoses. Respiratory conditions were subdivided into acute respiratory tract infections (ARTIs) for which antibiotics are potentially indicated such as pneumonia, ARTIs for which antibiotics are rarely indicated such as laryngitis, and respiratory conditions that rarely merit antibiotic treatment such as asthma. Similar divisions were made for GU and GI visits. The study also classified antibiotics as either broad spectrum or narrow spectrum. Broad-spectrum drugs included extended-spectrum penicillin, such as amoxicillin/clavulinic acid, second- to fourth-generation cephalosporin, macrolides, quinolones, and lincomycin injections.

The authors found that 10%, or about 100 million ambulatory visits, resulted in an antibiotic prescription. The most commonly used antibiotics were quinolones (25% of prescriptions), macrolides (20%), and aminopenicillins (12%). Antibiotics were most commonly prescribed for respiratory conditions (41% of all antibiotic prescriptions) and urinary tract infections (9%). Using a logistic regression model, broad-spectrum antibiotics were more likely to be prescribed than narrower spectrum ones for respiratory infections, including conditions such as bronchitis for which they are rarely indicated, at emergency department (ED) visits, and for patients older than 60 years of age. The authors estimated that more than 25% of the broad-spectrum antibiotics were given for conditions where antibiotics are rarely indicated.

■ COMMENTARY

It would appear from this study that the battle against antibiotic overuse is far from over. While overall use might be declining marginally, a concern is that the use of broad-spectrum antibiotics is increasing. Unnecessary scripts add expense and contribute to resistance. Although these drugs are typically well tolerated in the outpatient setting, given the millions of patients taking them, even if only a small percentage of patients have a significant side effect, overprescribing results in a significant burden on the nation's health.

Another recent study also affirms Shapiro et al's findings that antibiotic overuse is still a major problem. Barnett and Linder found that antibiotics were prescribed at 60% of all ED visits for sore throats, even though only about 10% of these infections are bacterial.[2]

While physicians may know that antibiotics are unnecessary, they still seem willing to write the prescriptions. Likely reasons include patient pressure and expectations. It is often easier to prescribe an antibiotic than to take the time to explain why they do not work for an illness. Patients may interpret not receiving an antibiotic for bad bronchitis as the doctor failing to recognize how sick they are rather than the medicine will not help the condition. One helpful strategy may be to acknowledge upfront how badly a patient is feeling and that the reason for not giving an antibiotic is not because the patient is not ill but because it will not help. In working with medical students and residents, I would often overhear attending physicians tell a trainee that antibiotics were probably not indicated for the patient but that they were going to prescribe them because they either wanted to be on the safe side or because the patient pressured them to do so. This study reaffirms that we need to end our practice of telling students to do as I say not as I do but instead to be a role model for the judicious use of these often overprescribed medications. ■

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ARBs in Diabetes — Some Good, Some Better!

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

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

Synopsis: *Telmisartan and valsartan were both associated with lower risk of hospital admission for macrovascular events in older adults with diabetes and hypertension when compared to other angiotensin-receptor blockers.*

Source: Antoniou T, et al. Comparative effectiveness of angiotensin-receptor blockers for preventing macrovascular disease in patients with diabetes: A population-based cohort study. *CMAJ* 2013;185:1035-1041.

It is estimated that approximately 26 million Americans suffer from diabetes, including almost one-third who continue to remain unaware of the disease diagnosis. Almost 2 million people in the United States are diagnosed with diabetes each year. Additionally, with the prevailing obesity epidemic, it is estimated that approximately 79 million more Americans suffer from a condition termed prediabetes. It is anticipated that unless prevented, a significant proportion of these individuals are likely to advance to overt diabetes thereby further raising the economic costs. Diabetes is also an expensive disease. The total costs of diagnosed diabetes in the United States in 2012 were estimated to be $245 billion. This means that after adjusting for population age and sex differences, average medical expenditures among people with diagnosed diabetes are 2.3 times higher than what expenditures would be in the absence of diabetes. Such significant increases in costs relative to other illnesses can be attributable to resultant complications from both macrovascular disease (atherosclerosis) as well as microvascular disease (retinopathy, nephropathy, and neuropathy). The risk of developing such complications as well as disease progression can be reduced with interventions aimed at strategies to achieve multifactorial risk reduction, early screening, and management. Many interventions intended to prevent and control diabetes are very cost-effective and supported by strong evidence.[1] Multifactorial cardiac risk reduction includes blood pressure, lipid and glycemic control, routine use of aspirin (unless contraindicated), smoking cessation, diet, and exercise, as well as the use of an angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB).

Although in clinical practice ARBs are often considered to be essentially interchangeable, some evidence from studies suggests that may not be the case. For example, some research from small clinical trials suggests that telmisartan may exhibit slightly different properties than other members of this drug class, and may therefore be superior in cardiovascular health.[2]

Antoniou et al conducted research to evaluate whether there is a difference in the risk of developing acute myocardial infarction, heart failure, and stroke among older patients with diabetes who are managed with telmisartan, candesartan, irbesartan, losartan, or valsartan. In this population-based, retrospective, cohort study of Ontario residents, data were evaluated for 54,186 patients with diabetes ≥ 66 years who received ARBs between April 1, 2001 and March 31, 2010. The primary outcome was a composite of admission to the hospital for acute myocardial infarction, stroke, or heart failure. Secondary analyses included all-cause mortality as well as evaluating each outcome individually. Among the patients excluded were those taking ACE inhibitors in conjunction with ARBs.

In the main analysis, researchers reported that patients who received either telmisartan (adjusted hazard ratio [HR] 0.85; 95% confidence interval [CI], 0.74-0.97) or valsartan (adjusted HR, 0.86; 95% CI, 0.77-0.95) had a significantly lower risk of the primary outcome (i.e., admission to hospital for acute myocardial infarction, stroke, or heart failure) when compared to patients who received irbesartan. In contrast, researchers found no difference in the risk of the primary outcome between irbesartan and other ARBs (losartan or candesartan). In secondary analyses, researchers found a lower risk of admission to the hospital for heart failure with telmisartan compared with irbesartan (adjusted HR, 0.79; 95% CI, 0.66-0.96), but no significant differences in risk were seen between other ARBs. The authors concluded that compared with other ARBs, telmisartan and valsartan were both associated with a lower risk of hospital admission for acute myocardial infarction, stroke, or heart failure among older adults with diabetes and hypertension and, consequently, these may be the preferred ARBs to prescribe in such patients.

■ COMMENTARY

Compared with non-diabetics, men and women with type 2 diabetes have at least 6-8 years' decreased life expectancy, and disease-related vascular illnesses are the main causes of death. For a majority of patients, by the time they are diagnosed with type 2 diabetes, one or more risk factors for macrovascular disease such as obesity, dyslipidemia, hypertension, or smoking already exist. A number of patients already have evidence of overt athero-

sclerosis by the time they are diagnosed with type 2 diabetes. Therefore, it is vital that when clinicians place such patients on a course of multifactor risk-reduction strategy, the best clinical data available are utilized for each pharmacotherapy in order to optimize medical management. This study suggests that there are statistically important differences in the effectiveness of ARBs when used for the prevention of diabetes-related macrovascular diseases. In other words, not all ARBs are the same. Therefore, it is imperative that we do not assume a class effect for these agents when prescribing for this purpose. While this is a retrospective study, this research confirms some of the smaller studies conducted to date as well as reinforces the concept that drugs, such as telmisartan, exhibit several pleoiotropic properties that distinguish it from other members of this drug class. There is also some pharmacological basis to believe this as well, since telmisartan exhibits a partial peroxisome proliferator activator receptor gamma-agonist effect that may favorably impact lipid metabolism and insulin sensitivity. Similarly, valsartan has also been shown to have a cardioprotective effect by inhibiting platelet aggregation, a benefit that may be more pronounced in diabetics.[3] My takeaway from this study is that if I had to prescribe an ARB to a diabetic with the intent to reduce the macrovascular complications, I would prefer telmisartan and valsartan over all others. ■

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Long-Term Results of Dabigatran vs Warfarin for Stroke Prevention in AF Patients

ABSTRACT & COMMENTARY

By Edward P. Gerstenfeld, MD

Professor of Medicine, Chief, Cardiac Electrophysiology, University of California, San Francisco

Dr. Gerstenfeld does research for Biosense Webster, Medtronic, and Rhythmia Medical. This article originally appeared in the September 2013 issue of Clinical Cardiology Alert.

Synopsis: *The authors concluded that long-term follow-up of dabigatran 150 mg vs 110 mg twice daily therapy showed similar rates of stroke and death, but a higher incidence of major bleeding on the 150 mg dose.*

Source: Connolly SJ, et al. The long-term multicenter observational study of dabigatran treatment in patients with atrial fibrillation (RELY-ABLE) study. *Circulation* 2013;128:237-243.

Dabigatran etexilate, a direct thrombin inhibitor, is one of a new class of oral anticoagulants that was recently demonstrated in a Phase 3 trial to be effective for the prevention of stroke or systemic embolism (SSE) in patients with atrial fibrillation (AF). The original Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial randomized 18,113 patients with AF and at least one stroke risk factor to either warfarin or one of two blinded doses of dabigatran, 150 mg twice daily or 110 mg twice daily.[1] The 150 mg dose was superior to warfarin for preventing SSE with a similar rate of major bleeding, while the 110 mg was noninferior to warfarin for preventing SSE, but had a reduced risk of major bleeding after a mean follow-up of 2 years. The RELY-ABLE study continued to follow patients in the RE-LY study who were randomized to receive either dose of dabigatran for an additional 2.25 years.

Patients were eligible for RELY-ABLE if they were randomized to dabigatran and had not discontinued the medication at the last study visit. They continued on the original randomized, blinded dose of dabigatran. The outcomes of RELY-ABLE were identical to those of RE-LY.

There were 5851 patients (48% of those randomized to dabigatran in RE-LY) enrolled and followed for a mean of 2.3 additional years after the conclusion of RE-LY. The rates of SSE in RELY-ABLE were 1.46% and 1.60% per year for the dabigatran 150 mg and 110 mg doses, respectively (hazard ratio [HR], 0.91; 95% confidence interval [CI], 0.69-1.20). There were no differences in the rates of ischemic or hemorrhagic stroke between the two groups. Annual rates of major bleeding were significantly higher with the 150 mg dose compared to the 110 mg dabigatran dose (3.74% vs 2.99% per year; HR, 1.26; 95% CI, 1.04-1.53). There was no difference in mortality between the two groups. The authors concluded that long-term follow-up of dabigatran 150 mg vs 110 mg twice daily therapy showed similar rates of stroke and death, but a higher incidence of major bleeding on the 150 mg dose.

■ COMMENTARY

Dabigatran is one of a new class of anticoagulants that is rapidly replacing the old standard, warfarin, for prevention of thromboembolism in patients with AF and stroke risk factors. The major advantages of the newer anticoagulants over warfarin are: 1) fixed dosing without need for

frequent blood tests, 2) lack of dietary interactions, and 3) lower rate of intracerebral hemorrhage. The negatives include cost, nuisance side effects such as dyspepsia, and lack of reversibility. Based on the results of the RE-LY trial, the Food and Drug Administration (FDA) approved the 150 mg twice-daily dose for the prevention of SSE in AF patients, but not the 110 mg dose. This was in part because the 150 mg dose met criteria for superiority to warfarin while the 110 mg dose met only the criteria for noninferiority, despite a reduction in major bleeding with the 110 mg compared to warfarin. Interestingly, the FDA also approved a twice-daily 75 mg dabigatran dose in patients with renal insufficiency based on pharmacokinetic studies, even though that dose was not included in the RE-LY randomized trial.

For those physicians who have yet to adopt the use of the newer anticoagulants over warfarin, the RELY-ABLE data should provide additional evidence supporting the long-term use of dabigatran for prevention of SSE in AF patients. The rates of stroke and major bleeding in RELY-ABLE remained similar to those reported in the original RE-LY trial, with a very low rate of intracerebral bleeding (0.13-014%/year) after a mean of 4.3 years of follow-up. The major question remaining is why the FDA did not approve the twice-daily 110 mg dabigatran dose. The dose was clearly shown to be equivalent to warfarin in preventing SSE with a lower risk of bleeding in a prospective randomized multicenter study — the "gold-standard" of evaluating new drug therapies. The RELY-ABLE data provide further support that the 110 mg dose provides stroke reduction in AF patients with a lower bleeding risk than the 150 mg dose. The lack of availability of the 110 mg dose in the United States has handicapped physicians and patients concerned about bleeding risk, particularly in elderly patients. Hopefully the RELY-ABLE data will persuade the FDA to reconsider this decision.

In summary, dabigatran 150 mg twice-daily has been shown to be superior to warfarin for the prevention of SSE in AF patients and should be considered preferred over warfarin in newly diagnosed AF patients with a CHADS2-Vasc score ≥ 1 who were eligible for the RE-LY study. For elderly AF patients or those with a higher bleeding risk, there are now several agents available for physicians and patients to consider. Clinicians should also be aware that there remains a paucity of data regarding the safety of the newer anticoagulants in patients already on aspirin/clopidogrel therapy after stent implantation. ■

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Pharmacology Update

Vortioxetine Tablets (Brintellix™)

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.

A NEW ANTIDEPRESSANT THAT ACTS ON THE SEROTONERGIC system in the central nervous system has been approved by the FDA. Vortioxetine is believed to act as a serotonin reuptake inhibitor as well as an agonist, partial agonist, and antagonist on various serotonin receptor subtypes. It is marketed by Lundbeck and Takeda Pharmaceuticals as Brintellix.

Indications

Vortioxetine is indicated for the treatment of major depressive disorder (MDD).[1]

Dosage

The recommended dose is 10 mg taken orally once daily without regard to meals.[1] The dose may be increased to 20 mg daily. For patients who are taking CYP2D6 inhibitors, the maximum dose is 10 mg daily. No dose adjustment is required for mild renal impairment or mild-to-moderate hepatic impairment. Dose increase may be needed if vortioxetine is coadministered with a stong CYP2D6 inducer (e.g., rifampin, carbamazepine, phenytoin). Vortioxetine is available as 5 mg, 10 mg, 15 mg, and 20 mg tablets.

Potential Advantages

Driving performance, psychomotor, or cognitive effects were not impaired following single and multiple doses of 10 mg in healthy subjects.[1] Vortioxetine was less likely than mirtazapine to impair driving, cognition, or psychomotor performance after single or multiple doses.[3]

Potential Disadvantages

The most common adverse effect is nausea,[1] with an incidence of 21-26% for the 5-10 mg dose and 32% for the 15 mg and 20 mg dose compared to 9% for placebo. Nausea severity is mild-to-moderate with a median duration of 2 weeks and is more common in females. Sexual dysfunction assessed with the Arizona Sexual Experience Scale showed an incidence of 22-33% in females and 16-

29% in males compared to 20% and 14%, respectively.[1] Vortioxetine shares the same box warning for suicidal thoughts and behavior as other antidepressants. Other adverse effects common with other serotonergic antidepressants include serotonin syndrome, abnormal bleeding, and hyponatremia.

Comments

Vortioxetine's pharmacological profile differs from currently marketed selective serotonin reuptake inhibitors. In addition to inhibition of 5-HT transporters (SERT), the drug modulates 5-HT1A, 5-HT1B, 5-HT3, and 5-HT7 receptors by combinations of agonism, partial agonism, and antagonism.[3] Its efficacy and safety was shown in six randomized, double-blind, placebo-controlled, fixed-dose studies of 6-8 months' duration.[1] Five studies included subjects aged 18-75 years who met DSM-IV-TR criteria for MDD who were randomized to 5 mg, 10 mg, 15 mg, 20 mg, or placebo. The primary efficacy endpoint was change from baseline of scores on the Hamilton Depression Scale or the Montgomery-Asberg Depression Rating Scale (MADRS). The numbers of subjects ranged from 100-155 per treatment arm. The 5 mg dose was statistically better than placebo in one out of two studies, while the 10 mg dose was better in two out of three studies, 15 mg in one out of two studies, and the 20 mg dose in three of three studies. Placebo-subtracted change across studies ranged from -4.1 to 5.9 for 5 mg, -2.2 to 5.7 for 10 mg, -1.5 to 5.5 for 15 mg, and -2.8 to -7.1 for 20 mg, suggesting a wide variation in dose response and placebo. In one study involving older subjects (aged 64-80 years), the 5 mg dose was statistically better than placebo. Benefit was observed at week 2, and full benefit at week 4 or later.[1] Subjects (n = 396) who achieved remission were randomized to their final dose (75% were on 10 mg) or placebo and followed for 24-64 weeks. At week 28, the recurrence rate was about 13% for vortioxetine compared to 28% for placebo. In a long-term, 52-week, open-label study (n = 328), the response rate as assessed by MADRS continued to improve from 63% to 94% at week 52.[4] There were no clinically important changes in laboratory tests (except sodium) in terms of serum chemistry, hematology, and urinalysis associated with vortioxetine.[1] Vortioxetine was not associated with significant effects on weight or vital signs (blood pressure, heart rate). Five to 8% of subjects in the clinical studies discontinued use due to adverse events.

Clinical Implications

Vortioxetine is the newest antidepressant to be approved. It augments inhibition or SERT with modulation of other serotonin receptor subtypes. Whether this translates to clear clinical advantages remains to be determined. Cost was not available at the time of this review. ■

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Brief Report

FDA: Fluoroquinolones Pose Risk of Permanent Nerve Damage

THE FDA IS REQUIRING DRUG LABELS AND MEDICATION Guides for all fluoroquinolone antibacterial drugs to be updated to better describe the serious side effect of peripheral neuropathy.

"This serious nerve damage potentially caused by fluoroquinolones may occur soon after these drugs are taken and may be permanent," the FDA stated in a Safety Alert issued August 15, 2013.

The risk of peripheral neuropathy occurs only with fluoroquinolones that are taken by mouth or injection. According to the FDA, approved fluoroquinolone drugs include levofloxacin (Levaquin), ciprofloxacin (Cipro), moxifloxacin (Avelox), norfloxacin (Noroxin), ofloxacin (Floxin), and gemifloxacin (Factive). The topical formulations of fluoroquinolones, applied to the ears or eyes, are not known to be associated with this risk.

"Make sure your patients know to contact you if they develop symptoms of peripheral neuropathy," the FDA stated. "Make sure your patients receive the Medication Guide with every prescription. If a patient develops symptoms of peripheral neuropathy, the fluoroquinolone should be stopped, and the patient should be switched to another, non-fluoroquinolone antibacterial drug, unless the benefit of continued treatment with a fluoroquinolone outweighs the risk."

Health care professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program. For more information, go to: http://www.fda.gov/Drugs/DrugSafety/ucm365050.htm. ■

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PS Form **3526,** October 1999 *(Reverse)*

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.

CME Instructions

To earn credit for this activity, follow these instructions:

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3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
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CME Questions

1. About what percent of all ambulatory visits result in a prescription for antibiotics?
   a. 5%
   b. 10%
   c. 15%
   d. 20%

2. The most common reason for prescribing an antibiotic in the outpatient setting is for:
   a. respiratory conditions.
   b. genitourinary conditions.
   c. gastrointestinal conditions.
   d. surgical or post-surgical conditions.

3. In the study by Antoniou et al, among angiotensin II receptor blocker(s), which is associated with lower risk of admission to hospital for acute myocardial infarction, stroke, or heart failure in older diabetics?
   a. Candesartan
   b. Irbesartan
   c. Losartan
   d. Telmisartan

Clinical Briefs

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Post-Stroke Blood Pressure Targets: Recent Lacunar Stroke

Source: The SPS3 Study Group. *Lancet* 2013;382:507-515.

Cerebral infarction related to small vessel disease, known as lacunar stroke, is strongly associated with hypertension (HTN). Numerous clinical trials have confirmed that control of HTN provides substantial stroke reduction overall (≥ 40%), without specifically distinguishing the effects on lacunar stroke.

The Secondary Prevention of Small Subcortical Strokes trial compared two levels of systolic blood pressure (SBP) among patients with a recent MRI-confirmed lacunar stroke for impact on recurrent stroke. Because of concern that excessive SBP lowering in the face of acute cerebral ischemia might be detrimental, subjects were randomized at least 2 weeks after the identifying event. Subjects (n = 3020) were randomized to one of two groups: SBP goal 130-149 mmHg or SBP goal < 130 mmHg. Clinicians were allowed to use whatever medications they preferred to attain SBP goals.

At 3.7 years, there was no statistically significant difference in the primary outcome of the study: all stroke. On the other hand, a secondary endpoint (which must be considered "hypothesis generating" since the primary endpoint failed) of hemorrhagic stroke was reduced by almost two-thirds in the SBP < 130 group. This finding prompted the consideration by the authors that since there was no difference in overall outcomes, but the suggestion of substantial reduction in hemorrhagic stroke by more strict blood pressure control, some clinicians might consider the more stringent SBP at least potentially beneficial. ■

Wedge Insoles for Knee Osteoarthritis: Probably Not

Source: Parkes MJ, et al. *JAMA* 2013;310: 722-730.

In the United States, osteoarthritis is the No. 1 cause of disability. The "graying" of America, in concert with an ever-growing prevalence of obesity, portends an equally expanding population of osteoarthritis.

Osteoarthritis of the knee (OA-K) can be particularly disabling, and currently available medical treatments, such as NSAIDs, topical analgesics, and opioids, each have limitations. Hence, short of surgical intervention, alternatives — such as non-pharmacologic treatment — are sought.

Medial OA-K is one of the most common subtypes. In theory, load reduction on the medial compartment might alleviate symptoms, disease progression, or both. By placing an angulated wedge under the sole of the foot, such load reduction can be achieved. A meta-analysis was performed (n = 885) by Parkes et al to evaluate the efficacy of mechanical interventions intended to unload the medial knee compartment including wedges or structured shoes.

Overall, studies did confirm a positive effect of devices to unload the medial compartment, although the effect size was not large. Additionally, trials with an active control (such as a neutral vs an offloading wedge) failed to confirm positive effects. These mixed results call into question whether clinicians can be confident in the efficacy of wedge insoles. ■

Can We Identify Persons on Zolpidem at Risk for Driving Mishap?

Source: Farkas RH, et al. *N Engl J Med* 2013;369:689-691.

Benzodiazepines can impair consciousness. It has been recognized that the elderly — and anyone with renal impairment because they metabolize zolpidem (ZOL) more slowly — should receive a lower dose (ZOL 5 mg) than other adults (ZOL 10 mg). Soon after the advent of immediate-release ZOL, a controlled-release formulation became available. Prospective studies of ZOL indicated that plasma levels > 50 ng/mL were associated with impairment in driving skills. As formulations of ZOL evolved, pharmacokinetic studies found that the 10 mg approved dose of immediate-release ZOL was associated with ZOL levels > 50 ng/dL in as many as 15% of women (who metabolize ZOL more slowly).

Recognition of the potential for ZOL to produce impairment in driving has resulted in FDA recommendations for dose reductions in various ZOL formulations, especially in women.

Insomnia and other sleep disorders are, of course, associated with an increased risk of auto accidents due to excessive daytime sleepiness. Clinicians should maintain vigilance that appropriate dose limitations are observed — since patients often do not perceive the impairment induced by benzodiazepines — and that patients do not drive sooner than the recommended interval after taking their dose of medication. ■

In Future Issues:

Anxiety, Anger, and Mortality Risk Among Survivors of Myocardial Infarction