PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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SGLT2 Inhibitors and Necrotizing Fasciitis

The FDA has issued a warning about the possibility of necrotizing fasciitis of the perineum associated with use of sodium-glucose cotransporter-2 inhibitors for diabetes. This rare and serious infection, also known as Fournier's gangrene, can cause tenderness, redness, or swelling of the genitals or the surrounding area, along with fever and general feeling of being unwell. Symptoms can worsen quickly and require broad-spectrum antibiotics and, in some cases, surgical debridement. If the infection develops, the SGLT2 inhibitor should be discontinued and an alternative therapy for glycemic control initiated.

SGLT2 (sodium-glucose cotransporter-2) inhibitors for diabetes: drug safety communication–regarding rare occurrences of a serious infection of the genital area. Available at https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm618908.htm.

Safety of Switching to Sulfonylureas

According to the results of a population-based cohort study, patients who receive sulfonylureas as second-line therapy for type 2 diabetes are at increased risk of myocardial infarction (MI), severe hypoglycemia, and death, compared with those who continue metformin (*Glucophage*) monotherapy. The risk increase is driven by switching to sulfonylurea monotherapy, which suggests continuing metformin while introducing a sulfonylurea may be safer than switching.

Methods: The investigators analyzed data from the U.K.'s Clinical Practice Research Datalink and other databases. The cohort consisted of patients newly started on metformin for type 2 diabetes between 1998 and 2013. At cohort entry, participants who did and did not receive a sulfonylurea were individually matched using propensity scores* based on an extensive range of likely confounders and on hemoglobin A_{1c} levels. Cardiovascular death, all-cause mortality, severe hypoglycemia, and hospital admission for MI or ischemic stroke were compared between patients who subsequently added or switched to a sulfonylurea and those who remained on metformin monotherapy.

Results: The analysis was based on >23,000 matched pairs of patients, with an average follow-up of 1.1 years. Sulfonylurea therapy was associated with significant increases in risk for MI (hazard ratio [HR],* 1.26), all-cause mortality (HR, 1.28), and severe hypoglycemia (HR, 7.6). Trends were also found toward increased risk of ischemic stroke (HR, 1.24) and cardiovascular death (HR, 1.18). The risk increase was driven by patients who switched to a sulfonylurea rather than those who added it to metformin, who had a significantly higher rate of MI than those who received combined therapy (HR, 1.51) and a borderline increase in all-cause mortality. The risk difference was especially pronounced for patients with shorter durations of sulfonylurea use, particularly ≤3 months of use.

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Discussion: Previous studies have examined the risks of introducing sulfonylureas as first-line drugs or in comparison with other second-line drugs. This study compared the safety of second-line sulfonylureas with those of continuation of metformin, a drug with potential cardioprotective effects and low risk of hypoglycemia. Several potential mechanisms may explain the present observations. Sulfonylureas are associated with weight gain, and their hypoglycemia-inducing effect may contribute to the development of arrhythmias and cardiac ischemia. The higher risk estimates with short-term use indicate short-term mechanisms such as arrhythmias may be more important. The absence of increased MI risk when sulfonylureas are added to metformin supports the cardioprotective effect of metformin, which has also been observed after adding other second-line antidiabetic drugs.

Douros A, et al: Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study. *BMJ* 2018; doi 10.1136/bmj.k2693. From Jewish General Hospital, Montreal, Canada; and other institutions. **Funded by the German Research Foundation; and other sources. One of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Antibody Treatment for Episodic Migraine

Fremanezumab (*Ajovy*), an injectable antibody that binds to calcitonin gene-related peptide (CGRP), was superior to placebo in preventing episodic migraine in a phase III trial.[1] The agent recently received FDA approval for the prevention of migraine in adults.[2]

Methods: Study subjects (n=875) had a history of migraine for ≥1 year before screening and had experienced migraines on 6–14 days of the 28-day screening period. Patients were excluded if they had inadequate response to ≥2 multi-medication approaches. Participants were randomly assigned to receive 1 of 3 study treatments: 3 monthly doses of 225 mg fremanezumab via subcutaneous injection; a single 675-mg dose followed by 2 monthly placebo injections; or 3 placebo injections. The single high dose was intended to support a quarterly dose regimen. The primary efficacy endpoint was the mean change from baseline in the number of migraine days per month during the 12-week follow-up period. Migraine-related disability was measured with the Migraine Disability Assessment (MIDAS).

Results: At baseline, patients had severe disability, based a mean MIDAS score of 39. Both doses of fremanezumab were associated with statistically significant reductions in migraine days per month, compared with placebo. The mean number of migraine days decreased from 8.9 to 4.9 days with monthly fremanezumab and from 9.2 to 5.3 days with the single, higher dose of fremanezumab, compared with a decrease from 9.1 to 6.5 days with placebo ($p<0.001$ for both fremanezumab doses vs placebo). Fremanezumab was also associated with a higher rate of response (≥50% reduction in migraine days): 48% and 44% in the monthly and single fremanezumab groups, respectively, compared with 28% for placebo ($p<0.001$ for both doses). Migraine-related disability was also reduced to a significantly greater degree. Adverse effects of fremanezumab were primarily related to injection-site reactions. These reactions also occurred in the placebo group, although at a lower frequency.

Discussion: CGRP is a neuropeptide involved in the central and peripheral mechanisms of migraine. Fremanezumab binds to the CGRP peptide ligand, not the receptor. Given the need for long treatment durations, there is some concern over off-target effects of CGRP antibodies.[3] CGRP suppression may have cardiovascular effects and disrupt airway homeostasis; and psychiatric effects are a possibility. However, long-acting injected CGRP antibodies offer the advantage of convenience and a low likelihood of drug interactions.

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

[1]Dodick D, et al: Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. *JAMA* 2018:319 (May 15):1999–2008. From the Mayo Clinic, Phoenix, AZ; and other institutions including Teva Pharmaceuticals, Frazer, PA. **Funded by Teva Pharmaceuticals, Petach Tikva, Israel. All study authors disclosed relevant financial relationships with commercial sources including Teva.**

[2]Teva Announces U.S. Approval of AJOVY™ (fremanezumab-vfrm) Injection, the First and Only Anti-CGRP Treatment with Both Quarterly and Monthly Dosing for the Preventive Treatment of Migraine in Adults [press release]. Jerusalem, Teva Pharmaceutical Industries: September 14, 2018. Available at www.tevapharm.com/news.

[3]Loder E, Robbins M: Monoclonal antibodies for migraine prevention: progress, but not a panacea [editorial]. *JAMA* 2018:319 (May 15):1985–1987. From Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and Albert Einstein College of Medicine, Bronx, NY. **Both authors disclosed potentially relevant financial relationships.**

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Aspirin Benefits and Body Weight

According to the results of a pooled analysis of primary and secondary prevention trials, the optimal dose of aspirin to prevent cardiovascular events and cancer increases with body size.[1]

Methods: The meta-analysis included randomized trials of aspirin versus control treatments in primary prevention of vascular events or secondary prevention of stroke. Within studies, aspirin dosages and scheduling were uniform—either low (≤100 mg) or high (≥300 mg), daily or on alternate days. Individual patient data were obtained, when available, and pooled for the meta-analysis. Study outcomes were major vascular events, cancers (a secondary outcome of many of the individual trials), and all-cause mortality. Analyses were stratified by patient body weight: <154 lbs versus ≥154 lbs.

Results: The authors identified 9 primary prevention trials (7 of low-dose and 2 of high-dose aspirin) and 4 trials of secondary prevention of stroke with individual data available for a combined total of 117,279 patients. In the primary prevention trials, median patient weight ranged from 132 lbs to 179 lbs, in part due to differences in the proportions of men and women. In the low-dose aspirin trials, risk of cardiovascular events was reduced in patients weighing <154 lbs (pooled odds ratio,* 0.77; p<0.0001), but not in those with a higher body weight. The differences from control with low-dose aspirin were particularly evident in the lowest weight range (110–152 lbs) and with daily versus alternate-day dosing, and they were attenuated with enteric dosage forms. Low-dose aspirin prevented stroke in women but not in men. The preventive effects of higher aspirin doses increased with body weight, with consistent effects for cardiovascular events and death and in primary and secondary prevention trials. The interacting effect of weight and aspirin dose on cardiovascular risk reduction was consistent in men and women, in people with or without diabetes, in relation to height, and in secondary prevention trials.

Five primary prevention trials, with a combined sample size of 73,372, reported on the effects of aspirin in preventing colorectal cancer. There was a significant 20-year risk reduction in patients weighing <154 lbs (hazard ratio,* 0.64; p=0.0004), but not in patients weighing more. Higher doses of aspirin prevented colorectal cancer in patients weighing up to 176 lbs (hazard ratio, 0.69; p=0.0014).

Discussion: These results may help to explain the modest effects of aspirin in reducing risk of vascular events in clinical trials. Aspirin's effects may be dependent on lean body mass, which is correlated with the mass of intestinal wall, blood cells, and other tissues that metabolize aspirin and that could influence its systemic bioavailability. Obesity and increased body mass index seem to be less of an influence.

Editorial.[2] According to these findings, the prevalent one-dose-fits-all strategy is less effective than weight-adjusted dosing. However, dosing adjusted by weight would result in increased exposure in the majority of patients, possibly increasing bleeding risk. Further research should more precisely define the effect of weight-adjusted aspirin dosing on both benefit and risk.

[1]Rothwell P, et al: Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. *Lancet* 2018; doi 10.1016/S0140–6736(18)31133–4. From the University of Oxford, U.K.; and other institutions. **Funded by the Wellcome Trust; and the National Institute for Health Research Oxford Biomedical Research Centre. Three of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Theken K, Grosser T: Weight-adjusted aspirin for cardiovascular prevention [editorial]. *Lancet* 2018; doi 10.1016/S0140–6736(18)31307-2. From the University of Pennsylvania, Philadelphia. **The authors declared no competing interests.**

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Bleeding Risk with Antidepressants

Serotonergic antidepressants (SRIs) are associated with increased risk of bleeding, especially early in the course of treatment, according to a nonsystematic literature review. Clinicians should be aware of options when prescribing for high-risk patients, including antidepressants with low potential to induce bleeding and strategies for preventing gastrointestinal (GI) bleeding.

SRI-related bleeding is believed to be the result of inhibition of the serotonin transporter on platelets, leading to reduced platelet aggregation. SRIs also increase gastric acidity, which can predispose to GI bleeding. SRIs with high serotonin transporter binding affinity may place patients at higher bleeding risk than agents with intermediate or low affinity. (See table, next page.) Cytochrome P450-mediated drug interactions further contribute to bleeding risk with selective SRIs

(SSRIs), particularly duloxetine, fluoxetine, fluvoxamine, and paroxetine.

Serotonin transporter binding affinity of antidepressants		
High	**Intermediate**	**Low**
Clomipramine	Amitriptyline	Bupropion
Duloxetine	Citalopram	Doxepin
Fluoxetine	Escitalopram	Mirtazapine
Paroxetine	Imipramine	Nortriptyline
Sertraline	Venlafaxine	Phenelzine
Vilazodone		Tranylcypromine
Vortioxetine		Trazodone

A literature search identified 9 meta-analyses of SRI-related bleeding and 1 meta-analysis of bleeding risk with bupropion and mirtazapine. SRIs have been associated with GI bleeding, intracranial hemorrhage, postpartum hemorrhage, and perioperative bleeding. Most of the studies have focused on GI bleeding, which makes it difficult to assess the risk at other sites. In 1 meta-analysis encompassing nearly 1.5 million patients, SSRIs increased bleeding risk by 41% (odds ratio,* 1.41; p<0.001). Risk was especially high for GI bleeding (odds ratio, 1.55) and lower for intracranial hemorrhage (odds ratio, 1.16). However, in another analysis, SSRIs were associated with elevated risk of brain hemorrhage (odds ratio, 1.61). Women who take antidepressants during pregnancy have an increased risk of postpartum hemorrhage (odds ratio, 1.32; p<0.001). It has been difficult to estimate risk of perioperative bleeding because of the use of other medications that affect coagulation. Concomitant medications can add to the risk of bleeding in patients taking SRIs. Increased risk has been documented in patients taking NSAIDs, antiplatelet therapy, and anticoagulants.

Some evidence suggests that acid-suppressing agents decrease risk of GI bleeding in patients taking SRIs with NSAIDs. Proton pump inhibitors (PPIs) have not been investigated directly, but subgroup analyses in some studies suggest they may reduce bleeding risk. However, depression is a potential adverse effect of PPIs in the elderly.

Clinicians should consider preventive strategies for GI bleeding in high-risk patients and the elderly. Agents with low serotonin transporter binding affinity or bupropion, which has a mechanism independent of serotonin, may be prudent antidepressant choices in patients with bleeding risk.

Bixby A, VandenBerg A, Bostwick J: Clinical Management of bleeding risk with antidepressants. *Annals of Pharmacotherapy* 2018; doi 10.1177/1060028018794005. From Michigan Medicine and the University of Michigan College of Pharmacy, Ann Arbor. This review was not funded. The authors declared no competing interests.

Common Drug Trade Names*: amitriptyline—*Elavil*; bupropion—*Wellbutrin*; citalopram—*Celexa*; clomipramine—*Anafranil*; doxepin—*Silenor*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; imipramine—*Tofranil*; mirtazapine—*Remeron*; nortriptyline—*Pamelor*; paroxetine—*Paxil*; phenelzine—*Nardil*; sertraline—*Zoloft*; tranylcypromine—*Parnate*; trazodone—*Oleptro*; venlafaxine—*Effexor*; vilazodone—*Viibryd*; vortioxetine—*Trintellix

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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.

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.

Propensity Score Matching: A correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

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).