PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XL / December 2019/ Number 12 www.alertpubs.com

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Metformin: Possible Contamination

Following the recall of several metformin formulations in Singapore and a request by the European Medicines Agency that manufacturers test their products for N-nitro-sodimethylamine (NDMA), the FDA has begun testing metformin samples for the carcinogen. While levels above the acceptable daily intake have not been confirmed in U.S. metformin products, contamination with the potential carcinogen has led to recent recalls of the angiotensin receptor blockers irbesartan, losartan, and valsartan and the H_2 blocker ranitidine. According to an FDA statement, a person taking a drug daily that contains NDMA at or below the acceptable daily intake is not expected to be at increased risk of cancer.

Koenig D: FDA investigating metformin for possible carcinogen. Medscape Medical News: Available at www.medscape.com/viewarticle/922248.

Common Drug Trade Names*: irbesartan—*Avapro*; losartan—*Cozaar*; metformin—*Glucophage*; ranitidine—*Zantac*; valsartan—*Diovan

Pneumonia Vaccine Recommendations

In their updated recommendation, the CDC's Advisory Committee on Immunization Practices (ACIP) now advises use of a single dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23; *Pneumovax 23*) for most patients age ≥65 years. The previous recommendation of serial vaccination with 13-valent pneumococcal polysaccharide vaccine (PCV13; *Prevnar 13*) followed by PPSV23 is superseded because, given the widespread use of PCV13 in children, few older adults are exposed to serotypes uniquely covered by that vaccine. PPSV23 contains 12 serotypes in common with PCV13 and an additional 11 serotypes for which there are no indirect effects from PCV13 use in children. The additional serotypes account for about one-third of invasive pneumococcal disease in older adults.

The ACIP still recommends serial administration of the 2 vaccines in adults, aged ≥19 years, who are immunocompromised or have a cerebrospinal fluid leak or cochlear implant. PCV13 can still be used in adults ≥65 who do not meet those criteria but are at increased risk of exposure to PCV13 serotypes (e.g., nursing home residents) or who have underlying medical conditions that increase risk of developing pneumococcal disease (e.g., chronic heart, lung, or liver disease; diabetes; alcoholism; smoking; >1 chronic medical condition). If PCV13 is used in older adults, it should be given first and ≥1 year before PPSV23. Patients who received the PPSV23 vaccine before age 65 years should receive an additional dose of PPSV23 after turning 65 and at ≥5 years after the first dose.

Matanock A, et al: Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults 65 years: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2019;68 (November 22):1069–1075. From the Centers for Disease Control, Atlanta, GA., and Stanford University, CA. **The authors declared no competing interests.**

Primary Care Drug Alerts® (ISSN 1559-5668) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: donna@alertpubs.com. Subscription $105.00 a year in the U.S.; $113.50 Canada; $123.50 elsewhere; $157 institutional. Individual issues are available for $10.00 each. M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

Bempedoic Acid for Hypercholesterolemia

In a phase 3 trial, bempedoic acid, a first-in-class lipid-lowering agent, was an effective adjunct to maximally tolerated statins in patients at high risk of cardiovascular disease.[1] Bempedoic acid (currently under FDA review by) acts by inhibiting cholesterol synthesis in the liver, via a similar mechanism to statins but without affecting skeletal muscle. Results of a long-term trial targeting clinical atherosclerotic cardiovascular disease outcomes are anticipated in 2022.

Methods: Study subjects were adults at high cardiovascular risk because of atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both. Participants were required to have a fasting LDL-C of >100 mg/dL at the first screening visit and ≥70 mg/dL 1 week before randomization, despite receiving stable, maximally tolerated lipid-lowering therapy. Following a 4-week placebo run-in, patients were randomly assigned in a 2:1 ratio to receive 180 mg/day bempedoic acid or placebo for 52 weeks in addition to their background therapy, which could be adjusted in response to cholesterol elevation after 24 weeks of study treatment. The primary study outcome was change from baseline to week 12 in LDL-C.

Results: A total of 779 patients were randomized and 740 (95%) completed the study. The mean baseline DL-C level was 120.4 mg/dL. At week 12, reductions were significantly larger with bempedoic acid than with placebo (15.1% vs 2.4%; p<0.001) to levels of 97.6 mg/dL with bempedoic acid and 122.8 mg/dL with placebo. Bempedoic acid was also associated with greater reductions in HDL-C than placebo, and effects on triglycerides were similar in the 2 groups. Between-group differences in LDL-C and in other lipid parameters remained at weeks 24 and 52. A post-hoc analysis showed similar effects of bempedoic acid in patients receiving high- and moderate/low-intensity statins, no statins, or no medication.

Adverse effects occurred in about 70% of both the active treatment and placebo groups. Gout and increased blood uric acid levels were reported in 2.1% and 2.7% of the bempedoic acid group, respectively—higher rates than with placebo. Nearly 11% of patients discontinued bempedoic acid, compared with 9% in the placebo group, with no imbalance for any single adverse effect.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Editorial. Given the recent introduction of other nonstatins, the clinical role of bempedoic acid remains unclear.[2] It may be an alternative for patients with statin intolerance, or could be added to existing therapy, even with multiple agents, to achieve ever-lower LDL-C targets in high-risk patients. Patient preferences and cost considerations are likely to determine the sequence of nonstatin therapies

[1]Goldberg A, et al: Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR Wisdom randomized clinical trial. *JAMA* 2019;322 (November 12): 1780–1788. From Washington University School of Medicine, St. Louis, MO.; and other institutions including Esperion Therapeutics Inc., Ann Arbor, MI. **Funded by Esperion. Five of 10 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Honigberg M, Natarajan P: Bempedoic acid for lowering LDL cholesterol [Editorial]. *JAMA* 2019;322 (November 12):1769–1771. From Massachusetts General Hospital, Boston, MA.; and other institutions. **Funded by the National Heart, Lung, and Blood Institute. One author disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

***See Reference Guide.**

Generic Eliquis

The FDA has announced approval of the first generic *Eliquis* (apixaban) tablets. The agent is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; for the prophylaxis of deep vein thrombosis (DVT) in patients who have undergone hip or knee replacement; for the treatment of DVT and pulmonary embolism (PE); and for the reduction in the risk of recurrent DVT and PE following initial therapy. Apixiban should not be prescribed for patients with prosthetic heart valves or for patients with atrial fibrillation that is caused by a heart valve problem. Treatment has been associated with increased risk of thrombotic events and stroke in patients who discontinue apixiban too soon. In addition, epidural and spinal hematomas, which can result in long-term or permanent paralysis, have been reported in patients receiving apixaban who undergo neuraxial anesthesia or spinal puncture. Bleeding, including life-threatening and fatal bleeding, is the most serious risk with apixaban treatment.

FDA News Release: FDA approves first generics of Eliquis. Available at www.fda.gov/news-events/press-announcements/fda-approves-first-generics-eliquis.

HRT and Breast Cancer Risk

According to the results of a meta-analysis of observational studies, increases in the risk of invasive breast cancer related to menopausal hormone replacement therapy vary according to the timing and type of therapy.

Methods: A literature search identified all published and unpublished observational studies of HRT and invasive breast cancer that included individual-level data for >1,000 postmenopausal women. Randomized clinical trials were not included because none were identified that had a large enough sample size. Prospective studies were analyzed using a case–control design with up to 4 matched controls for each woman in whom invasive breast cancer developed. Current users were included for up to 5 years after their last reported HRT use. Risk ratios* (RRs) were calculated for specific types of HRT in relation to the timing of use.

Results: The analysis was based on data from 58 studies comprising 128,000 cases and nearly 367,000 controls: 24 prospective studies contributing 75% of breast cancer cases and 34 retrospective studies contributing the remaining 25%. In the prospective studies, mean age at menopause and mean age at first HRT use were both 50 years and mean duration of use was 10 years for current users and 7 years for past users. Hysterectomy largely determined whether women received estrogen-only therapy. Compared with untreated women, risk of breast cancer was increased in those who received HRT. Increases were greater in women who received estrogen–progestagen (RR, 2.08) than in estrogen-only users (RR, 1.33). Risk was not increased in women who used only vaginal estrogen. For each type of therapy, risk increased steadily with duration of use and was evident even among women with 1–4 years of use. In past users of MHT, excess risk persisted for >10 years after stopping. Relative risks of breast cancer were similar for women who started treatment in their 40s and 50s. Little information was available for women who started earlier or later.

Breast cancer risk was not substantially affected by women's ethnicity, education, age at menarche, height, or past oral contraceptive use. Adiposity was the only personal factor significantly associated with breast cancer risk, with excess risk associated with HRT in leaner women. For a fairly typical user—a woman of average weight who received 5 years of estrogen plus daily progestagen beginning at age 50 years—breast cancer risk would be increased by 2%, or 1 case in 50 users.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Collaborative Group on Hormonal Factors in Breast Cancer: type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet* 2019;394 (September 28):1159–1168. From the University of Oxford, U.K.; and other institutions. **Funded by Cancer Research U.K.; and other sources. The authors declared no financial relationships with commercial sources.**

***See Reference Guide.**

Ubrogepant for Migraine

The first in class oral calcitonin gene-related peptide receptor antagonist ubrogepant (*Ubrevly*) has received FDA approval for the acute treatment of migraine with or without aura in adults. Ubrogepant is not indicated for the preventive treatment of migraine.

Efficacy of ubrogepant was demonstrated in 2 randomized controlled trials in nearly 1500 adults with a history of migraine. In both studies, the percentages of patients who were pain free 2 hours after treatment and whose most bothersome migraine symptom (e.g., nausea, light sensitivity, sound sensitivity) abated within 2 hours were significantly greater among patients who received active treatment vs placebo at all doses. The most common adverse effects of ubrogepant were nausea, tiredness and dry mouth. The agent is contraindicated for coadministration with strong CYP3A4 inhibitors.

FDA News Release: FDA approves new treatment for adults with migraine. Available at www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-adults-migraine.

Revised AAP Guideline for ADHD

Given the nationwide shortage of mental health specialists, pediatricians and other primary-care clinicians are increasingly called upon to care for young patients with mild-to-moderate ADHD. The American Academy of Pediatrics has revised its clinical practice guideline for ADHD in children and adolescents to reflect recent research and the introduction of DSM-5. Key action statements have been updated and the guideline includes a revised process of care algorithm and recommendations about overcoming systemic barriers to the care of children and adolescents with ADHD.

AAP key action statements on the diagnosis, treatment, and monitoring of ADHD

1. Evaluate for ADHD any child or adolescent aged 4–18 years who presents with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity.

2. Determine that DSM-5 criteria have been met, including documentation of symptoms and impairment in >1 major setting with information obtained from parents or guardians, teachers, other school personnel, and mental health clinicians, and rule out any alternative cause.

3. Screen for comorbid conditions, including emotional or behavioral conditions, developmental conditions, and physical conditions.

4. Because ADHD is a chronic condition, manage children and adolescents with ADHD in the same manner as patients with special health care needs, following the principles of the chronic care model and the medical home.

5. For preschool-aged children, evidence-based parent training and/or behavioral classroom interventions should be used as first-line of treatment.

Methylphenidate may be considered if these interventions do not provide significant improvement and there is at least moderate disturbance in functioning.

For elementary and middle school-aged children with ADHD, prescribe approved medications along with parent training and/or behavioral classroom intervention.

For older adolescents, prescribe FDA-approved medications (with the patient's agreement) along with evidence-based training interventions and/or behavioral interventions.

For all patients attending school, educational interventions and individualized instructional supports, including school environment, class placement, instructional placement, and behavioral supports, are a necessary part of the treatment plan.

6. Titrate medication doses to achieve maximum benefit with tolerable side effects.

7. Initiate treatment of comorbid conditions or make a referral to an appropriate subspecialist for treatment. In some cases, treating ADHD may resolve or substantially improve comorbid conditions.

The guideline also identifies areas that require further research. These focus on creating new or improved processes for developmentally appropriate assessment of ADHD in preschoolers; assessment of common comorbidities and functional impairment; and monitoring improvement over time (including determination of an optimal monitoring schedule). In addition, research is needed to further evaluate medication efficacy across age groups; off-label use of medications and other therapies; adverse effects of medication combinations; and effectiveness of school-based interventions. Finally, to provide effective collaborative care, methods to involve parents and patients in their own care; improvements to systems for communicating with schools, mental health professionals, and other community agencies; and electronic and web-based treatment aids are needed.

Wolraich M, et al: Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 2019;144(4):e20192528. doi 10.1542/peds.2019-2528. From the University of Oklahoma, Oklahoma City; and other institutions.
This guideline was compiled without external funding. Four of 17 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.

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Risk Ratio: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.