DRUG INTERACTIONS

Risk of hypoglycemia if repaglinide is given with clopidogrel (February 2017)

Clopidogrel, an antiplatelet drug whose glucuronide metabolite inhibits CYP2C8 hepatic metabolism, can increase levels of repaglinide, a CYP2C8 substrate, and cause hypoglycemia [1,2]. The prescribing information in the United States was recently revised to recommend against concomitant use and, if the combination cannot be avoided, to limit the total daily dose of repaglinide to 4 mg or less. Characterizing this interaction has contributed to a growing appreciation of CYP2C8 as a clinically relevant drug metabolizing enzyme leading to potential drug interactions with strong CYP2C8 inhibitors or inducers [2]. (See "Sulfonylureas and meglitinides in the treatment of diabetes mellitus", section on 'Precautions and side effects'.)

Dabigatran combined with certain statins associated with increased risk of major bleeding (February 2017)

An analysis of health records of nearly 46,000 Canadian patients showed that older adults (age ≥66) with atrial fibrillation taking dabigatran who also received simvastatin or lovastatin had approximately a 50 percent greater risk of hospitalization for major hemorrhage relative to those who used other statins [3]. Although the mechanism for this interaction is uncertain, until additional information becomes available, it may be prudent to choose a statin other than lovastatin or simvastatin for older patients receiving dabigatran, and for those with an elevated risk for serious bleeding. (See "Statins: Actions, side effects, and administration", section on 'Drug interactions'.)

NEW DRUGS

Tranexamic acid for management of postpartum hemorrhage (May 2017)

Tranexamic acid, an antifibrinolytic drug, reduces bleeding in surgical and trauma patients. In a pragmatic randomized trial involving over 20,000 women with postpartum hemorrhage in over 20 countries (the World Maternal Antifibrinolytic Randomized Trial [WOMAN]), tranexamic acid, compared with placebo, reduced the relative risk of death due to bleeding by 20 to 30 percent, reduced the incidence of laparotomy to control bleeding, and was not associated with an increase in adverse effects [12]. Overall mortality was not reduced. We now recommend administration of tranexamic acid as a component of the treatment for postpartum hemorrhage. (See "Management of postpartum hemorrhage at vaginal delivery".)

Dosing interval for zoledronic acid in patients with bone metastases (January 2017)

For patients with bone metastases from a solid tumor, the approved dose and schedule of administration for zoledronic acid to reduce the frequency of skeletal-related events (SREs) is 4 mg every three to four weeks. Less frequent dosing is supported by data from CALGB (Alliance) trial 70604, which randomly assigned 1822 patients with bone metastases from breast or prostate cancer or multiple myeloma to the same dose of zoledronic acid every 4 or every 12 weeks for

two years, starting with the first dose. There was no difference in the proportion of patients who developed at least one SRE (29.5 versus 28.6 percent) [44]. There are now sufficient data in breast and castration-resistant prostate cancer to support dosing of zoledronic acid every 12 rather than every 4 weeks, and we suggest this approach for most patients. We still prefer every-four-week dosing, at least initially, for patients who have extensive or highly symptomatic bone metastases. (See "Osteoclast inhibitors for patients with bone metastases from breast, prostate, and other solid tumors", section on 'Dosing interval'.)

ADVERSE REACTIONS AND WARNINGS

HBV reactivation during HCV antiviral therapy (May 2017)

Reactivation of hepatitis B virus (HBV) can occur during direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) infection. Among 29 cases reported to the US Food and Drug Administration (FDA) or described in the literature between 2013 and 2016, reactivation occurred at an average of 53 days into DAA treatment and was not associated with a particular HCV genotype or DAA regimen [51]. Two cases were fatal, and one patient required liver transplant. Patients should be tested for HBV coinfection prior to initiation of HCV therapy, with HBV treatment initiated for those who meet criteria (table 2). HBV coinfected patients who do not initially meet HBV treatment criteria should be monitored for reactivation during HCV treatment. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'HBV coinfection' and "Overview of the management of chronic hepatitis C virus infection", section on 'Monitoring during antiviral therapy'.)

Safety warnings issued for codeine and tramadol in breastfeeding women and children under age 12 years (April 2017)

The US Food and Drug Administration (FDA) issued a strong warning to restrict use of codeine and tramadol in breastfeeding women and children <12 years old because of increasing reports of life-threatening respiratory depression in young children exposed to these drugs [52]. Children who are ultra-rapid metabolizers metabolize these drugs faster than normal, leading to dangerously high levels of active drug. We suggest avoiding codeine and tramadol in breastfeeding women and children <12 years old. (See "Evaluation and management of pain in children", section on 'Agents not recommended'.)

Adverse events with short-term oral glucocorticoid use in adults (April 2017)

Chronic steroid use is associated with a wide spectrum of adverse effects. However, there is a paucity of clinical data on the adverse effects associated with short-term use. A retrospective cohort study and self-controlled case series assessed the risk of three adverse events (sepsis, venous thromboembolism [VTE], and fracture) in over 300,000 adults younger than 65 who received at least one short-term (<30 days) outpatient prescription for oral glucocorticoids over a three-year period [53]. The most common indications for use were upper respiratory tract infections, spinal conditions, and allergies. Within 30 days of drug initiation, there was a two- to fivefold increase in the rates of sepsis, VTE, and fracture, which then decreased over the subsequent 31 to 90 days. These findings suggest that even short courses of oral steroids are

associated with adverse effects that should be considered before prescribing. (See "Major side effects of systemic glucocorticoids", section on 'Dose effects'.)

Concurrent benzodiazepines in opioid-using patients and overdose risk (April 2017)

Benzodiazepines can potentiate the respiratory depressant effects of opioid medication, and concurrent use may be a factor in the rising rate of opioid overdose. In an analysis of a large sample of patients prescribed an opioid, the proportion who concurrently received a benzodiazepine nearly doubled over 12 years [55]. Concurrent use of both medications was associated with an increased risk of opioid overdose compared with patients receiving only the opioid. Avoiding this medication combination may prevent some overdoses. (See "Prevention of lethal opioid overdose in the community", section on 'Risk factors'.)

Switching MI patients from ticagrelor to clopidogrel (March 2017)

The potent platelet P2Y12 receptor blocker ticagrelor, rather than clopidogrel, is initiated in hospital for many patients with myocardial infarction. However, some of these individuals will need to switch to clopidogrel either before or after hospital discharge for a variety of reasons, including cost, bleeding risk, and nonbleeding side effects (eg, dyspnea). The optimal strategy to make the switch while avoiding a subtherapeutic antiplatelet effect is not known. This issue was addressed in a randomized trial comparing the pharmacodynamic effects of switching from ticagrelor to clopidogrel with or without a loading dose of clopidogrel [56]. The study identified a period of time after the first dose of clopidogrel (12 hours after the last dose of ticagrelor) when there was greater antiplatelet effect with the loading dose than without. Based on this pharmacodynamic study, we give a clopidogrel loading dose of 600 mg at 12 hours when switching from ticagrelor to clopidogrel therapy. (See "Antiplatelet agents in acute non-ST elevation acute coronary syndromes", section on 'Switching from a P2Y12 agent to clopidogrel' and "Antiplatelet agents in acute ST elevation myocardial infarction", section on 'Switching from a P2Y12 agent to clopidogrel'.)

Antipsychotic drugs and risk of falls and fracture (March 2017)

In a large, population-based sample of Finnish people with Alzheimer disease, new users of antipsychotic medication had an increased risk of hip fractures from the first days of use [57]. Subsequent to multiple similar reports in patients with varied disorders, the US Food and Drug Administration (FDA) issued a warning that antipsychotic drugs may cause falls and fractures as a result of somnolence, postural hypotension, and/or motor and sensory instability, and recommended that a fall risk assessment be completed when initiating antipsychotic treatment and recurrently for patients continuing on long-term antipsychotics. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section on 'Falls'.)

Differences in anaphylaxis treatment by age (February 2017)

Epinephrine given by intramuscular (IM) injection is the treatment of choice for anaphylaxis, but clinicians are sometimes reluctant to administer it, particularly to older adults. In a retrospective study of nearly 500 children and adults with anaphylaxis presenting to the emergency

department, patients >50 years of age were less likely to receive epinephrine (36 versus 61 percent) compared with younger patients [58]. In addition, among patients who were given epinephrine, older adults were more likely to receive excessive doses when epinephrine was administered intravenously (IV). IM epinephrine was well-tolerated by patients of all ages, while IV administration was associated with a higher rate of cardiovascular complications. These findings support our recommendations to administer epinephrine by IM injection whenever possible and reserve IV administration for refractory cases. (See "Anaphylaxis: Emergency treatment", section on 'Situations requiring caution'.)

High-risk drug prescribing in adults with dementia (February 2017)

Older adults with dementia are at heightened risk for adverse drug effects from anticholinergic drugs, benzodiazepines, and opioids, among many others. Despite these risks, polypharmacy remains common in this population. In a study that included over 75,000 adults with dementia, 44 percent of patients were prescribed at least one potentially unsafe medication (mostly drugs with high anticholinergic activity), and rates were consistently higher in patients receiving care from multiple providers [59]. These results highlight the need for careful monitoring of drug therapy in patients with dementia and the importance of communication among providers before starting new therapies. (See "Safety and societal issues related to dementia", section on 'Polypharmacy'.)

Metformin use in patients with diabetes and renal impairment, heart failure, or chronic liver disease (January 2017)

In a systematic review of 17 observational studies comparing diabetes regimens with and without metformin, metformin use was associated with lower all-cause mortality among patients with heart failure, renal impairment, or chronic liver disease with hepatic impairment [60]. In addition, metformin use in patients with renal impairment or heart failure was associated with fewer heart failure readmissions. This study supports a recent US Food and Drug Administration (FDA) labeling revision for metformin, which will increase use in patients with renal impairment. Metformin remains contraindicated in patients with estimated glomerular filtration rate (eGFR) <30 mL/min, concurrent active or progressive liver disease, or unstable or acute heart failure with risk of hypoperfusion and hypoxemia. Recommendations regarding metformin use in patients with an eGFR between 30 and 45 mL/min vary and UpToDate authors individualize decisions about metformin use in such patients. (See "Metformin in the treatment of adults with type 2 diabetes mellitus", section on 'Contraindications'.)

Relative cardiovascular safety of celecoxib, naproxen, and ibuprofen (December 2016)

The cardiovascular (CV) safety of celecoxib, the COX-2 selective nonsteroidal anti-inflammatory drug (NSAID), compared with other NSAIDs, is a matter of debate. In a randomized trial (PRECISION) involving over 24,000 patients with arthritis and either known CV disease or CV risk factors, the CV safety of celecoxib was noninferior to both naproxen and ibuprofen, two nonselective NSAIDs [61]. Depending upon the analysis, about 2 to 5 percent of subjects experienced a CV event during follow-up, which was slightly lower than the expected event rate. Despite some limitations, this trial suggests that celecoxib in

moderate doses can be administered, when indicated, without concern about increased CV risk compared with the nonselective nonsteroidal agents naproxen and ibuprofen. (See "COX-2 selective inhibitors: Adverse cardiovascular effects", section on 'Celecoxib' and "Nonselective NSAIDs: Adverse cardiovascular effects", section on 'Risk of myocardial infarction, stroke, and death'.)

FDA issues warning about anesthesia for pregnant patients and children under three years of age (December 2016)

The US Food and Drug Administration has warned about potential negative effects on the developing brain from administration of anesthetics and sedatives to pregnant women and children under age three, especially for repeated exposures or procedures lasting more than three hours [62]. However, the degree of risk remains unclear. A single, brief exposure to anesthesia probably does not cause neurotoxicity in healthy young children. Further study is required to determine the effects of prolonged or repeated anesthetics, variability among anesthetic agents and combinations of drugs, and patient factors that may confer vulnerability to anesthetic neurotoxicity. At present, there is no compelling evidence that any specific anesthetic agent should be avoided during pregnancy or in young children, or that necessary surgery should be delayed because of concerns about neurotoxicity. (See "Management of the pregnant patient undergoing nonobstetric surgery", section on 'Fetal brain development'.)

FDA warning removed from varenicline for smoking cessation (December 2016)

In 2009, the US Food and Drug Administration (FDA) required varenicline packaging to include a boxed warning about potential neuropsychiatric side effects, but this warning has been removed in 2016 [63], based on results of a randomized trial that found no difference in adverse neuropsychiatric events comparing varenicline with nicotine patch or placebo in patients with or without a coexisting psychiatric disorder [64]. As with any medication, we advise that patients should be told to contact their clinician if they or their family notice any unusual behavior or mood symptoms as well as any new or worsening symptoms of cardiovascular disease. (See "Pharmacotherapy for smoking cessation in adults", section on 'Safety'.)

Type 1 diabetes mellitus and anti-PD-1 immunotherapy (December 2016)

Checkpoint inhibitor immunotherapy with an anti-programmed cell death 1 (PD-1) receptor antibody, often in conjunction with ipilimumab, has resulted in the acute onset of type 1 diabetes mellitus in rare cases. This may be manifested by severe hyperglycemia or diabetic ketoacidosis [66]. These patients have remained insulin-dependent for diabetic control following management of their acute episode. Blood glucose is typically monitored weekly during the first 12 weeks of therapy with the combination of nivolumab plus ipilimumab. (See "Toxicities associated with checkpoint inhibitor immunotherapy", section on 'Type 1 diabetes mellitus'.)

VACCINES

Missed opportunity for MMR vaccination during pretravel consultation (May 2017)

Measles is a highly contagious viral illness spread by respiratory droplets; complications include pneumonia, otitis media, and encephalitis. Travelers are at risk for measles infection, and measles, mumps, and rubella (MMR) vaccination is recommended for all international travelers without evidence of immunity. However, in a retrospective review including more than 6600 adults who visited a United States pretravel clinic and were eligible for MMR vaccine, fewer than half of these individuals received it during the consultation [67]. The pretravel visit provides an important opportunity to reduce the likelihood of importation and transmission of measles by ensuring that MMR vaccination (in addition to other routine immunizations) is current. (See "Immunizations for travel", section on 'Measles, mumps, and rubella'.)

Pregnancy outcomes with HPV vaccination (March 2017)

Human papillomavirus (HPV) vaccination during pregnancy is not recommended, but mounting evidence suggests that it is safe. In a large cohort study from Denmark, the risks of spontaneous abortion, major birth defects, preterm birth, and low birth weight were comparable among women who received quadrivalent HPV vaccine during pregnancy (mostly during the first trimester) and matched controls who did not [69]. Women who inadvertently receive HPV vaccine during pregnancy can be reassured that it does not increase their risk of adverse pregnancy or fetal outcomes. (See "Immunizations during pregnancy", section on 'Human papillomavirus'.)

High-dose influenza vaccine in older adults (March 2017)

For influenza vaccination of adults ≥65 years of age, we recommend the high-dose inactivated influenza vaccine, which has previously been shown to be more immunogenic and modestly more effective at preventing influenza infection than the standard-dose vaccine. In a study of United States Medicare beneficiaries ≥65 years of age, the high-dose vaccine was more effective than the standard-dose vaccine for preventing postinfluenza death during the 2012-2013 influenza season, a season when circulation of H3N2 influenza A (a strain associated with severe disease) was common [70]. In contrast, it was not more effective for preventing postinfluenza death during the following season, when H1N1 influenza A (a strain associated with mild disease) predominated. This difference was likely due to the difficulty in demonstrating benefit during a mild influenza season, when death is a rare outcome. The high-dose vaccine was associated with a reduced risk of hospitalization during both seasons. (See "Seasonal influenza vaccination in adults", section on 'High-dose vaccine'.)