Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

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

Volume 19, Number 7 Pages 13-14 July 2014

Daily Use of PDE5 Inhibitors

Source: Shim Y, et al. *Int J Impot Res* 2014;26:76-80.

In the United States, most men who use PDE5 inhibitors (i.e., avanafil, sildenafil, tadalafil, vardenafil) for restoration of sexual function use them on a PRN basis. One of the reasons for PRN use is that the short half-life of all currently FDA-approved PDE5 inhibitors, except tadalafil, is too short to provide sustained 24-hour enhancement of cyclic GMP, the chemical messenger responsible for corpora cavernosa vascular dilation. Because of its 18-hour half-life, tadalafil is well suited to low-dose daily administration, but the time to onset of efficacy may be somewhat slower than the other PDE5 inhibitors.

In Korea, another PDE5 inhibitor — udenafil — is approved for the treatment of erectile dysfunction (ED). Similar to tadalafil, udenafil has a long half-life (11-13 hours), making it suitable for once-daily administration. In contrast to tadalafil, it has a more rapid onset of action (time to maximum plasma concentration = 0.8-1.3 hours) than tadalafil (2 hours). Shim et al performed a 2-month, placebo-controlled trial of once-daily udenafil among men (n = 49) with ED. The outcomes included not only erectile function but also assessments of depression (PHQ-9), somatization (PHQ-15), and cognitive function (Korean MMSE and Seoul Neuropsychological Screening Battery).

As has been shown with other PDE5 inhibitors, there was a substantial improvement in erectile function. In addition, treatment with udenafil improved measurements of cognition, depression, and somatization compared to placebo. Improved erectile function has previously been shown to improve depression and quality of life, but Shim et al suggest that there may also be direct central nervous system, vascular, and nitrergic pathways that could lead to the outcomes improvement they detected. ■

Refining the List of Things *Not* to Do for Long-Term Care Residents

Source: *Ann Long-Term Care: Clin Care Aging* 2014;22:18-19.

The American Geriatrics Society has identified some commonly used treatments that may either lack benefit or even be harmful to long-term care residents. The five specific items are: 1) If you are going to treat dementia with cholinesterase inhibitors, perform periodic cognitive assessments. 2) When you consider screening tests (e.g., mammography, colonoscopy, PSA), consider the likely life expectancy of your patient, as well as the potential consequences of overdiagnosis. 3) Instead of relying on appetite stimulants to enhance waning appetite, consider behavioral and social factors affecting appetite, such as support for eating at mealtime. 4) Don't prescribe a new medication without confirming other currently prescribed medications to avoid duplication and adverse interactions. 5) When possible, do not use physical restraints in the face of delirium since they have been associated with injury and even death; instead treat the underlying cause(s), promote a physiologic sleep-wake cycle, and consider options to manipulate the environment to enhance orientation.

Remembering to include these five issues in managing long-term care residents will hopefully improve outcomes and reduce medical misadventure. ■

Do Clinicians Really Need to Know What microRNAs Are?

Source: Leroith D. *Diabetes Care* 2014; 37:1176-1177.

Primary care clinicians are sometimes *mistakenly* described as not caring about the pathophysiology, but rather, more pragmatically interested in "just tell me what to do." Instead, in my experience, primary care clinicians are very interested in the pertinent pathophysiology: i.e., having insight into the story line that gives clarity about why a particular medication is chosen, why some medications are complementary, and others not, etc.

Recently, microRNAs (miRNA) have been recognized to play an important role in diabetes, cardiovascular disease, and even cancer. Although miRNA literature at this point may seem "alien" to most clinicians, there have been more than 25,000 publications on the topic since their discovery in 2000. miRNA is measurable in plasma, saliva, and urine. Particular subgroups of miRNA have been identified in persons with diabetic retinopathy.

The basic function of miRNA is to regulate the activity of specific target messenger RNA, thereby altering production of individual proteins. A primary action of miRNA appears to be to suppress protein production, such that activation of miRNA results in reduction of specific

proteins. A recent study found an association between specific miRNA and glucose perturbations, such that essentially half of abnormal glucose excursions could be explained by abnormalities in miRNA.

At the current time, miRNA is primarily a research tool, but investigators are hopeful that identification of specific miRNA associated with disorders as diverse as obesity, diabetes, and cancer may lead to early identification of pathology, and hopefully even the opportunity for improved disease modification. ■

Hepatitis C: Shorter, Successful Treatment

Source: Kowdley KV, et al. *N Engl J Med* 2014;370:20:1879-1888.

The current and future epidemiologic burden of hepatitis C virus (HCV) is increasingly recognized as a major public health issue. Even though the greatest wave of liver disease attributable to HCV could be ahead of us, even now HCV is the most common cause of chronic liver disease, liver transplantation, and hepatic carcinoma in the United States. Because of insufficient identification of at-risk persons based on risk-factor profiles alone, the CDC has recommended that clinicians screen all persons born from 1945-1965 for HCV.

Supporting such initiatives is the recent evolution of treatment regimens characterized by higher success rates, greater efficacy in resistant subgroups, better tolerability, and more consistent across-genotype applicability than prior regimens.

Genotype 1 among HCV patients has been noted to be relatively refractory to older treatment regimens. Recently, a highly effective regimen combining ledipasvir (LED) and sofosbuvir (SOF) for 12 weeks demonstrated cure (i.e., sustained viral response, defined as absence of detectable HCV for at least 6 months post-treatment) in more than 95% of this highly resistant group.

To evaluate the potential efficacy of an even shorter course, Kowdley compared LED + SOF (8 weeks) vs LED + SOF (12 weeks) vs LED + SOF + ribavirin (12 weeks). They determined that not only was the LED + SOF 8-week course non-inferior to 12 weeks of the same, but that ribavirin imparted no meaningful additional efficacy and was associated with more adverse effects. Patients with HCV can look forward to a variety of highly effective, well tolerated, short-course treatments. ■

Can Potassium Prevent Sodium Adversities?

Source: Rodrigues SL, et al. *J Am Soc Hypertens* 2014;8:232-238.

On an epidemiologic basis, it is clear that for most populations there is a linear risk between levels of salt intake and cardiovascular (CV) endpoints, directly related — it appears — through the impact on blood pressure (BP). While it is intuitive as well as enticing to assume that the linear relationship between salt-BP-CV disease should be a two-way street, convincing proof of that has been remarkably elusive; that is, we do not have evidence from a large, randomized clinical trial proving that dietary sodium reduction improves CV outcomes. Nonetheless, since there is no suggestion that elevated ingestion of sodium is a health benefit, most experts advocate that a population-wide reduction in sodium, most of which excess comes from processed foods with lesser nutritional value than fresh food, would be a good thing.

There are, however, flies in the ointment. For instance, some individuals appear to ingest large amounts of sodium without incurring BP increases. Why that might be was explored by Rodrigues et al in a population of Brazilians (n = 1285). Investigators compared the amount of salt intake per day and evaluated potassium intake with the hunch that higher potassium levels in the diet might protect against sodium-induced elevations in BP. Their supposition was quite sensible based on two earlier population studies which found that BP was inversely associated with dietary potassium intake.

Among persons consuming high levels of sodium (> 6 gm/d), those in the top quartile sodium/potassium ratio had mean SBP 8 mmHg higher than the lowest quartile. Similarly, the highest quartile of dietary potassium intake had SBP that was 6 mmHg lower than the lowest quartile.

Having a strong component of potassium in the diet appears to mitigate sodium-associated elevations in BP. ■

SGLT2 Inhibitors and Blood Pressure

Source: Baker WL, et al. *J Am Soc Hypertens* 2014;8:262-275.

It has not gone unnoticed that there are multiple competing pathologies in diabetes that weigh as heavily or even more heavily on the scale of risk factors than glucose. Glucose control has not been shown to improve macrovascular outcomes (MI, stroke). On the other hand, BP control and lipid control have been shown to have more broad favorable impact, extending beyond microvascular endpoints to include macrovascular benefit. SGLT2 inhibitors (e.g., canagliflozin, dapagliflozin), in addition to lowering glucose by enhancing urinary glucose excretion, are also associated with BP reduction, a combination that has great appeal since diabetics suffer a disproportionate burden of hypertensive cardiovascular disease.

Baker et al performed a meta-analysis of the BP effects of SGLT2 inhibitors. Their data analysis included not only agents FDA-approved for use in the United States, but also agents with data reported in Phase 2 and 3 clinical trials not yet approved in the United States (e.g., empagliflozin, ipragliflozin, remogliflozin).

From clinical trial data, SGLT2 inhibitors reduce SBP by a mean of 4 mmHg. While this may seem a modest amount, it should be recognized that the population studied was not exclusively hypertensive. Rather, the baseline SBP mean among the 27 trials they assessed (n = 12,960) ranged from 123-140 mmHg. In addition to their favorable effects upon glucose, SGLT2 inhibitors favorably affect BP. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media, LLC.
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