ABSTRACTS IN URGENT CARE

- Oral Antibiotics and Kidney Stones
- A New Nonopioid Treatment for Opioid Withdrawal
- DRE and Screening for Prostate Cancer
- Assessing Treatments for Symptoms of Vulvovaginal Atrophy
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- Good News for Coffee Drinkers

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Each month the College of Urgent Care Medicine (CUCM) provides a handful of abstracts from or related to urgent care practices or practitioners. Glenn Harnett, MD leads this effort.

Some Oral Antibiotics Up Risk for Kidney Stones

Key point: Oral antibiotics are associated with an increased risk for nephrolithiasis in adults and children, with the risk highest in those exposed at a younger age.

Citation: Tasian GE, et al. Oral antibiotic exposure and kidney stone disease. *J Am Soc Nephrol*. 2018; May 10. [Epub ahead of print]

The prevalence of kidney stones has increased 70% during the last 30 years, with the most disproportionate increase in children, adolescents, and young women. This study, published in the *Journal of the American Society of Nephrology*, determined the association between 12 classes of oral antibiotics and nephrolithiasis in a population-based, case-control study from 641 general practices including >13 million children and adults from 1994 to 2015 in the United Kingdom. They used incidence density sampling to match 25,981 patients with nephrolithiasis to 259,797 controls by age, sex, and practice at date of diagnosis of the kidney stone(s). The results revealed that five classes of oral antibiotics were associated with a diagnosis of kidney stone disease: oral sulfas, cephalosporins, fluoroquinolones, nitrofurantoin, and broad-spectrum penicillins. The investigators found patients who received sulfa drugs were more than twice as likely as those not exposed to antibiotics to have kidney stones; exposure to cephalosporins, fluoroquinolones, and nitrofurantoin increased the risk by 60%-80%; for broad-spectrum penicillins, the increased risk was 27% greater. The magnitude of associations was greatest for exposure at younger ages and 3-6 months before diagnosis date, with all but broad-spectrum penicillins remaining statistically significant 3-5 years from exposure. In a press release, the lead author, Dr. Gregory Tasian, a pediatric urologist, stated "These findings demonstrate that exposure to certain antibiotics is a novel risk factor for kidney stones and that the risk may be greatest when exposure to these antibiotics occurs at younger ages. Consequently, these results suggest that the risk of nephrolithiasis may be decreased by reducing inappropriate antibiotic exposure and choosing alternative antibiotics, particularly for those patients who are at increased risk of stone formation." The authors also speculated that antibiotic-induced alteration of the gut microbiome could change macronutrient metabolism, thus leading to kidney stones. They noted that they couldn't exclude direct antibiotic crystallization in the kidney. ■

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A Nonopioid Approach to Treat Opioid Withdrawal

Key point: First new nonopioid drug approved by FDA to treat opioid withdrawal.

Citation: Food and Drug Administration. FDA approves the first non-opioid treatment for management of opioid withdrawal symptoms in adults. May 16, 2018. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm607884.htm.

On May 16, 2018 the FDA approved Lucemyra (lofexidine), an

oral nonopioid, for the mitigation of withdrawal symptoms and to facilitate abrupt discontinuation of opioids in adults. While Lucemyra may lessen the severity of withdrawal symptoms, it may not completely prevent them and is only currently approved for treatment for up to 14 days. Lucemyra is not a treatment for opioid use disorder (OUD), but can be used as part of a broader, long-term treatment plan for managing OUD. Lucemyra is an oral, selective alpha 2-adrenergic receptor agonist that reduces the release of norepinephrine. The actions of norepinephrine in the autonomic nervous system are believed to play a role in many of the symptoms of opioid withdrawal. The manufacturer presented two randomized trials reflecting 866 adults with opioid dependence who were treated with lofexidine. The trials showed that patients receiving lofexidine had fewer opioid withdrawal symptoms than those taking placebo and that those taking lofexidine were more likely to complete their entire treatment. Side effects of the drug include cardiac arrhythmias, bradycardia, hypotension, sedation, and somnolence. Also of note, patients often developed a marked transient spike in their blood pressure upon discontinuation of treatment. The FDA is requiring 15 postmarketing safety studies, including both animal and human studies. Additional animal safety studies will be required to support longer-term use (such as during a gradual opioid taper in pain patients discontinuing opioid analgesics) and use in children. The FDA had previously granted the drug Priority Review and Fast Track designations due to the fact that the physical symptoms of opioid withdrawal can be among the biggest barriers for patients seeking help and ultimately overcoming addiction. They noted that the fear of experiencing withdrawal symptoms often discourages those suffering from opioid addiction from seeking help. ■

Where Are the Data Supporting DRE in Prostate Cancer Screening?

Key point: Although digital rectal examination is commonly performed to screen for prostate cancer, there are limited data to support its use.

Citation: Naji, L et al. Digital rectal examination for prostate cancer screening in primary care: a systematic review and meta-analysis. *Ann Fam Med*. 2018;16(2):149-154.

A meta-analysis published in the *Annals of Family Medicine* concluded that digital rectal examination (DRE) for prostate cancer screening in primary care should be discouraged, given the lack of evidence supporting its use. Previous studies have suggested DREs are associated with a high rate of false-positives and no reduction in prostate cancer mortality, while subjecting patients to unnecessary and invasive follow-up procedures and perhaps overdiagnosis and overtreatment of prostate cancer. Using a MEDLINE and Cochrane Database review, this analysis encompassed seven studies measuring the effectiveness of DRE in screening for prostate cancer in primary care settings. The studies included 9,241 patients who underwent a DRE by primary care clinicians and, based on the results, a subsequent biopsy. The studies showed a high risk for bias, and the overall quality of evidence for performing routine DRE screening was rated as "very low." In the analysis, pooled sensitivity of the DRE for prostate cancer among primary care physicians was 0.51 and pooled specificity was 0.59 with a positive predictive value of only 0.41. The researchers stated that, "On the basis of the lack of evidence supporting its use, we do not recommend routinely using DRE as a screening tool for prostate cancer in primary care, unless it is proven effective in future studies. Additionally, although we did not study possible harms of DRE, its invasiveness and potential to lead to unnecessary biopsy, overdiagnosis, and overtreatment argue against its routine use." ■

"The invasiveness and potential to lead to unnecessary biopsy, overdiagnosis, and overtreatment argue against using DRE as a screening tool for prostate cancer in primary care."

Another Look at Managing Postmenopausal Vulvovaginal Atrophy

Key point: Vaginal estradiol and moisturizing gel no better than placebo for menopausal vulvovaginal symptoms.

Citation: Mitchell, CM, et al. Efficacy of vaginal estradiol or moisturizer vs placebo for postmenopausal vulvovaginitis symptoms: a randomized clinical trial. *JAMA Intern Med*. 2018;178(5):681-690.

This study, published in *JAMA Internal Medicine*, was a randomized, double-blind, placebo-controlled, multisite trial of two existing, widely used treatments for postmenopausal vulvovaginal atrophy symptoms—a low-dose prescription vaginal estradiol tablet (Vagifem) and an OTC nonhormonal vaginal moisturizing gel (Replens). A little more than 300 postmenopausal women with at least one moderate-to-severe vulvovaginal symptom (eg, itching, pain, dryness, irritation, or pain with penetration) were randomized to use low-dose vaginal estradiol tablets plus a placebo gel, placebo tablets plus a nonhormonal vaginal moisturizer (containing the mucoadhesive polycarbophil), or double placebo for 12 weeks. At the end of treatment, symptoms had improved somewhat in all groups, but vaginal 10-µg estradiol tablet plus placebo gel and vaginal moisturizer plus placebo tablet were not more efficacious than

dual placebo at reducing symptom severity or improving sexual function. In an accompanying editorial, commenters wrote that, "Women and their physicians may want to conclude that postmenopausal women experiencing vulvovaginal symptoms should choose the cheapest moisturizer or lubricant available over the counter—at least until new evidence arises to suggest that there is any benefit to doing otherwise." ■

The Burden of Hearing Loss on Patients and the Healthcare System

Key point: Hearing loss is growing in prevalence and has implications beyond qualify of life.

Citation: Cunningham LL, et al. Hearing loss in adults. *N Engl J Med*. 2017;377(25):2465-2473.

This review article published in the *New England Journal of Medicine* addresses the high incidence of hearing loss, its burden on the U.S. healthcare system, the fact that hearing loss screening is still not routine, and that effective treatments are often inaccessible due to high costs or the perception that treatments are ineffective. The authors note that in the United States, the prevalence of hearing loss doubles with every 10-year increase in age and that approximately 50% of persons in their seventh decade (60 to 69 years of age) and 80% of those who are 85 years of age or older have hearing loss that is severe enough to affect daily communication. They express concern that because of the aging population in this and other developed countries, hearing loss is likely to become an increasingly prevalent disability. Untreated hearing loss in adults has been shown to have indirect health, psychosocial, and economic effects and can lead to social isolation and a reduced quality of life. As compared with age-matched adults with unimpaired hearing, older persons with hearing loss have higher rates of hospitalization, death, and falls and frailty, as well as higher rates of dementia and depression, even when known risks for these disorders are taken into account. Also, because of their hearing loss, those affected achieve significantly lower levels of education and have higher levels of unemployment or underemployment. Importantly, annual healthcare costs for middle-age U.S. adults with hearing loss are significantly higher than the costs of care for those without hearing loss. The frequency of use of hearing aids by adults with hearing loss remains very low, as the United States is one of the few developed countries that does not offer government assistance for the purchase of hearing devices. The good news on this front is that legislation has recently been signed into law requiring the FDA to create and regulate a category of over-the-counter hearing aids for adults who have mild-to-moderate hearing loss. Urgent care providers are in a unique position to recognize and identify this problem and should "keep their ears open" for the development and regulatory approval of OTC hearing-aids. ■

"Caffeinated coffee was linked to lower risks for cardiovascular disease, coronary heart disease, and stroke."

Coffee May Have Health Benefits

Key point: A new analysis of one of the country's largest and longest-running studies reveals that drinking coffee is linked to a lower risk of heart failure, stroke, and coronary heart disease.

Citation: Poole R, et al. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ*. 2017;359:j5024.

Researchers found that every extra cup of coffee consumed per day reduced heart failure, stroke, and coronary heart disease by 8%, 7%, and 5%, respectively, up to at least six cups per day. This study, an umbrella review, published in the *British Medical Journal*, analyzed data from the Framingham Heart Study, which has tracked the eating patterns and cardiovascular health of more than 15,000 people since the 1940s. Machine learning, which is used to look for patterns in big data sets, contributed to their ability to parse the huge amount of data. The researchers then confirmed their findings with more traditional analyses of two additional large study groups: The Cardiovascular Heart Study and the Atherosclerosis Risk in Communities Study. They found that coffee consumption, several cups daily in particular, is associated with a wide range of health benefits. Results showed that daily consumption of three cups of coffee (regular or decaffeinated) was associated with a 17% lower risk for all-cause mortality, relative to no coffee consumption. Caffeinated coffee was also linked to lower risks for cardiovascular disease, coronary heart disease, and stroke, with benefits highest at three-to-five cups daily. Among the myriad of other findings, caffeinated coffee was associated with lower risks for cancer and liver conditions, and both regular and decaf coffee appeared to lower risk for type 2 diabetes. In an accompanying editorial, they stated that "The evidence is so robust and consistent...that we can be reassured that drinking coffee is generally safe." They did note that pregnant women should be educated about the possible adverse effects, including pregnancy loss, low birth weight, and preterm birth. High consumption was also associated with higher fracture risk in women, but not men. Because these studies simply observed people's health and coffee consumption over time, the analyses were only able to determine a link between the two, not a cause-and-effect relationship. Previous research has suggested that coffee's caffeine content, along with its antioxidant and anti-inflammatory properties, may be responsible for its presumed health benefits. ■