Clinical Briefs in
Primary Care

By Louis Kuritzky, MD

Evidence-based updates in primary care medicine

Online Supplement to *Clinical Cardiology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Integrative Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports*

Volume 21, Number 3 March 2016

Sexual Health Supplement Leads to Priapism

SOURCE: Campanelli M, et al. *Int J Impot Res* 2015;28:39-40.

Were you to plug in "*Tribulus terrestris* supplement" into Google, numerous opportunities to purchase OTC supplements, within a wide range of affordability, would appear. It appears tribulus has some effects similar to PDE5 inhibitors (e.g., sildenafil) that would potentially enhance sexual function in males: enhancement of nitric oxide production in the endothelium of the corpora cavernosa, and cavernosal smooth muscle relaxation. Apparently, tribulus — also known as puncture vine or Gokhru — grows well in numerous countries around the world (especially China, India, the southern United States, and Spain), and has long been utilized by herbalists as a primary or contributing ingredient in herbal supplements. Since OTC supplements lack FDA oversight and regulation, it should not be surprising that unanticipated adversities occur. Such misadventure may be attributed to mislabeled amounts of constituents, adulterants, idiosyncratic reactions, or may represent spontaneous events unrelated to ingestion of the supplements. Campanelli et al reported a case of a young man with persistent priapism (duration = 72 hours) subsequent to 2 weeks of daily *Tribulus terrestris* supplementation. Invasive treatment (aspiration of corpus cavernosa and creation of a cavernoglandular shunt) was required for resolution, with restoration to nearly complete pre-morbid sexual function at 8 months follow-up. This is not the first reported case of *Tribulus terrestris* associated with priapism. In addition to personal preferences, which often motivate patients to seek non-traditional treatments, the current high cost of FDA-approved pharmacologic treatments may motivate some individuals to seek much less expensive OTC remedies. If clinicians become aware of patient tribulus use, they should caution users about the potential for priapism and encourage patients to seek prompt consultation if a prolonged erection occurs. ■

Eluxadoline for IBS-D

SOURCE: Lembo AJ, et al. *N Engl J Med* 2016;374:242-253.

The burden of suffering sustained by persons with diarrhea-predominant irritable bowel syndrome (IBS-D) is substantial, and clinicians often underestimate the condition. While OTC remedies (e.g., loperamide, fiber) may provide some relief for IBS-D, residual symptoms continue to plague most patients. Eluxadoline is a recently FDA-approved pharmacologic treatment for IBS-D. Mu-receptors are prominently active in the GI system, as evidenced by the commonplace development and persistence of constipation in patients using opioid analgesics. The primary mechanism of eluxadoline is peripheral (i.e., not in the CNS) mu-receptor mediated reduction in colonic visceral hypersensitivity. At the same time, an additional mechanism of eluxadoline — delta-receptor antagonism — appears to reduce the degree of constipation typically induced by pure mu-receptor agonists. Lembo et al reported results from placebo-controlled trials of eluxadoline in IBS-D (n = 2427). The primary outcome was the number of patients who experienced decreased abdominal pain as well as improved stool consistency for at least half the days throughout the studies (one study lasted 12 weeks, the other lasted 26 weeks). Eluxadoline demonstrated a modest but statistically significant greater ability to reach the primary endpoint and was generally well tolerated. Cases of pancreatitis occurred during eluxadoline treatment, but not during placebo treatment. Because these cases occurred in post-cholecystectomy patients or in persons who used excessive alcohol, until more information is available, clinicians would be wise to avoid eluxadoline in these populations. ■

A New Category of Orthostatic Hypotension

SOURCE: Gorelik O, Cohen N. *J Am Soc Hypertens* 2015;9:985-992.

Traditionally, orthostatic hypotension (OH) is defined as a drop in systolic blood pressure > 20 mmHg or diastolic blood pressure > 10 mmHg (or both) within 3 minutes of standing from a supine position. The consequences of OH include adverse symptoms, such as dizziness or "coat-hanger" headache, as well as serious or even fatal events consequent to falls. Studies on OH measured when patients transfer from supine to the seated position are infrequent; Gorelik and Cohen reviewed data from 17 different studies to elucidate the literature on seated postural hypotension (SOH). Similar to OH, the prevalence of SOH increases with age and is more frequent among patients ingesting antihypertensive medications. Probably because of the lack of a firmly established definition of SOH, measurement methods varied among studies, such that changes in blood pressure were measured within as

little as 1 minute to as long as 5 minutes or even longer after changing from the supine to seated posture; most data employed the standard blood pressure change (> 20/10 mmHg) to define SOH. Symptoms evoked among patients with SOH were essentially the same as those observed in patients with "typical" OH. Some experts have advised routinely measuring orthostatic blood pressure in patients with underlying neurologic disorders, such as Parkinson's disease, in which OH prevalence is distinctly higher. Measurement of postural changes in blood pressure from supine to seated may be helpful to sort out symptoms such as dizziness or falls, especially in older patients. ■

Ambulatory BP for All

SOURCE: Verdeechia P, et al. *J Am Soc Hypertens* 2015;9:911-915.

In 2011, the British were the first to include a recommendation that all patients identified with elevated blood pressure in the office undergo 24-hour ambulatory blood pressure monitoring (ABPM) before finalizing the diagnosis. They estimated that routinely employing ABPM would save tens of millions of dollars. In 2015, the United States Preventive Services Task Force evaluated the very same issue, and came to the same conclusion: ABPM should be routinely included as a diagnostic tool before confirming the diagnosis of hypertension. Why should we listen to this new advice? It has been shown that a substantial minority of patients who demonstrate elevated office blood pressure (OBP), when monitored by ABPM, are determined not to have hypertension at all; rather, they have what is usually called white-coat hypertension, a transient phenomenon seen among patients whose anxiety during medical encounters raises their blood pressure into the hypertensive range. As many as one-third of patients originally diagnosed with hypertension through OBP are ultimately determined to have white-coat hypertension. Fortunately, the epidemiologic data looking at outcomes among patients with white-coat hypertension suggests that cardiovascular outcomes are essentially no different than normotensive patients. Patients with white-coat hypertension, whether treated or not, typically show declines in blood pressure over time. When unnecessarily treated, they sustain the costs, adverse effects, and consequences of misdiagnosis (i.e., epidemiologic data have shown that simply being diagnosed as hypertensive is associated with lower quality-of-life scores). ABPM is readily available, has little or no adverse effects, and is not costly (typically around $100-$150). Considering that it could save a patient years of unnecessary treatment, we should follow the advice the British adopted long ago: ABPM for all initially diagnosed hypertensives to confirm the diagnosis. ■

CLINICAL BRIEFS IN PRIMARY CARE™
is published monthly by AHC Media, LLC.

Executive Editor: Leslie Coplin
Editor: Stephen Brunton, MD
Associate Managing Editor: Jonathan Springston

STATEMENT OF FINANCIAL DISCLOSURE
To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, Dr. Brunton is a retained consultant for Abbott, Actavis, AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Cempra, Exact Sciences, Janssen, Lilly, Mylan, Novo Nordisk, and Teva; he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Louis Kuritzky, MD (author), is a retained consultant for AbbVie, Allergan, AstraZeneca, Janssen, Lilly, Lundbeck, Medscape, Novo Nordisk, and Sanofi Aventis; he serves on the speakers bureau of Lilly and Lundbeck. Ms. Coplin and Mr. Springston report no financial relationships relevant to this field of study.

SUBSCRIBER INFORMATION
Customer Service: (800) 688-2421
Email Address: jonathan.springston@ahcmedia.com
Website: AHCMedia.com

Address Correspondence to: AHC Media, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

AHC Media

What's the Deal with Grapefruit Juice?

SOURCE: Lee JW, et al. *Am J Med* 2016;129:26-29.

FDA labeling for simvastatin changed several years ago because of the recognition that high doses of simvastatin were associated with a meaningful increase in risk for rhabdomyolysis. Drugs known to interact with the CYP450 hepatic enzyme system — specifically, CYP3A4 — were singled out since CYP3A4 is the primary metabolic pathway for many of the statins. Many patients with dyslipidemia also suffer hypertension, and drugs like amlodipine, which can also influence CYP3A4 metabolism, were promptly added to the list of agents that could potentially interact with simvastatin. About 3 years ago, new FDA labeling for simvastatin spoke to the issue of grapefruit juice, suggesting patients should avoid large quantities. Why grapefruit juice? Grapefruit juice has been known for more than a decade to be a prompt, potent, and persistent inhibitor of the CYP3A4 enzyme, and it doesn't take a lot: As little as 8 oz. of grapefruit juice (or one whole grapefruit) taken with simvastatin 40 mg elevates the simvastatin area under the curve by almost 400%. In evaluating the effect of grapefruit juice on risk, Lee et al extrapolated from data that link changes in low-density lipoprotein to cardiovascular outcomes. They also suggested that the combination of grapefruit juice with simvastatin would indeed increase simvastatin blood levels, but at the same time would possibly reduce cardiovascular event levels to a degree that would far counterbalance any increased risk of rhabdomyolysis. While their notion is intriguing, in the absence of prospective data corroborating that the simvastatin + grapefruit juice combination is safe and actually reduces cardiovascular events, clinicians would be wise to continue observing labeling restrictions. ■

Smoking and Low Back Pain

SOURCE: Shiri R, Falah-Hassani K. *Am J Med* 2016;129:64-73.

Low back pain and its consequences are responsible for the largest single expenditure of disability dollars in the United States. Whereas both the clinician and lay population have a high level of awareness of the consequences of smoking, such as heart disease, lung disease, and various cancers, the relationship between smoking and sciatica is not widely recognized. Of course, when an individual patient encounters a potential or real consequence of smoking (e.g., abnormal chest CT, pneumonia, etc.), he or she sometimes becomes — at least transiently — more motivated to quit. There are even data showing that among otherwise healthy young men who fracture their tibia, healing occurs weeks earlier in non-smokers, providing clinicians a teachable moment when they encounter such a patient. Might we add low back pain to that list? Shiri and Falah-Hassani reviewed data from 28 studies (n = 20,111) in which sciatica risk was compared between smokers and non-smokers. Overall, current smokers were more than 60% more likely to experience any radicular back pain, and 35% more likely to incur sciatica. Similarly, the odds ratio for back pain-related hospitalization or surgery was elevated to 1.45; encouragingly, former smokers demonstrated only slight risk elevation. This is the latest in a long list of reasons to encourage smoking cessation. ■