PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Romosozumab for Fracture Prevention

The injectable monoclonal antibody romosozumab (*Evenity*) has received FDA approval to treat osteoporosis in postmenopausal women at high risk for fracture. The agent blocks sclerostin, thereby increasing new bone formulation. However, the bone forming effects wane after 12 months, and patients who require continued treatment should receive bone-sparing therapy. In clinical trials, romosozumab reduced the risk of vertebral fractures by 50–73%, compared with placebo. Common adverse effects included joint pain, headache, and injection site reactions. Romosozumab may also increase risk of heart attack, stroke, and cardiovascular death and should not be used by patients who experienced a heart attack or stroke in the previous year. The benefits of treatment should be weighed against these risks in women with other risk factors for heart disease.

FDA News Release: FDA approves new treatment for osteoporosis in postmenopausal women at high risk of fracture. Available at www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-osteoporosis-postmenopausal-women-high-risk-fracture.

PPIs and Bone Health

In a randomized placebo-controlled trial, proton pump inhibitor therapy was associated with minimal changes in bone homeostasis in postmenopausal women. This result suggests that PPI use alone may not be a reason to evaluate bone mineral density beyond the normal screening recommendations in women aged ≥65 years.

Background: Epidemiologic studies have suggested an association between PPI therapy and fracture risk. Plausible biological explanations exist, including excess bone resorption due to gastrin-induced parathyroid hormone production and reduced calcium absorption due to increased gastric pH. However, odds ratios are low, there is no consistent dose-response relationship, and there are confounding factors in many of the studies.

Methods: This industry-funded, multicenter study enrolled postmenopausal women aged 45–75 years. After a 12-week screening period, women were randomly assigned to 26 weeks of double-blind treatment with either 60 mg/day dexlansoprazole, 40 mg/day esomeprazole, or placebo. All participants also received a calcium/vitamin D supplement. The primary study outcomes were change from baseline to week 26 in procollagen type 1 N-terminal propeptide (P1NP) a biomarker for bone formation and C-terminal telopeptide of type 1 collagen (CTX) a biomarker for bone resorption.

Results: A total of 115 women were enrolled and 93 completed the study. Most participants (91%) were white, the mean age was 62 years, and the mean body mass index was 25.2. Women in all groups took more than 95% of their prescribed medication.

By week 26, mean P1NP levels (the marker for bone formation) increased by 18–19% in the PPI groups, compared with a small decrease in the placebo group. Mean CTX (the marker for bone resorption) increased by 27% with dexlansoprazole

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and by 22% with esomeprazole, and remained relatively stable in the placebo group. Values for both markers in all treatment groups were within normal ranges. There were no between-group differences in lumbar spine, total hip, or femoral neck bone mineral density or in serum or urine levels of calcium, phosphorous, magnesium, or parathyroid hormone at 26 weeks. In a subgroup of randomly selected women, those receiving PPI therapy had no decreases in total fractional calcium absorption. No patient experienced a fracture during PPI therapy, and a single serious drug-related adverse event was reported: nephrolithiasis in a dexlansoprazole-treated patient.

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

Hansen K, et al: Dexlansoprazole and esomeprazole do not affect bone homeostasis in healthy postmenopausal women. *Gastroenterology* 2019;156:926–934. From the University of Wisconsin, Madison; and other institutions. **Funded by Takeda Pharmaceuticals International, Inc. All study authors disclosed potentially relevant financial relationships.**

Common Drug Trade Names*: dexlansoprazole—*Dexilant*; esomeprazole—*Nexium

***See Reference Guide.**

Stronger Warnings for Sleep Aids

Following reports of rare, but serious injuries related to complex sleep behaviors, the FDA is requiring the addition of boxed warnings to the prescribing information and medication guides for eszopiclone, zaleplon, and zolpidem. The reported behaviors include sleepwalking, sleep driving, and engaging in other unsafe activities while not fully awake. An ongoing safety review has identified 66 cases of these behaviors, 20 of which were fatal. The incidents can occur with the first or any subsequent use and have been reported even with the lowest recommended doses. Although the labeling already includes information on these events, the boxed warning is intended to make it more prominent. In addition, these agents will now be contraindicated in patients who have experienced an episode of complex sleep behavior associated with these agents.

FDA New Release: FDA requires stronger warnings about rare but serious incidents related to certain prescription insomnia medications: updated warnings for eszopiclone, zaleplon and zolpidem. Available at www.fda.gov/news-events/press-announcements/fda-requires-stronger-warnings-about-rare-serious-incidents-related-certain-prescription-insomnia.

Common Drug Trade Names*: eszopiclone—*Lunesta*; zaleplon—*Sonata*; zolpidem—*Ambien, Intermezzo, Zolpimist

Shingles Vaccine Safety

Postmarketing monitoring of the recombinant zoster vaccine (*Shingrix*) by the FDA and the Centers for Disease Control and Prevention found the safety profile consistent with that of premarketing trials. In addition, adverse event reporting patterns were similar to those for other vaccines.

Data was collected from the FDA Vaccine Adverse Event Reporting System (VAERS) between October 2017 and June 2018. During the study period, 4381 reports associated with *Shingrix* were added to the VAERS database; a rate of 136 reports per 100,000 doses administered. The most commonly reported reaction was fever (24%), followed by injection site reactions, pain, chills, headache, and fatigue (16–23%). Of the >4000 reports, 230 (5%) described vaccination errors, most commonly subcutaneous rather than intramuscular administration. While these early data are reassuring, the safety of the vaccine will continue to be closely monitored.

Hesse E, et al: Postlicensure safety surveillance of recombinant zoster vaccine (Shingrix)—United States, October 2017–June 2018. *Morbidity and Mortality Weekly Report* 2019;68 (February 1):91–94. From the Centers for Disease Control and Prevention, Atlanta, GA; and the FDA, Silver Spring, MD. **The authors declared no competing interests.**

Antidepressants, Anxiolytics in Pregnancy

According to the results of a large exploratory cohort study, women treated with antidepressants or anxiolytics in early pregnancy have a 3-fold increase in risk of preeclampsia. However, risk appears to be attenuated in women who discontinue the drugs before the 16th gestational week. It is unclear whether maternal disease is an underlying factor in the association.

Methods: The study cohort was derived from the population of women who received prenatal care at a Canadian university hospital clinic between 2005 and 2010. Women with singleton pregnancies were invited to participate in the study at the first prenatal visit, at an average of 15 weeks gestation. Those with chronic hepatic or renal disease or who were receiving treatment with antipsychotics, anticonvulsants, or stimulants were excluded. Use of antidepressants and anxiolytics was assessed throughout the pregnancy and extracted from patient records after delivery. Gestational hypertension was defined as new-onset of systolic blood pressure ≥140 mmHg and/or diastolic blood pres-

sure ≥90 mmHg after the 20th gestational week. Preeclampsia was defined as either gestational hypertension with proteinuria or preexisting hypertension with new or worsening proteinuria. Incidence of these outcomes was compared between women who did and did not receive an antidepressant and/or anxiolytic.

Results: A total of 6761 pregnant women were included in the analysis. Of these, 218 were exposed to antidepressants or anxiolytics before the 16th gestational week, an additional 41 women had depression or anxiety but did not receive pharmacotherapy, and 6502 had neither depression nor anxiety. Selective serotonin reuptake inhibitors (SSRIs) were the most widely used category (48.5% of women), followed by serotonin and norepinephrine reuptake inhibitors (SNRIs; 27%) and benzodiazepines (17.8%).

In the full cohort, gestational hypertension developed in 202 women and preeclampsia in 127. Risk of gestational hypertension was elevated but did not reach statistical significance in treated women. Because the frequency of preeclampsia was low, users of all the medications were grouped to estimate relative risks. Women who started using antidepressants or anxiolytics before the 16th week of gestation had a significantly increased risk of preeclampsia which remained after adjustment for other potential confounders (adjusted odds ratio,* 3.09; p=0.001). Among drug categories, tricyclic antidepressants were associated with the highest risk for preeclampsia (odds ratio, 7.36), but these drugs were used by few women and the increase did not reach significance. Odds ratios were significant for SNRIs and SSRIs (6.46 and 3.09, respectively). Women who continued their medication after the 16th week (n=167) continued to have increased risk of preeclampsia (odds ratio, 3.41; p=0.001), but in those who stopped the medication before the 16th week risk was not significantly greater than in unexposed women. Women with unmedicated depression or anxiety were also at increased risk of preeclampsia (odds ratio, 2.92), but the risk was not significantly greater than in women without depression or anxiety.

Discussion: There are plausible biological mechanisms for an association between antidepressant and/or anxiolytic exposure and gestational hypertensive disorders (e.g., antidepressant-mediated vasoconstriction, noradrenergic effects, increased levels of vasoactive amines). However, it is noteworthy that women with unmedicated depression or anxiety also had an elevated odds ratio for preeclampsia. While this did not reach significance, the statistical power was low because there were few women in this group.

Bernard N, et al: Use of antidepressants and anxiolytics in early pregnancy and the risk of preeclampsia and gestational hypertension: a prospective study. *BMC Pregnancy and Childbirth* 2019; doi 10.1186/s12884-019-2285-8. From Université Laval, Quebec City, Canada.
Funded by the Canadian Institutes of Health Research. The authors declared no competing interests.

***See Reference Guide.**

Canagliflozin and Renal Outcomes

In a large randomized placebo-controlled trial, canagliflozin (*Invokana*) lowered the risk of kidney failure in patients with type 2 diabetes and chronic kidney disease.

Background: Canagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor, developed as a glucose-lowering drug. This industry-sponsored study was conducted to confirm suggestions from earlier clinical trials that SGLT2 inhibitors might improve renal outcomes.

Methods: Study subjects were adults with type 2 diabetes and chronic kidney disease. All patients were required to be receiving an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) for ≥4 weeks. Participants were randomly assigned to double-blind treatment with 100 mg/day canagliflozin or placebo. The primary efficacy outcome was a composite of end-stage renal disease, doubling of the serum creatinine level from baseline, and death from renal or cardiovascular disease.

Results: The trial enrolled 4401 patients from 690 sites in 34 countries. Patients had a mean age of 63 years, and one-third were women. The trial was terminated after a median follow-up of 2.6 years, when an interim analysis showed that canagliflozin met prespecified efficacy criteria.

Canagliflozin was associated with a 30% reduction in the primary composite endpoint, as well as with reductions in each individual element. (See table, next page.) Estimates suggest that treating 1000 patients with canagliflozin for 2.5 years would result in 47 fewer occurrences of the primary composite endpoint (number needed to treat,* 22). Canagliflozin was also associated with reductions in secondary outcomes including a composites of cardiovascular death

Effects of canagliflozin on primary renal outcomes			
	Events per 1000 patient-years		Hazard ratio*
	Canagliflozin	Placebo	
Composite outcome	43.2	61.2	0.70
Doubling of serum creatinine	20.7	33.8	0.60
End-stage kidney disease	20.4	29.4	0.68
Cardiovascular death	19.0	24.4	0.78
Renal death	0.3	0.9	NA±
±Not calculated for events with <10 occurrences			

and hospitalization; cardiovascular death, MI, or stroke; and in hospitalization for heart failure. Canagliflozin was also associated with improvement in intermediate outcomes, such as glycated hemoglobin, systolic and diastolic blood pressure, and body weight.

Discussion: During the trial, a report from a different study suggested a possible link between canagliflozin and lower limb amputation. However, rates of lower limb amputation in this study did not differ between canagliflozin and placebo. It is notable that the benefits of canagliflozin were observed in patients receiving renoprotective medication, highlighting the clinical significance of the findings.

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

Perkovic V, et al: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *NEJM* 2019; doi 10.1056/NEJMoa.1811744. From the University of New South Wales, Sydney, Australia; and other institutions. **Funded by Janssen. All study authors disclosed potentially relevant financial relationships with commercial sources, including Janssen for 23 of the 24 authors.**

***See Reference Guide.**

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Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Number Needed to Treat (NNT): Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison 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.