

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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New Insulin Glargine Approved

Basaglar, a "follow-on" long-acting insulin glargine product, has received FDA approval for treatment of type 1 diabetes in adults and children and for type 2 diabetes in adults. The agent is the first approved through an abbreviated pathway that relies in part on safety and effectiveness of an already approved agent. Clinical trials showed *Basaglar* to be sufficiently similar to the already approved biologic *Lantus* to rely on its data to back the approval of the new agent. *Basaglar* is administered subcutaneously once daily (at the same time each day) using a KwikPen delivery system. Common adverse effects of the agent include hypoglycemia; allergic reactions; injection site reactions; lipodystrophy; itching; rash; edema; and weight gain. The agent should not be used during episodes of hypoglycemia or in patients who have had a hypersensitivity reaction to *Lantus*.

Editor's Note: A follow-on biologic (or biosimilar) is a biological product that is highly similar to an already approved biological product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biosimilar and the approved biological product in terms of safety, purity, and potency.

FDA News Release (December 16, 2015): FDA approves *Basaglar*, the first "follow-on" insulin glargine product to treat diabetes. Available at <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm477734.htm>.

Antihypertensives and Hip Fracture Risk

In a population-based study, treatment with an antihypertensive was associated with reduced risk of hip fracture in patients aged >60 years. Risk was reduced with most antihypertensive categories, but effects of loop diuretics and ACE inhibitors varied according to age.

Background: Both high blood pressure and systolic hypotension have been associated with falls, reduced bone mineral density (BMD), and hip fractures. Observational studies have shown an increased risk of falls and hip fractures after initiating antihypertensives. Meta-analyses, however, have not confirmed the finding—although most studies focused on diuretics and beta-blockers. The present cohort study evaluated the association between hip fracture and a wider range of antihypertensives.

Methods: Data on prescriptions dispensed in 2004–2010 and the occurrence of a first hip fracture beginning in 2005 were extracted from population-based health care registries covering the entire population of Norway. Study subjects were born before 1945 and living in Norway on January 1, 2005. Risk calculations were made overall and for 8 different categories of antihypertensives: thiazides; loop diuretics; beta-blockers; calcium channel blockers; ACE inhibitors; ACE inhibitor–thiazides; ARBs; ARB–thiazides. Standardized incidence ratios (SIRs; i.e., rate ratios* standardized to demographics of the Norwegian population) were

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calculated for each of the 8 categories. A standardized incidence ratio of <1 indicates reduced risk.

Results: The study cohort consisted of >900,000 people, with a mean age of 73 years in 2005. Mean follow-up was about 5 years. ARBs and beta-blockers were the most common antihypertensives, each used by about 30% of the cohort, followed by calcium channel blockers (22%).

Nearly 40,000 primary hip fractures occurred during follow-up, affecting 4.4% of the cohort. Most of the commonly used diuretics and combinations were associated with a significant reduction in fracture risk. (See table.) Loop diuretics and ACE inhibitors were associated with decreased fracture risk in persons born before 1925 and increased risk in persons born after 1924. The decrease in risk was larger in men than women for most drug categories, but gender-related differences were small. Risk was increased significantly for a new prescription of loop diuretics (SIR=1.6), but not for other categories.

Hip fractures during exposure to antihypertensive drugs, compared with periods of nonexposure			
Drug Category	Number of Fractures	SIR	Attributable Effect [†]
Thiazide	550	0.7	-0.6%
Loop diuretic	4752	1.0	0.1%
Beta blocker	4074	0.7	-3.5%
Calcium channel blocker	5028	0.8	-3.4%
ACE inhibitor	3438	0.9	-0.6%
ACE inhibitor-thiazide	662	0.7	-0.9%
ARB	2631	0.8	-1.9%
ARB-thiazide	2122	0.6	-3.6%

[†]Negative numbers indicate percent reduction in hip fractures attributable to drug exposure. Positive number indicates percent increase.

Discussion: Several types of antihypertensive have positive effects on mechanisms that maintain BMD: Thiazides reduce renal calcium depletion and stimulate osteoblasts; beta-blockers inhibit beta-adrenergic receptors in bone; and ACE inhibitors also have local effects in bone tissue.

ARBs and calcium channel blockers appear to have a neutral effect on mechanisms involved in bone health, and loop diuretics increase both calcium depletion and risk of falls. Despite the reassuring findings of the present study, prescribers should bear in mind older patients' greater vulnerability to hemodynamic effects and to follow the "start low and go slow" adage.

Ruths S, et al: Risk of hip fracture among older people using antihypertensive drugs: a nationwide cohort study. *BMC Geriatrics* 2015; doi 10.1186/s12877-015-0154-5. From the University of Bergen and Uni Research Health, Norway. **Source of funding not stated. The authors declared no competing interests.**

*See Reference Guide.

PPIs and Hypomagnesemia

According to results of an observational study, hypomagnesemia is a rare complication of proton pump inhibitor therapy. In addition, there are few reports of the complication in the literature. As a result, annual serum magnesium checks should be considered in elderly patients and in those on concurrent diuretics but appear to be unwarranted for the general patient population on PPI therapy.

Background: After several case reports linked profound hypomagnesemia and PPIs, the FDA recommended measuring serum magnesium before and periodically during treatment with these agents. The recommendation mentions no explicit time interval or whether monitoring should occur irrespective of risk factors. There have been few studies of serum magnesium changes in patients on PPIs.

Methods: The present study was carried out in 2 patient groups: 100 patients receiving long-term PPI therapy for Barrett's esophagus presenting consecutively for routine follow-up endoscopy, and 56 patients initiating PPI therapy. Serum magnesium was measured cross-sectionally in the long-term patients, and results were compared with pretreatment levels in the group initiating therapy, whose baseline characteristics served as the control group. Magnesium levels were also assessed longitudinally in the newly treated patients at 2, 4, and 8 months. In addition, urinary magnesium excretion was estimated by calculating the fractional excretion of magnesium relative to creatinine clearance.

Results: Patients receiving long-term PPI therapy had a mean age of 68 years and had an average treatment duration of 24 months. Mean serum

magnesium levels were identical in these patients and in the pretreatment controls (1.7 mEq/L). In addition, serum magnesium levels did not vary as a function of the duration of PPI therapy.

Longitudinally, there was no decline in average magnesium levels over the 8 months of follow-up in patients initiating PPI therapy. However, the 28 patients who attended all 4 follow-up visits experienced a slight but significant decline in magnesium ($p=0.02$ for the trend). No patient in this study experienced clinically relevant hypomagnesemia.

Discussion: The downward trend in magnesium levels in patients starting therapy coupled with the lack of incident hypomagnesemia cases suggests that PPI-induced hypomagnesemia may take many years to develop. Impairment of magnesium absorption is probably the mechanism for this effect. People with depleted magnesium stores, including the elderly, who may have limited dietary magnesium intake, are likely to be at greater risk of this complication.

Begley J, et al: Proton pump inhibitor associated hypomagnesaemia—a cause for concern? *British Journal of Clinical Pharmacology* 2015; doi 10.1111/bcp.12846. From Royal Bournemouth Hospital, UK; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

New Option for Treatment of Gout

Lesinurad, a new agent that inhibits uric acid reabsorption in the kidneys, has received FDA approval for use in combination with a xanthine oxidase inhibitor (e.g., allopurinol) to reduce high levels of uric acid associated with gout. In controlled trials involving >1500 patients, lesinurad was associated with reductions in uric acid. Common adverse effects included headache, influenza, increased creatinine levels, and GERD. The agent will carry a boxed warning about risk of acute kidney failure (which is more common when the agent is used at higher-than-usual doses and when used without a xanthine oxidase inhibitor), and postmarketing studies are required to evaluate the cardiovascular and renal safety of the agent.

FDA News Release (December 22, 2015): FDA approves Zurampic to treat high blood uric acid levels associated with gout. Available at <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm478791.htm>.

Common Drug Trade Names: allopurinol—*Zyloprim*; lesinurad—*Zurampic*

Neuropsychiatric Effects of Montelukast

According to an analysis of adverse drug events reported to VigiBase, the World Health Organization's global drug monitoring database, 60% of adverse event reports with the asthma medication montelukast (*Singulair*) are considered psychiatric or related to the central nervous system (CNS).

Background: Based on clinical trial data and case reports, the FDA issued an alert regarding psychiatric side effects of montelukast and related drugs in 2008. Elevated incidence of these adverse events has since been reported from several countries. The present study was conducted to explore the association worldwide.

Methods: The analysis included all case reports through January 1, 2015, in which montelukast, alone or as part of a multi-drug exposure, was associated with onset of psychiatric or CNS disorders in patients aged <18 years. The adverse events were examined in infants (aged <2 years), children (aged 2–11 years), and adolescents (aged 12–17 years) for all calendar quarters beginning in 1999 and continuing through January 2015.

Results: The database contained a total of 2630 case reports of a psychiatric disorder in young patients exposed to montelukast, including 114 in infants, 2007 in children, and 509 in adolescents. There were also 1225 additional reports of "nervous system disorders" in exposed children and adolescents. The most common disorders are listed in the table on the next page. Most of the reports included multiple psychiatric adverse events. The average time to onset varied from hours or days for sleep disorders and psychotic disorders, from 1 to several weeks for depression, and from months to years for the suicidal category.

There were statistically significant differences in reports of individual disorders across age categories. Children had the highest incidence of suicidal behavior, sleep disorders, and depressive and psychotic symptoms. The number of events in infants was too low to analyze except for sleep disorders, for which the incidence was significantly elevated. Incidence of depression/anxiety was similar in children and adolescents, and twice that found in adults.

Most common psychiatric disorders associated with montelukast in patients aged <18 years in VigiBase		
Disorder	Number of Cases	Percentage of Cases [†]
Personality disorders and disturbances in behavior	955	36%
Sleep disorders and disturbances	957	36%
Mood disorders and disturbances	955	36%
Anxiety disorders and symptoms	823	31%
Suicidal and self-injurious behaviors	674	26%
Depressed mood disorders and disturbances	608	23%

[†]Total percentage >100% because of reports listing multiple adverse events.

Of all VigiBase reports concerning pediatric suicidal and self-injurious behavior, 674 cases (10%) were linked with montelukast. The agent was associated with completed suicide in 35 patients. Completed suicide and suicide attempts were most often reported in adolescents, and suicidal ideation in children.

Discussion: Infants and children seem to be more prone to sleep disturbances and children to psychotic reactions with montelukast use, whereas adolescents are more prone to symptoms of depression/anxiety. Suicidal behavior

and completed suicide appear to occur more frequently than previously thought. Currently there is no biological explanation for the association of montelukast with psychiatric/ CNS adverse effects, and there continues to be a lack of well-designed epidemiologic studies that would shed further light on the link.

Perona A, et al: Psychiatric disorders and montelukast in children: a disproportionality analysis of the VigiBase. *Drug Safety* 2015; doi 10.1007/s40264-015-0360-2. From the Hospital Universitario de Canarias; and the University of La Laguna, Spain. **This study was conducted without funding. The authors declared no competing interests.**

Reference Guide

Rate Ratio: A comparison of the rates of a disease/event in two groups that differ by demographic characteristics or exposure history. The rate for the group of primary interest is divided by the rate for a comparison group.

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Orally Disintegrating Amphetamine Salts

Adzenys XR (extended-release mixed amphetamine salts) has received FDA approval as the first orally disintegrating extended-release product for the treatment of ADHD in children aged ≥ 6 years and adults. The agent was determined to be bioequivalent to *Adderall XR*, and will be available in the same 6 dosage strengths. *Adzenys XR* contains amphetamine in a mixture of immediate-release and polymer-coated delayed-release resin particles; it is not a generic version of *Adderall XR*. Product launch is expected after March 2016.

Neos Therapeutics announces FDA approval of *Adzenys XR ODT*[™] (amphetamine extended-release orally disintegrating tablet) for the treatment of ADHD in patients 6 years and older: first and only approved extended-release orally disintegrating tablet for the treatment of ADHD. [Press release]. Dallas and Fort Worth, TX: Neos Therapeutics, Inc.; Jan. 27, 2016.

Glucose Test Strips Recalled

Several lots of Arkray SPOTCHEM II Basic PANEL-1 Reagent Test Strips and SPOTCHEM II Glucose Reagent Test Strips have been recalled because of the possibility that they may report inaccurately low blood glucose levels. Although there have been no reports of illness, injury, or death associated with the false readings, they could cause hyperglycemia, diabetic ketoacidosis, and hyperosmolar hyperglycemic syndrome to go undetected; these complications can be fatal. Affected products include lots PN5C26 and EA4M78 distributed in Florida, Illinois,

Kentucky, Michigan, North Carolina, New York, Ohio, and Tennessee between February and October 2015.

FDA News Release (January 28, 2016): SPOTCHEM II test strips by Arkray: Class I recall – inaccurate blood sugar readings. Available at <http://www.fda.gov/medicaldevices/safety/listofrecalls/ucm483760.htm>.

Otitis Media: Guideline Update

An updated clinical practice guideline for diagnosis and treatment of otitis media with effusion (OME) in patients aged 2 months through 12 years is available from the American Academy of Otolaryngology—Head and Neck Surgery Foundation at http://oto.sagepub.com/content/154/1_suppl/S1.full. The new recommendations highlight "quality improvement opportunities" in such areas as diagnostic accuracy, identification of children most susceptible to developmental sequelae from the infections, and education of clinicians and parents about the favorable outcome of most OME and the lack of efficacy of medical therapy.

The guideline recommends using pneumatic otoscopy to document the presence of middle ear effusion and also to assess for OME in a child with otalgia, hearing loss, or both. The use of tympanometry is recommended in children with suspected OME that cannot be confirmed with pneumatic otoscopy. A subset of children—those with confirmed hearing loss; speech and language delay; autism spectrum disorder; Down syndrome and similar conditions; blindness; cleft palate; or developmental delay—are at risk for worsening

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of developmental difficulties with OME. These children should be evaluated for OME when their condition is diagnosed and again at age 12–18 months. Children who are not at risk for OME and do not have symptoms that might be attributable, such as hearing or balance symptoms or behavioral or school problems, should not be routinely screened. In otherwise healthy children, OME should be managed with 3 months of watchful waiting. Use of intranasal or systemic steroids, systemic antibiotics, antihistamines, or decongestants is not recommended.

Rosenfeld R, et al: Clinical practice guideline: otitis media with effusion executive summary (update). *Otolaryngology—Head and Neck Surgery* 2016;154 (February):201–214. From SUNY Downstate Medical Center, Brooklyn, NY; and other institutions. **Funded by the American Academy of Otolaryngology—Head and Neck Surgery Foundation. Six study authors declared financial relationships with commercial sources; the remaining 9 authors declared no competing interests.**

Ciprofloxacin/Asenapine Interaction

A 44-year-old woman with bipolar I disorder was admitted for worsening depression. She had been receiving 5 mg/day asenapine for 1.5 months prior to admission. Additional medications, continued on admission, included 20 mg/day baclofen, 60 mg/day dexlansoprazole, 20 mg/day fluoxetine, 1 mg/day lorazepam, and 2250 mg/day divalproex. A urinary tract infection detected on admission precipitated additional treatment with 500 mg ciprofloxacin b.i.d. Within 33 hours of starting ciprofloxacin, the patient was unable to close her jaw, which was consistent with an acute dystonic reaction. Treatment with 50 mg intramuscular diphenhydramine resolved the dystonia, and the antibiotic was switched to 100 mg nitrofurantoin b.i.d. with no further complications. The patient had previously experienced a severe dystonic reaction to haloperidol.

A potential interaction between ciprofloxacin and asenapine has not been previously reported. However, ciprofloxacin is a potent inhibitor of CYP1A2, the pathway via which asenapine is primarily metabolized, and interactions between it and other second-generation antipsychotics that are metabolized through this pathway have been reported. Other possible contributing factors to the reaction include the effects of inflammation/infection on CYP1A2, as well as potential inhibition of asenapine glucuronidation by divalproex. These may have exacerbated the patient's symptoms, but the dystonia was more likely related to ciprofloxacin as it was not noted until after the

drug was initiated. According to the Drug Interaction Probability Scale,* the likelihood of drug/drug interaction in this case is probable.

Ridout K, et al: Sudden-onset dystonia in a patient taking asenapine: interaction between ciprofloxacin and asenapine metabolism. *American Journal of Psychiatry* 2015;172 (November): 1162–1163. From Brown University, Providence, RI. **The authors declared no competing interests.**

Common Drug Trade Names: asenapine—*Saphris*; ciprofloxacin—*Cipro*; dexlansoprazole—*Dexilant*; divalproex—*Depakene, Depakote*; haloperidol—*Haldol*; fluoxetine—*Prozac*; lorazepam—*Ativan*; nitrofurantoin—*Macrobid, Macrochantin*

*See Reference Guide.

Opioid Prescribing

Based on a clinical review of available evidence, the CDC has issued a guideline for prescribing opioids for chronic pain in primary care settings. The guideline includes the following 12 specific recommendations. The complete guideline, which includes the rationale for each recommendation, can be found at <http://www.regulations.gov/#!documentDetail;D=CDC-2015-0112-0002>.

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are the preferred options for treatment of chronic pain.
2. Before starting opioid therapy for chronic pain, providers and patients should establish realistic goals for improvements in pain and function, and therapy should not be started without consideration of how it will be discontinued if unsuccessful.
3. Before starting and periodically during opioid therapy, providers should discuss the risks and benefits with patients, as well as the responsibilities of both patient and prescriber for managing therapy.
4. When starting therapy for chronic pain, immediate-release opioids should be prescribed rather than extended-release/long-acting opioids.
5. The lowest effective dose of opioids should be prescribed, and care should be taken when increasing dosage to ≥ 50 morphine milligram equivalents per day (MME/day). Dosage of ≥ 90 MME/day should be avoided.
6. Opioids should not be prescribed in greater quantities than needed for the expected duration of acute pain. A total of ≤ 3 days will usually be sufficient for most nontraumatic pain that is not related to major surgery.

7. Within 1 to 4 weeks of starting opioid therapy or of dose escalation, benefits and harms of treatment should be evaluated. Continued therapy should be re-evaluated at least every 3 months. If the benefits of treatment no longer outweigh potential harms, the opioid dosage should be reduced and then treatment discontinued.

8. Before starting and periodically during continuation of opioid therapy, prescribers should evaluate risk factors for opioid-related harms (e.g., history of overdose or substance use disorder, or higher opioid dosages [≥ 50 MME]). Strategies to mitigate these risks should be included in the treatment plan.

9. History of controlled substance prescriptions should be reviewed before starting and then periodically during opioid therapy to determine whether the patient is receiving high dosages or dangerous combinations that put him or her at high risk for overdose.

10. Urine drug testing should be completed before opioid therapy is started to assess for prescribed medications as well as other controlled prescription and illicit drugs. Repeated urine drug testing should be considered at least annually if opioids are continued.

11. Opioid pain medications should be avoided for patients receiving benzodiazepines whenever possible.

12. For patients with opioid use disorder, providers should offer or arrange treatment—usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies.

Dowell D, et al: CDC guideline for prescribing opioids for chronic pain—United States, 2016. Available at <http://www.regulations.gov/#!documentDetail;D=CD-2015-0112-0002>.

Zepatier Approved for Hepatitis C

A single tablet combination of the NS5A replication complex inhibitor elbasvir and the NS3/4A protease inhibitor grazoprevir (*Zepatier*) has received FDA approval to treat chronic hepatitis C genotypes 1 and 4 in adults.^{1,2} Hepatitis C affects about 3 million Americans. (Genotype 1 is the most common variant, while genotype 4 is the least common.) *Zepatier* received its approval under the "breakthrough therapy designation" program, which is designed to expedite development and review of drugs for serious conditions

when preliminary evidence indicates it may provide substantial improvement over currently available drugs.

In clinical trials of >1300 patients, rates of sustained viral response 12 weeks after finishing treatment ranged from 94% to 97% in patients with genotype 1 and from 97% to 100% in those with genotype 4. *Zepatier* can be used with or without ribavirin (*Rebetol*), and the product label includes recommendations for dosing and duration of treatment based specifically on individual characteristics of patients and their virus. Patients should be screened for viral genetic variations before starting *Zepatier* to determine dosage and treatment regimen, and the agent should not be used in patients with moderate or severe liver impairment.

Common adverse effects of *Zepatier* in clinical trials included fatigue, headache, and nausea in patients receiving monotherapy and anemia and headache in those also receiving ribavirin. Liver enzyme elevations to >5 times the upper limit of normal were also reported in about 1% of study patients. These typically developed after ≥ 8 weeks of treatment.

¹FDA News Release (January 28, 2016): FDA approves zepatier for treatment of chronic hepatitis C genotypes 1 and 4. Available at <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm483828.htm>.

²Merck receives FDA approval of ZEPATIER™ (elbasvir and grazoprevir) for the treatment of chronic hepatitis C virus genotype 1 or 4 Infection in adults following priority review. [Press release]. Kenilworth, NJ: Merck; January 28, 2016.

Flibanserin for Hypoactive Sexual Desire

The only FDA-approved treatment for hypoactive sexual desire disorder (HSDD), flibanserin can be considered for use in selected premenopausal women, according to a review. However, use should be limited to patients who are premenopausal; not pregnant; in stable, healthy relationships; willing to abstain from alcohol; and who do not take medications that may cause interactions.

Flibanserin was approved by the FDA in August 2015 for treatment of HSDD. The disorder is recognized by the American College of Obstetrics and Gynecology but has been dropped from the American Psychiatric Association's diagnostic manual, the DSM-5, where its symptoms were instead included in the criterion for female sexual interest/arousal disorder. Other treatments for

diminished sexual desire in women include off-label bupropion, transdermal testosterone (in postmenopausal patients), and various psychological treatments. Other medications and supplements, including sildenafil, have been shown to be ineffective.

Flibanserin addresses the proposed pathophysiology of HSDD, a relative deficiency in noradrenergic and dopaminergic activity and a relative excess in serotonergic activity in the prefrontal cortex. Flibanserin has a terminal half-life of about 11 hours and requires administration for 3 days to achieve steady-state levels. Because it may cause CNS depression leading to hypotension and dizziness, bedtime administration is required. Its availability is limited to a REMS (Risk Evaluation and Mitigation Strategy) program because of the risk of hypotension/syncope, which is increased with concomitant alcohol use. Patients should discontinue flibanserin after 8 weeks if they do not experience any benefit.

A total of 4 industry-sponsored phase III clinical trials of flibanserin have been conducted, along with an extension study, and a phase II pharmacokinetic trial. Three of the placebo-controlled trials were 24 weeks in duration, 1 was 48 weeks, and the extension trial lasted 1 year. Study participants experienced a strong placebo response but a marginal, statistically significant increase in the

average number of satisfying sexual events per month with flibanserin. A variety of secondary outcome measures also showed improvement, although inconsistently across trials. Flibanserin was generally well tolerated, with dizziness, somnolence, nausea, fatigue, and insomnia the most common adverse events. Some women became pregnant while participating in the trials, and several spontaneous abortions or other pregnancy complications occurred, but investigators did not attribute them to study medication.

Additional concerns regarding flibanserin include the use of industry-supported questionnaires in the trials, the possibility of unpublished negative trials, and the perception of external pressure on the FDA to approve the drug. There is also concern about possible off-label use, particularly in postmenopausal women, who may be more likely to take interacting medications and to experience dangerous falls as a result of dizziness.

Robinson K, et al: First pharmacological therapy for hypoactive sexual desire disorder in premenopausal women: flibanserin. *Annals of Pharmacotherapy* 2016; 50 (February):125–132. From the University of South Florida, Tampa. **This review was not funded. The authors declared no competing interests.** See related story in *Primary Care Drug Alerts* 2015;36 (September):35.

Common Drug Trade Names: bupropion—*Wellbutrin*; flibanserin—*Addyi*; sildenafil—*Viagra*

*See Reference Guide.

Reference Guide

Drug Interaction Probability Scale (DIPS): A tool similar to the Naranjo Probability Scale designed to evaluate the causation of an adverse event thought to be produced by the interaction between 2 drugs. Based on a score generated by answering 10 questions, the probability is assigned as doubtful, possible, probable, or highly probable. The DIPS is available online at <http://www.pmidcalc.org>

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Lixisenatide in Acute Coronary Syndrome

Cardiovascular morbidity and mortality are increased in patients with type 2 diabetes, particularly those with concomitant cardiovascular disease. The investigational glucagon-like peptide 1–receptor agonist lixisenatide (*Lyxumia*) reduces glycosylated hemoglobin levels in patients with type 2 diabetes. However, because there is insufficient evidence to determine its cardiovascular safety, a manufacturer-sponsored controlled trial evaluated cardiovascular events in treated patients with diabetes with high cardiac risk. In the study, lixisenatide, when added to other antidiabetic therapy, had a neutral cardiovascular profile.

Methods: Subjects (n=6068) with type 2 diabetes who had experienced an acute coronary event within 6 months of study screening were randomly assigned to once-daily subcutaneous injections of lixisenatide or placebo, in addition to other antidiabetic medication and excluding other incretin therapies. The primary study endpoint was a composite of death from cardiovascular causes and nonfatal MI, stroke, or unstable angina, after a median follow-up of 2 years.

Results: Cardiovascular events occurred in 406 patients in the lixisenatide group (13.4%) and 399 in the placebo group (13.2%), a nonsignificant difference. No difference was observed in rates of any of the 4 events that made up the composite endpoint, nor in the additional endpoints of hospitalization for heart failure or coronary revascularization.

Study Rating*—16 (94%): This study met most criteria for a randomized controlled trial; however, potential limitations and/or biases were not discussed.

Pfeffer M, et al: Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *NEJM* 2015;373 (December 3):2247–2257. From Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and other institutions. **Funded by Sanofi. Fourteen study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

*See Reference Guide.

ACE Inhibitors vs. ARBs

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are equally effective in the treatment of cardiovascular disease in patients without heart failure, according to a meta-analysis of decades of clinical trial data.

Background: Current treatment guidelines favor ACE inhibitors over ARBs but may be based on a biased interpretation of the data. ARB clinical trials were conducted a decade later than most ACE-inhibitor trials, during which time other treatment advances, such as more aggressive use of statins, antihypertensives, and cardiovascular risk factor control (including smoking cessation), led to better outcomes in the placebo groups.

Methods: All randomized clinical trials were identified of ACE inhibitors or ARBs compared with a placebo, an active control treatment, or each other. Studies were included if they had ≥100 participants, including a cohort without heart failure, and ≥1 year of follow-up. Study outcomes were

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all-cause mortality; cardiovascular death; MI; angina; stroke; heart failure; revascularization; new-onset diabetes; end-stage renal disease; doubling of serum creatinine; hyperkalemia; and drug withdrawal due to adverse events.

Results: The meta-analysis included 106 studies comprising >250,000 patients. Of 32 placebo-controlled ACE-inhibitor trials, only 18 were conducted after 2000 and 9 were conducted after 2005. All of the 18 placebo-controlled ARB trials were conducted after 2000, and 14 were conducted after 2005.

The rate of adverse cardiovascular outcomes in patients receiving placebo was lower in the ARB trials than the ACE-inhibitor trials. Compared with placebo, ACE inhibitors were associated with significantly lower risk of most poor outcomes. ARBs were not associated with reduced all-cause mortality, cardiovascular death, or MI. However, a sensitivity analysis limited to studies conducted after 2000, when ARBs first became available, showed no difference in outcomes between ACE inhibitors and ARBs. In the 8 head-to-head comparisons, ACE inhibitors and ARBs had similar outcomes. The only difference, which occurred in all analyses, was that rates of drug withdrawal for adverse events were higher with ACE inhibitors.

Discussion: The comparative safety of ACE inhibitors and ARBs has been a matter of debate, owing to most ACE-inhibitor trials being "positive" and most ARB trials being "negative." The authors suggest this difference may be driven entirely by the different placebo event rates in the trials.

Study Rating*—16 (89%): This study met most criteria for a systematic review / meta-analysis, but the source of funding was not included.

Bangalore S, et al: Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients without heart failure? Insights from 254,301 patients from randomized trials. *Mayo Clinic Proceedings* 2016;91 (January):51–60. From the New York University School of Medicine, NY; and other institutions. **Source of funding not stated. Three of the 6 study authors declared financial relationships with commercial sources.**

*See Reference Guide.

Beta-Agonist Exposure and Autism Risk

Fetal exposure to anti-asthmatic β -2-adrenergic agonist drugs was associated with increased risk of autism, according to a population-based study from Denmark. However, the overall risk of

autism is estimated to be small, and uncontrolled maternal asthma may also be harmful to the fetus.

Methods: The study cohort consisted of >600,000 children born in 1997–2006. They were singletons delivered between 23 and 43 weeks gestation. All children from the birth cohort with an autism spectrum disorder diagnosis before mid-2011 were identified and matched with up to 10 controls, based on month and year of birth. Exposure to β -2-agonists was determined from a drug prescription register that did not include hospital pharmacies and therefore did not include the off-label use of these agents as tocolytics in the third trimester. Exposure windows were the 90 days before conception and each trimester of pregnancy.

Results: A total of 5200 children with autism were identified. β -2 agonists were used in 3.7% of cases and in 2.9% of controls. Exposure to these drugs was associated with increased risk of autism (odds ratio,* 1.3). Risk estimates did not vary with exposure over the 3 trimesters of pregnancy, and adjusting for maternal asthma did not change the effect estimates.

Discussion: The association of β -2-agonists with childhood autism is plausible. These drugs can cross the placenta and affect the fetal brain by disrupting replication or differentiation of neurons. Their effects are not trimester-specific, and there may be multiple windows of vulnerability throughout pregnancy. However, an association on the order of that seen in the present study would explain <1% of autism cases in the population.

Gidaya N, et al: In utero exposure to β -2-adrenergic receptor agonist drugs and risk for autism spectrum disorders. *Pediatrics* 2016; doi 10.1542/peds.2015-1316. From Drexel University, Philadelphia, PA; and the University of Copenhagen, Denmark. **Funded by Drexel University. The authors declared no competing interests.**

*See Reference Guide.

Statin plus Vitamin D for Migraine

In a placebo-controlled trial, the combination of simvastatin (*Zocor*) and vitamin D reduced migraine frequency.

Methods: Study participants (n=57) had a \geq 3-year history of episodic migraines that occurred \geq 4 (but not \geq 15) days per month. Patients kept migraine diaries during a 12-week baseline period before receiving 24 weeks of randomized treatment with 20 mg simvastatin plus 1000 IU vitamin D3 b.i.d. or a double placebo. Patients continued

to use their prior prophylactic and abortive migraine treatments but were asked to keep their regimen as stable as possible during the study. The primary study outcome, measured using the migraine diaries, was change from baseline in the number of days with migraine at weeks 12 and 24. Response was defined as a $\geq 50\%$ reduction in migraine days.

Results: Simvastatin plus vitamin D was associated with a significantly greater change than placebo in the average number of days with migraine: -8 versus +1 at week 12, and -9 versus +3 at week 24. Response rates were 25–29% with active treatment versus 3% with placebo. Patients who received active treatment also used abortive medication on fewer days and in fewer doses compared with the placebo group.

Discussion: The most commonly used drugs for migraine prophylaxis—anticonvulsants, β -blockers, and tricyclic antidepressants—have adverse effects that may limit their use, including weight gain and cognitive alterations. Besides lowering cholesterol, statins have several effects that may be important in migraine: They improve endothelial function, reduce vascular wall inflammation, and may improve autonomic function and sympathetic reflex regulation. Protecting against vitamin-D deficiency may have additional antiinflammatory and vascular effects and may prevent statin-induced musculoskeletal pain. The present study lacked the statistical power to compare rates of adverse events, but the tolerability of active treatment and placebo were similar.

Buettner C, et al: Simvastatin and vitamin D for migraine prevention: a randomized, controlled trial. *Annals of Neurology* 2015;78 (December):970–981. From Beth Israel Deaconess Medical Center, Boston, MA; and other institutions. **Funded by Beth Israel Deaconess Medical Center; and other sources. Two study authors disclosed financial relationships with commercial sources as well as a patent application for the study-drug combination; the remaining 5 authors declared no competing interests.**

Antidepressants and Glycemic Control

In an epidemiologic study, treating depression with pharmacotherapy in patients with type 2 diabetes was associated with improved glycemic control.

Background: Major depression and diabetes often co-occur, and the relationship between the disorders is bidirectional—i.e., diabetes increases depression risk, and depression increases diabetes

risk. Patients with both disorders have particularly poor glycemic control and functioning.

Methods: Data for the study were extracted from electronic medical records from a primary care registry consisting of family medicine and general internal medicine practices affiliated with a U.S. academic health system. Study subjects were patients, aged 18–90 years, who had ≥ 1 clinical contact between July 2008 and July 2013. Medical records of patients with type 2 diabetes were examined for a diagnosis of depression recorded on ≥ 2 visits within a 12-month span and for treatment with any available antidepressant drug, regardless of dose, duration, or adherence. The analysis was adjusted for covariates including demographic characteristics, anxiety disorders, health behaviors, and any other identifiable factors that could confound the relationship among depression, its treatment, and glycemic control. The effects of antidepressant therapy on glycemic control were the primary outcome.

Results: The sample consisted of 1399 patients with type 2 diabetes (mean age, 62 years; 74% with obesity). Of these, 265 patients (19%) also had a diagnosis of major depression, 225 of whom (85%) received treatment with antidepressants and 40 who did not. Cardiovascular comorbidities were common. Anxiety disorders were present in 15% of patients with untreated depression, 21% of patients who received treatment, and in 1% of those with no depression. Comorbid medical conditions were not significantly associated with depression.

The proportion of patients who met the American Diabetes Association definition of glycemic control (i.e., glycated hemoglobin A1c level of $< 7\%$) was higher and the average A1c was lower in patients with treated depression than in those with untreated depression. (See table, next page.) After adjusting for all confounders considered to be associated with the disorder, depression treatment, or glycemic control (e.g., obesity, hyperlipidemia, hypertension, use of insulin or other diabetic medication, volume of health care utilization), patients with treated depression were significantly more likely to achieve A1c control than those with untreated depression (odds ratio,* 1.95). Anxiety was associated with lower A1c values and the prescription of insulin or oral hypoglycemics with higher values.

Percent A1c Control and Mean A1c Values			
	No depression (n=1134)	Untreated depression (n=40)	Treated depression (n=225)
Percent with A1c control	43%	35%	51%
Mean A1c value	7.76%	8.13%	7.41%

Discussion: There have been few randomized controlled trials of the effect of depression treatment on glycemic control. The present study shows an association but does not shed additional light on the directionality of the association. It is possible that some antidepressants directly affect glucose metabolism. Depression symptom severity was not measured in the study so it could not be determined whether glycemic control and depression relief were associated. In addition, the relatively small number of patients with both diabetes and depression who did not receive antidepressants may be cause for concern regarding the extent to which the results can be generalized.

Brieler J, et al: Antidepressant medication use and glycaemic control in co-morbid type 2 diabetes and depression. *Family Practice* 2016;33 (February):30–36. From St. Louis University School of Medicine, MO; and other institutions. **This study was conducted without funding. The authors declared no competing interests.**

*See Reference Guide.

Antihypertensive Nonadherence

Analysis of data from a longitudinal study of antihypertensive adverse effects found genitourinary symptoms to be the only symptom category that predicted nonadherence. These symptoms—specifically excessive urination and a decrease in sexual drive—may be used to screen patients at high risk of nonadherence.

Methods: In a cohort of 214 patients newly prescribed drug treatment for essential hypertension

or who restarted treatment after a ≥ 2 -month lapse, medication adverse effects were assessed every 3 months for 1 year using a subset of items from the Physical Symptoms Distress Index to record data on 24 known effects of antihypertensives. Symptoms were grouped into 7 categories: anticholinergic; GI; genitourinary; cardiopulmonary; functional; neuropsychiatric/cognitive; and miscellaneous (e.g., itching, weight gain, muscle cramps). Scores for the frequency and severity of each symptom were combined to provide an overall symptom distress score. Medication adherence was determined at each 3-month visit using pill counts. Nonadherence was defined as taking $< 80\%$ of prescribed medication.

Results: The most frequently prescribed antihypertensives were diuretics (40% of patients) and ACE inhibitors (32%). Adverse effects were reported by 86% of patients. Nonadherence showed only a modest association with the number of adverse effects or the overall symptom distress score. Only the genitourinary symptom category was significantly associated with taking a lower proportion of prescribed pills. Of the 4 specific symptoms in this group, excessive urination was associated with a 6.5% higher rate of discontinuation than the absence of this symptom. A reduced sexual drive was associated with a 7.6% higher rate of nonadherence ($p=0.01$). The 2 other symptoms in this category, urinating at night and erection problems, were not associated with poor adherence.

Tedla Y, et al: Drug side effect symptoms and adherence to antihypertensive medication. *American Journal of Hypertension* 2015; doi 10.1093/ajh/hpv185. From Northwestern University, Chicago, IL; and the University of Wisconsin at Madison. **Funded by the American Heart Association; and the University of Wisconsin. The authors declared no competing interests.**

Reference Guide

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.

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Fluconazole Safety in Pregnancy

Exposure to oral fluconazole (*Diflucan*) during pregnancy was associated with increased risk of spontaneous abortion in a nationwide, register-based cohort study from Denmark.

Background: Fluconazole owes its antifungal effect to inhibition of a fungal enzyme and can interfere with human CYP450 enzymes, which are expressed during in-utero development. Previous studies showed no association of oral fluconazole with fetal loss but were relatively small and may have lacked sufficient statistical power.

Methods: Data for the study were collected from national birth and healthcare registers. The study cohort included >1.4 million pregnancies that ended with a singleton live birth, stillbirth, or spontaneous abortion in 1997–2013. Pregnancies with exposure to oral fluconazole after the 7th week of gestation were matched with ≤4 unexposed control pregnancies with an equal probability of exposure. Spontaneous abortion was defined as pregnancy loss occurring between weeks 7 and 22 of gestation, and stillbirth as occurring at ≥23 weeks.

Results: A total of 147 spontaneous abortions occurred in 3315 pregnancies exposed to oral fluconazole during weeks 7–22, and 21 stillbirths occurred in 5382 pregnancies between 7 weeks and birth. Risk for spontaneous abortion was significantly increased in exposed pregnancies compared with matched control pregnancies

(hazard ratio,* 1.48). Stillbirth risk was also elevated (hazard ratio, 1.32), but the increase was not statistically significant. Risks of spontaneous abortion did not differ according to fluconazole dose. However, risks of stillbirth were significantly increased for high-dose fluconazole (hazard ratio, 4.10) but not low-dose fluconazole. The timing of treatment during pregnancy did not affect risk of either outcome.

Molgaard-Nielsen D, et al: Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. *JAMA* 2016;315 (January 5):58–67. From Statens Serum Institut, Copenhagen, Denmark. **Funded by the Danish Medical Research Council. The study authors declared no competing interests.**

*See Reference Guide.

Long-Term Tamoxifen and Dementia Risk

In a population-based cohort study, tamoxifen was associated with reduced risk of dementia in women with breast cancer.

Background: In experimental studies, estrogen has had neurotrophic and neuroprotective effects in the brain, providing a convincing rationale for estrogen replacement therapy in preventing and treating dementia. Tamoxifen is a partial agonist or antagonist of the estrogen receptor, depending on the target tissue.

Methods: The study was based on Taiwanese national health data covering nearly the entire population. The investigators identified >24,000 women, aged ≥20 years, newly diagnosed with breast cancer in 2000–2004 and free of dementia at the time. The cohort included >16,500 women

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who had received treatment with tamoxifen and >7600 who had not. A control group consisted of nearly 97,000 women without any type of cancer or dementia. Among the potential confounders included in the analysis were diabetes, hypertension, stroke, head injury, and different cancer treatments.

Results: Women with breast cancer had a median age of nearly 50 years when diagnosed. The mean follow-up was >7 years in women with breast cancer and >8 years in controls. Between 2% and 3% of each group had onset of dementia during follow-up.

The incidence of dementia in women with breast cancer was somewhat lower than in controls, but not significantly. Among women with breast cancer, dementia incidence was significantly lower in those who received tamoxifen than in those who did not (adjusted hazard ratio,* 0.83; $p < 0.05$). Tamoxifen use was not associated with increased incidence of dementia in separate comparisons of age groups 20–54 years or ≥ 55 years. The apparent benefit of tamoxifen was limited to women receiving treatment for ≥ 5 years, in whom the adjusted hazard ratio for dementia was 0.47 ($p < 0.001$) compared with breast cancer patients who did not receive tamoxifen.

Discussion: These study results do not support previously raised concerns that tamoxifen could increase dementia risk due to estrogen deprivation. The present study accounted for many potential confounders of the relationship, including a longer life expectancy in patients treated with tamoxifen and the adverse effects of chemotherapy and benzodiazepines on cognitive function.

Sun L-M, et al: Long-term use of tamoxifen reduces the risk of dementia: a nationwide population-based cohort study. *QJM: An International Journal of Medicine* 2016;109 (February):103–109. From Kaohsiung Armed Forces General Hospital, Taiwan; and other institutions. **Funded by the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence; and other sources. The authors declared no competing interests.**

Common Drug Trade Names: tamoxifen—*Nolvadex*, *Soltamox*

*See Reference Guide.

Suicide Risk with Zolpidem

Zolpidem (*Ambien*) was associated with a 2-fold elevation in risk of suicidal behavior in patients with or without a psychiatric diagnosis, according to results of a population-based case-control study.

Methods: Claims data were analyzed from a sample of 1 million patients covered by national health insurance in Taiwan. Cases ($n=2199$) were patients who had attempted or completed suicide between 2002 and 2011. Each case was matched with 10 controls who had no history of a suicide attempt. Zolpidem exposure before the suicide attempt was the major risk factor of interest.

Results: Significantly more cases than controls had received treatment with zolpidem—45% versus 13%. After adjustment for mental-health disorders, benzodiazepine and antidepressant use, insomnia, substance use, and medical comorbidity, the adjusted odds ratio* for a suicide attempt in zolpidem users was 2.08. Cumulative exposure to zolpidem was associated with greater risk, with an odds ratio of 2.81 in patients with ≥ 180 cumulative defined daily doses. Suicide risk was increased with zolpidem use in all age groups, but especially in those aged <25 years (odds ratio, 13.01). Risk was increased by a similar magnitude regardless of use or nonuse of antidepressants or benzodiazepines. Psychiatric and medical comorbidities did not appear to affect risk.

There were a total of 208 completed suicides in the study. After adjusting for multiple factors, zolpidem was associated with an odds ratio of 1.45 for death from suicide. Nearly 60% of suicide attempts were by poisoning, some likely involving zolpidem overdose.

Discussion: While these results demonstrate a significant association between zolpidem use and suicide, the causality of the association is unclear.

Sun Y, et al: Association between zolpidem and suicide: a nationwide population-based case-control study. *Mayo Clinic Proceedings* 2016;91 (March):308–315. From En Chu Kong Hospital, New Taipei, Taiwan; and other institutions. **Funded by the Taiwan Ministry of Health and Welfare; and other sources. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

Flibanserin: Benefits/Risks Reviewed

Despite its recent approval for treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women, flibanserin has minimal clinical benefits, potentially serious risks, and very low quality evidence supporting its efficacy and safety, according to a meta-analysis of published and unpublished clinical trials.¹

Methods: A comprehensive literature search identified all clinical trials of flibanserin, published or

unpublished, in any language, and that were conducted in women of any age. Eight randomized, double-blind, placebo-controlled trials comprising nearly 6000 women were identified and included in the meta-analysis; 3 of the studies were unpublished. All participants met the American Psychiatric Association's DSM-IV criteria for HSDD. Trials were conducted in the U.S., Canada, or Europe and included premenopausal women (6 studies) and postmenopausal women (2 studies). All studies used the number of satisfactory sexual events per month as a primary efficacy outcome.

Results: At baseline, participants had a mean of 2.5 satisfactory sexual events per month. Relative to placebo, flibanserin was associated with an average increase of 0.49 events per month. Average subjective ratings of improvement ranged from minimal to no change.

Several adverse effects had a higher incidence with flibanserin than placebo: dizziness, somnolence, nausea, and fatigue. Serious adverse events, including appendicitis, cholelithiasis, and concussion, were reported in 2 of the studies, in small percentages of patients. Concomitant use of flibanserin with alcohol or CYP3A4 inhibitors, such as fluconazole and oral contraceptives, can worsen adverse effects.

The quality of evidence for both efficacy and safety of flibanserin was rated as very low. Study publications were light on details; dropout rates were high; participants were not representative of all women who might be given the drug; efficacy endpoints changed during studies; and there was evidence of publication bias.

Editorial.² Flibanserin was presented for FDA review twice before receiving approval the third time. This occurred despite a lack of new efficacy data and a vote against approval by the FDA's regulatory clinical reviewers, which occurred in part because of evidence on flibanserin-related harms that was presented during the FDA hearings. In addition, substantial somnolence and dangerous hypotension due to interactions with alcohol and other drugs have been reported. A single study indicated little risk of impaired driving due to somnolence but identified additional risks of hypotension in poor metabolizers.

Discussion: Women with a wide range of concomitant diseases and medication use, as well as those not in a stable relationship, were excluded

from participation in the flibanserin trials, potentially limiting the generalizability of the findings. In addition, it is unclear to what extent they represent typical women with HSDD, given that they reported an average of 2.5 satisfying sexual events per month. Because patient selection for the conducted trials may not have been representative of the population for whom the drug was approved, uncertainties remain about flibanserin, which provides minimal improvement and substantial adverse-effect risk, in a real world setting.

Study Rating*—16 (89%): This study met most criteria for a systematic review / meta-analysis. However, the source of funding was not stated.

¹Jaspers L, et al: Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder in women: a systematic review and meta-analysis. *JAMA Internal Medicine* 2016; doi 10.1001/jamainternmed.2015.8565. From Erasmus University Medical Center, Rotterdam, the Netherlands; and other institutions. **Source of funding not stated. Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.** See related stories in *Primary Care Drug Alerts* 2015;36 (September):35 and 2016;37 (February):7–8.

²Woloshin S, Schwartz L: US Food and Drug Administration approval of flibanserin: even the score does not add up [editorial]. *JAMA Internal Medicine* 2016; doi 10.1001/jamainternmed.2016.0073. From the Dartmouth Institute for Health Policy and Clinical Practice and Dartmouth-Hitchcock Medical Center, Lebanon NH. **Both study authors disclosed financial relationships with commercial sources.**

Common Drug Trade Names: flibanserin—*Addyi*; fluconazole—*Diflucan*

*See Reference Guide.

Eluxadoline for IBS with Diarrhea

In 2 manufacturer-sponsored clinical trials, eluxadoline—a new drug with mixed opioid-receptor activity in the GI tract—was superior to placebo in patients with irritable bowel syndrome with diarrhea (IBS-D).

Methods: The trials were conducted at hundreds of medical centers in the U.S., Canada, and the U.K. Patients with IBS-D were randomly assigned to receive ≥ 26 weeks of 75 or 100 mg eluxadoline or placebo twice daily. Each day, patients recorded scores for abdominal pain, discomfort, bloating, stool consistency, and other symptoms of bowel function. The primary study endpoint was a composite response, defined as a $\geq 30\%$ reduction in the worst abdominal pain on $\geq 50\%$ of days and, on the same days, a stool consistency score of < 5 on the Bristol Stool Form scale. The endpoint was measured after 12 and 26 weeks. Patients were

followed for an additional 26 weeks after discontinuation to observe any withdrawal symptoms.

Results: A total of 2425 patients (mean age, 45 years) participated in the 2 studies. Study patients had an average of about 5 bowel movements per day and reported mean daily abdominal pain severity of 6 on a 10-point scale. More patients who received eluxadoline than placebo reported reaching the primary study endpoint at week 12: 26–27% with 75 mg eluxadoline b.i.d. and 100 mg b.i.d., respectively, compared with 17% of the placebo group ($p < 0.001$ for both). Results were similar at week 26 when 27–31% of the eluxadoline groups reached the primary endpoint compared with 19–20% of the placebo group ($p < 0.001$ for both). Patients who received eluxadoline also reported improvement in the secondary endpoints of stool consistency, frequency, and urgency, although not in episodes of incontinence. Both doses of eluxadoline were superior to placebo with regard to global symptom and quality-of-life ratings, but not ratings of the worst daily abdominal pain.

The most common adverse events reported with eluxadoline were nausea in 8% of patients, and constipation in 8%. Few patients discontinued treatment because of these effects. There were 13 cases of pancreatitis or abdominal pain with elevated hepatic enzymes, all of which were mild and resolved. Treatment discontinuation at end-of-study was not associated with worsening of IBS or with withdrawal symptoms.

Discussion: Eluxadoline is a peripherally acting agent with minimal systemic absorption. It has mixed effects on the 3 types of gut opioid receptors, reducing visceral hypersensitivity without completely disrupting intestinal motility. Its

efficacy seems on a par with alosetron and rifaximin, the other approved agents to treat IBS-D.

Lembo A, et al: Eluxadoline for irritable bowel syndrome with diarrhea. *NEJM* 2016;374 (January 21):242–253. From Harvard Medical School, Boston, MA, and other institutions including Furiex Pharmaceuticals, Morrisville, NJ. **Funded by Furiex Pharmaceuticals. Nine study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

Common Drug Trade Names: alosetron—*Lotronex*; eluxadoline—*Viberzi*; rifaximin—*Xifaxan*

ACP Guideline: Treating Depression

According to a new guideline from the American College of Physicians, there is moderate evidence suggesting second-generation antidepressants and cognitive behavioral therapy (CBT) are equally effective as monotherapy for major depression in adults. Low-quality evidence provides little support for combining the treatments. Conflicting evidence suggests there may be a slight increase in the rate of treatment discontinuation with antidepressants, compared with CBT, which probably has fewer adverse effects than medication. CBT is also associated with lower relapse rates than antidepressant therapy. In patients whose depression does not respond to an antidepressant, there is little evidence to support the options of switching among drugs, augmentation with another drug, or switching to or augmenting with CBT.

Qaseem A, et al for the Clinical Guidelines Committee of the American College of Physicians: Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine* 2016;164 (March 1):350–359. From the American College of Physicians, Philadelphia, PA, and other institutions. **Funded by the American College of Physicians. Three study authors disclosed financial relationships with commercial sources.**

Reference Guide

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.

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Generic *Crestor*

Watson Pharmaceuticals has received FDA approval to market the first generic formulation of rosuvastatin (*Crestor*). As with the branded drug, generic rosuvastatin is indicated in combination with diet for treatment of hypertriglyceridemia in adults and primary Type III hyperlipoproteinemia, as well as in combination with other cholesterol treatments or as monotherapy in homozygous familial hypercholesterolemia. The generic version is required to have the same quality and strength as the brand-name drug.

FDA News Release: FDA approves first generic *Crestor*. Available at <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm498373.htm>.

Aloe Vera for GERD

In a randomized pilot study, an aloe vera gel syrup reduced symptoms of gastroesophageal reflux disease.

Methods: In this open-label parallel-group trial, aloe vera was compared with 2 active medications: 20 mg/day omeprazole and 150 mg ranitidine b.i.d. Aloe vera was formulated for the study in a syrup with a standardized dosage and taken once a day. Study participants were 79 patients referred for evaluation of GERD. The primary efficacy outcome measure was the modified Reflux Disease Questionnaire, a patient-reported instrument that rates 8 different GERD symptoms.

Results: The frequency of GERD symptoms decreased with all 3 therapies at weeks 2 and 4.

With each of the 3 treatments, scores for all of the 8 symptoms (i.e., heartburn; food regurgitation; dysphagia; flatulence; belching; nausea; vomiting; acid regurgitation) were decreased by week 2; most decreases were statistically significant. Aloe vera was somewhat less effective than the other agents at treating heartburn, flatulence, and belching. Adverse events led to treatment discontinuations in 2 patients with ranitidine, 2 with omeprazole, and none with aloe vera.

Discussion: Pharmaceuticals are effective in treating GERD, but concerns over their safety have led to growing interest in natural remedies. Aloe vera is a plant with antioxidant, antiinflammatory, and analgesic properties. It also has antimicrobial activity against *H. pylori* and reduces gastric acid secretion. Aloe vera is also inexpensive, widely available in multiple preparations, and generally recognized as safe.

Panahi Y, et al: Efficacy and safety of Aloe vera syrup for the treatment of gastroesophageal reflux disease: a pilot randomized positive-controlled trial. *Journal of Traditional Chinese Medicine* 2015;35 (December 15): 632–636. From Baqiyatallah University of Medical Sciences, Tehran, Iran; and other institutions. **Funded by the Clinical Trial Research Center, Tehran. The authors did not include disclosure of potential conflicts of interest.**

Common Drug Trade Names: omeprazole—*Prilosec*; ranitidine—*Zantac*

DPP-4 Inhibitors and Heart Failure

An FDA safety review has found the DPP-4 inhibitors alogliptin and saxagliptin, marketed as monotherapies and in combinations with other antidiabetic medications, are associated with

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increased risk of heart failure, particularly in patients with pre-existing heart or kidney disease. In clinical trials, 3.5% of saxagliptin-treated patients and 3.9% of alogliptin-treated patients were hospitalized for heart failure, compared with 2.8% and 3.3% of placebo-treated patients. The FDA will now require added label warnings for these drugs. Symptoms of heart failure in these patients include unusual shortness of breath; trouble breathing while lying down; tiredness, weakness, or fatigue; and weight gain with swelling in the feet, ankles, legs, or stomach.

FDA MedWatch Alert: Diabetes medications containing saxagliptin and alogliptin: Drug safety communication—risk of heart failure. Available at <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm494252.htm>.

Common Drug Trade Names: alogliptin—*Nesina*; alogliptin-metformin—*Kazano*; alogliptin-pioglitazone—*Oseni*; saxagliptin—*Onglyza*; saxagliptin-metformin extended release—*Kombiglyze XR*

NSAIDs and Heart Failure

According to results of a meta-analysis of observational studies, nonsteroidal antiinflammatory drugs are associated with increased risk of heart failure.

Background: NSAIDs are among the most commonly prescribed medications in the U.S., despite their known risks. These drugs are believed to increase risk of heart failure as a result of blood-pressure elevation caused by vasoconstriction and fluid volume expansion, secondary to reduced prostaglandin synthesis.

Methods: The analysis included all observational studies (3 cohort and 4 case-control studies; total population of >7.5 million) published before April 2015 that investigated heart failure in patients taking conventional NSAIDs and/or selective COX-2 inhibitors.

Results: The overall relative risk* of new-onset heart failure in NSAID users was 1.17. Risk was consistently increased in all individual studies, although often without reaching statistical significance. The 5 studies of conventional NSAIDs showed a larger increase in relative risk (1.35). The 2 studies of COX-2 inhibitors showed a small increase in risk that was not statistically significant.

Discussion: It is important to note that most of the included studies were conducted in older populations (mean ages, 50–75 years), and the results

cannot be generalized to younger patients with low baseline cardiovascular risk.

Ungprasert P, Srivali N, Thongprayoon C: Nonsteroidal anti-inflammatory drugs and risk of incident heart failure: a systematic review and meta-analysis of observational studies. *Clinical Cardiology* 2015; doi 10.1002/clc.22502. From the Mayo Clinic, Rochester, MN; and Siriraj Hospital, Mahidol University, Bangkok, Thailand. **Source of funding not stated. The authors declared no competing interests.**

*See Reference Guide.

Asthma Inhaler Technique Errors

The Pulmojet, a recently introduced dry powder inhaler, may be easier to learn to use than other commonly available inhalers for patients switched to a new device, according to a manufacturer-sponsored study. After reading the devices' instructions, patients made fewer errors when using the Pulmojet for the first time, compared with the other inhalers.

Methods: Adults with asthma and/or COPD were studied in a single visit during which their current Diskus, Turbohaler, or pressurized metered-dose inhaler (pMDI) administration technique was assessed. Patients then repeated the procedure using an empty version of their current inhaler and again with 2 additional devices in a randomized, crossover sequence. (All randomized tests were conducted with empty inhalers.) Patients used the new devices after reading the manufacturers' information booklets, and those who made errors were shown an instructional video and tested again. Technique was evaluated by nurses and with an electronic inhalation profile recorder.

Results: A total of 421 patients completed the study. When tested using their current device, ≥ 1 serious error was made by 92% of patients using a pMDI, 39% of those using a Diskus, and 76% of those using a Turbohaler.

According to nurse observations, patients were more likely to have error-free use of the Pulmojet than the Diskus after reading the instruction leaflet and watching the video (78% vs. 61% with no errors; odds ratio,* 0.31). Error-free use was also more likely with the Pulmojet than the Turbohaler (74% vs. 48%; odds ratio, 0.2).

Discussion: Correct inhaler technique is fundamental for effective treatment of asthma and COPD, but errors in using these devices are common. Current guidelines suggest patients' inhaler technique should be assessed before increasing or changing therapy. The Pulmojet was

designed with features to optimize the delivery of active drug and to provide audio, visual, and sensory feedback to improve ease of use.

Chrystyn H, et al: Comparison of serious inhaler technique errors made by device-naive patients using three different dry powder inhalers: a randomised, crossover, open-label study. *BMC Pulmonary Medicine* 2016; doi 10.1186/s12890-016-0169-5. From Inhalation Consultancy Ltd., U.K., and other institutions. **Funded by Zentiva, Prague, Czech Republic. All study authors disclosed financial relationships with commercial sources.**

*See Reference Guide.

Tdap Booster: Low Effectiveness

The 2014 California pertussis outbreak occurred despite routine booster Tdap vaccination in adolescents who received acellular pertussis vaccines as children, according to an analysis of data from a large health plan. The Tdap booster was protective for only the first year after vaccination, after which protection waned rapidly to low levels.

Background: The U.S. switched from whole-cell to acellular pertussis vaccines in the 1990s and now vaccinates children with the diphtheria-tetanus-acellular pertussis (DTaP) vaccine. A booster vaccination with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) is recommended in early adolescence. Because DTaP-conferred immunity wanes rapidly in school-age and younger children, there is now a cohort of young people that relies on the DtaP booster for protection against pertussis.

Methods: Data from the Kaiser Permanente Northern California health plan, which covers about 3.5 million subscribers, were analyzed to evaluate vaccine effectiveness in patients who had exclusively received DTaP vaccines in infancy and childhood. Study subjects were born in the mid-to-late 1990s or later. The follow-up period included 2 large pertussis outbreaks, in 2010 and 2014. Cases were patients who tested positive for pertussis by real-time polymerase chain reaction.

Results: The age-specific incidence of pertussis peaked at age 10–11 years during each outbreak. In the 2010 outbreak, pertussis incidence declined rapidly after the peak ages and stayed low at older ages, a decline that the authors attributed both to the use of whole cell pertussis vaccine in childhood and to Tdap booster vaccination.

Pertussis incidence in the 2014 outbreak declined rapidly in 12 year olds, who had recently received the Tdap vaccine, but was higher in 14–16 year olds, despite Tdap coverage rates close to 90%.

Rates of pertussis were low in 18–19 year olds, an age cohort that would have received whole-cell pertussis vaccine in childhood. Tdap vaccine effectiveness decreased every year after vaccination, from 69% in year 1 to 57% in year 2, 25% in year 3, and 9% in year 4 or later. Pertussis infections were mild to moderate in severity, regardless of Tdap status; there were no hospitalizations or fatalities.

Klein N, et al: Waning Tdap effectiveness in adolescents. *Pediatrics* 2016; doi 10.1542/peds.2015-3326. From Northern California Kaiser Permanente Vaccine Study Center, Oakland, CA. **Funded by Kaiser Permanente. Two study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

Benzodiazepines and Dementia Risk

Results of a population-based cohort study do not support a causal association between dementia and benzodiazepine use.

Background: Studies have shown that benzodiazepines may impair memory and attention; however, it remains uncertain whether long-term use is associated with global cognitive decline. Evaluating the relationship is challenging because dementia can be preceded by insomnia, anxiety, and depression, all of which can be treated with benzodiazepines. Research on the cognitive risks of long-term use has had conflicting results.

Methods: The study was conducted within an integrated healthcare delivery system in the northwestern U.S. Participants were a random sample of plan members, aged ≥ 65 years, living in the Seattle area, who did not have dementia at baseline. The analysis was limited to persons who had ≥ 10 years of plan membership and had a valid cognitive score at baseline. Participants were followed until the onset of dementia, disenrollment from the health plan, or last study visit before October 2012. Cognition was measured every 2 years using the Cognitive Abilities Screening Instrument to screen for dementia and to calculate a cognitive trajectory. Patients whose scores fell below a threshold underwent a standardized diagnostic evaluation, and diagnoses of dementia and Alzheimer's disease were made using standard research criteria. Benzodiazepine use was ascertained from prescriptions filled during the 10 years before dementia onset or end of study, excluding the most recent year, which could have been for treatment of prodromal symptoms of dementia. Use was categorized as low, medium, or high based on

the distribution of exposure and clinically meaningful cutpoints. The highest level of exposure was equivalent to a total of >4 months of use, which could have been continuous or intermittent.

Results: The 3434 study participants had a median age of 74 years at study entry, and 60% were women. A total of 30% had filled ≥ 1 benzodiazepine prescription. The mean follow-up was 7.3 years, during which 23% of participants had onset of dementia.

No association was found between dementia and the highest level of benzodiazepine exposure, relative to non-exposed individuals (hazard ratio,* 1.07). There was a slight, but not statistically significant, increase in risk of dementia in patients with ≤ 1 month of exposure (hazard ratio, 1.25) and those with 1–4 months of exposure (hazard ratio, 1.31). This slight increase could represent treatment of prodromal symptoms. Results were similar for Alzheimer's disease, which represented about 80% of all dementia diagnoses. Cognitive trajectories did not differ according to benzodiazepine use.

Discussion: Although these results do not support a causal relationship between benzodiazepine use and incident dementia or cognitive decline, given the known adverse effects of these agents in the elderly, the authors suggest that avoiding their use in this population might be prudent.

Gray S, et al: Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. *BMJ* 2016; doi 10.1136/bmj.i90. From the University of Washington School of Pharmacy, Seattle; and other institutions. **Funded by the NIH; and the Branta Foundation. Four study authors disclosed financial relationships with commercial sources; the remaining 4 authors disclosed no competing interests.**

*See Reference Guide.

Opioids and Depression Risk

Patients taking long-term opioid analgesics are at increased risk of new-onset depression, according to an analysis of 3 large databases.

Methods: Data were analyzed from electronic medical records from the Veterans Health Administration (VHA) and from 2 large regional health systems. The analysis included adults with no opioid use and no diagnosis of depression, cancer, or HIV who were given a prescription for an opioid during follow-up. Patients were followed until the onset of depression or the end of study; 2002–2012 for the VHA and 2005–2012 for the private health systems.

Results: The sample consisted of about 71,000 veterans and nearly 37,000 patients from the 2 private health systems. Minorities of each sample received opioid analgesics for >30 days (7–22%). In each of the 3 samples, rates of depression increased with longer duration of opioid use. Based on the VHA data, which is the most complete in terms of covariates, depression can be expected to develop in 1 in 12 patients receiving opioid medication for >90 days. Incidence of depression was not associated with opioid dosage.

Discussion: The study authors suggest that long-term opioid use may lead to hyperalgesia and subsequently to depression. It is also possible that consequences of chronic opioid analgesic use, such as low testosterone and opioid misuse, could be involved in new-onset depression.

Scherrer J, et al: Prescription opioid duration, dose, and increased risk of depression in 3 large patient populations. *Annals of Family Medicine* 2016;14 (January / February):54–62. From St. Louis University School of Medicine, MO; and other institutions. **Funded by the NIMH; and the VHA. The authors declared no competing interests.**

Reference Guide

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.

Relative Risk: 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.

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Canagliflozin Safety

Interim results from the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) indicate an increased incidence of leg and foot amputations in patients with diabetes who receive the sodium-glucose cotransporter-2 (SGLT2) inhibitor canagliflozin (*Invokana*, *Invokamet*). It has not yet been determined whether the increased risk can be attributed to canagliflozin use, but the FDA is investigating the issue. In the meantime, patients receiving canagliflozin should be closely monitored for new pain or tenderness, sores or ulcers, or infections in their legs or feet.

FDA MedWatch Alert: Canagliflozin (Invokana, Invokamet): Drug Safety Communication - Clinical Trial Results Find Increased Risk of Leg and Foot Amputations. Available at <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm501565.htm>.

Sumatriptan Burns

Reports of serious burns and permanent scarring with the sumatriptan iontophoretic transdermal system (*Zecuity*), approved for treatment of migraine headaches, have led the FDA to launch a safety investigation. The transdermal system is designed to deliver sumatriptan via a single-use, battery-powered patch that is to be wrapped around the upper arm or thigh. *Zecuity* patches should not be worn for >4 hours, and patients should not bathe, shower, or swim while wearing the patch. Adverse events reported by a large number of patients include severe redness; pain; skin discoloration; blistering; and cracked skin.

Patients who report moderate-to-severe pain at the patch site should remove the patch immediately, and a different sumatriptan formulation or an alternate migraine medication should be considered. Teva Pharmaceuticals, the manufacturer of *Zecuity*, has temporarily suspended sales and distribution of the product.

FDA MedWatch Safety Alert: Zecuity (sumatriptan) Migraine Patch: Drug Safety Communication - FDA Evaluating Risk of Burns and Scars. Available at <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm504736.htm>.

Proton Pump Inhibitors and Dementia

In an analysis of data from a German claims-based study of elderly patients, proton pump inhibitor (PPI) use was associated with a nearly 50% increase in risk of dementia.

Methods: Analyses were conducted using a database of patients insured by the largest German health insurer from 2004 through 2011. Patients were aged ≥ 75 years and free of dementia at both study entry and 1-year follow-up. Regular PPI use was defined as prescriptions covering an 18-month period. Analyses were adjusted for age; gender; polypharmacy with ≥ 5 additional drug prescriptions; depression; stroke; ischemic heart disease; and diabetes.

Results: Of >200,000 study patients, nearly 74,000 met inclusion criteria and were enrolled in the study. Of these, approximately 30,000 had onset of dementia during follow-up. Nearly 3000 patients regularly used a PPI. Omeprazole was the most commonly used by far (45%), followed

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by pantoprazole (22%) and esomeprazole (10%). Regular use of PPIs was associated with a significant increase in risk of dementia (adjusted hazard ratio,* 1.44; $p < 0.001$). PPI-associated risk was elevated in men and women and in all age groups. PPI-associated risk was further increased in the presence of depression, stroke, and to a lesser degree diabetes. Risk was slightly reduced in patients with ischemic heart disease, perhaps because they were receiving protective antihypertensive drugs. Dementia risk was elevated with each of the 3 most common PPIs in separate analyses. Risk was elevated modestly in patients with only occasional use of PPIs, compared with non-users (hazard ratio, 1.16).

Discussion: The mechanism for the association between PPI use and dementia is unknown, but PPIs are known to cross the blood-brain barrier and interact with brain enzymes. In animal models, PPI exposure has been associated with increased beta-amyloid levels in the brain.

Gomm W, et al: Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurology* 2016; 73 (April): 410–416. From the German Center for Neurodegenerative Diseases, Bonn, Germany; and other institutions. **This study was conducted without external funding. The authors declared no competing interests.**

Common Drug Trade Names: esomeprazole—*Nexium*; omeprazole—*Prilosec*; pantoprazole—*Protonix*

*See Reference Guide.

Ketoconazole Death with Off-Label Use

In 2013, the FDA removed the indication for treatment of skin and nail infections from oral ketoconazole (*Nizoral*), because the risks for liver injury, adrenal problems, drug interactions, and death outweighed the benefits of treatment. Topical ketoconazole formulations have not been associated with these potential risks and remained indicated for fungal skin and nail infections. A recent drug safety review found that oral ketoconazole continues to be prescribed for these types of infections and that this off-label use led to the death of 1 patient who experienced liver failure. In otherwise healthy patients, skin and nail infections are not life-threatening; oral ketoconazole should be prescribed only for serious fungal infections when no other antifungal agent is available.

FDA MedWatch Alert: Nizoral (ketoconazole) Oral Tablets: Drug Safety Communication - Prescribing for Unapproved Uses including Skin and Nail Infections Continues; Linked to Patient Death. Available at <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm502073.htm>.

Pioglitazone After Stroke

In a large, international clinical trial, treatment with pioglitazone (*Actos*) following a stroke reduced risk of recurrent stroke and MI by 24% in nondiabetic, insulin-resistant patients.¹

Background: Insulin resistance in the absence of diabetes is present in up to half of patients who experience ischemic stroke or transient ischemic attack (TIA) and increases the risk of vascular disease. The present study was undertaken to investigate whether improving insulin sensitivity with pioglitazone would have a protective effect against MI or stroke.

Methods: The multicenter IRIS (Insulin Resistance Intervention after Stroke) trial enrolled nearly 4000 patients, aged ≥ 40 years, who had experienced an ischemic stroke or TIA in the previous 6 months. Participants were required to be nondiabetic, but to have insulin resistance, defined as a HOMA-IR (homeostasis model assessment of insulin resistance) index value of 3.0, a cutoff that identifies the highest diabetes risk quartile among individuals without diabetes. Patients with heart failure were excluded. Participants were randomized to up to 5 years of treatment with pioglitazone, flexibly dosed to a target of 45 mg/day, or placebo. The primary outcomes were stroke and MI.

Results: The median time from initial stroke or TIA to the start of randomized treatment was 80 days. Participants had a mean HOMA-IR of about 4.6 and a mean baseline HbA1c of 5.8%. About 6% had an HbA1c of $\geq 6.5\%$, meeting the cutoff included in the American Diabetes Association's 2010 diagnostic criteria for diabetes. At the 5-year study endpoint 60% of the pioglitazone group remained available and were still receiving treatment. More pioglitazone patients discontinued treatment because of edema and weight gain.

The primary outcome of stroke or MI occurred in 9% of the pioglitazone group, compared with 12% of the placebo group (hazard ratio,* 0.76; $p = 0.007$). The rate of progression to diabetes was also reduced by about half in the pioglitazone group (hazard ratio, 0.48; $p < 0.001$). Pioglitazone was associated with a mean weight gain of 5.7 lbs, compared with a 1-lb weight loss with placebo at 4 years, when the between-group weight difference was largest. Pioglitazone was also associated with higher rates of edema (36% vs. 25%; $p < 0.001$) and serious fracture requiring

hospitalization or surgery (5% vs. 3%; $p=0.003$). Pioglitazone was also associated with shortness of breath, but rates of heart failure were the same in the 2 groups.

Discussion: Although the mechanism is unclear, the study results suggest that administering pioglitazone to 100 patients similar to those selected for study for 5 years could prevent an estimated 3 strokes or MIs. However, the benefits might be offset by serious bone fractures that could be expected in 2 of 100 patients.

Editorial.² Although the study results are promising, widespread prescribing of pioglitazone for secondary prevention is premature given the restrictive enrollment criteria for this study, along with the potential for weight gain, edema, and serious fractures with pioglitazone.

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

¹Kernan W, et al: Pioglitazone after ischemic stroke or transient ischemic attack. *NEJM* 2016; doi 10.1056/NEJMoa1506930. From Yale University, New Haven, CT; and other institutions. **Funded by the National Institute of Neurological Disorders and Stroke. Twelve study authors disclosed potentially relevant financial relationships, including 9 with commercial sources; the remaining 15 authors declared no competing interests.**

²Semenkovich C: Insulin resistance and a long, strange trip [editorial]. *NEJM* 2016; doi 10.1056/NEJMe1600962. From Washington University, St. Louis, MO. **The authors disclosed financial relationships with commercial sources.**

*See Reference Guide.

Antidiabetic Drug Interactions

Patients with type 2 diabetes often require polypharmacy to lower blood glucose levels and/or to treat cardiovascular or other problems. Polypharmacy places these patients at risk for adverse drug interactions involving antidiabetic drugs. According to a comprehensive literature review, among antidiabetic drug categories, the most common clinically relevant drug/drug interactions occur with metformin, sulfonylureas, meglitinides, and thiazolidinediones.

Metformin is recommended as first-line therapy in part because of its safety, but risk of lactic acidosis precludes its use within 48 hours before or after the ingestion of iodinated contrast materials. Caution is also required when prescribing metformin with some other renally eliminated drugs, such as cimetidine, procainamide, trimethoprim, digoxin, amiloride, quinine, quinidine, ranitidine, vancomycin, and cephalexin.

Anticholinergics can increase the oral bioavailability of metformin by altering GI motility, again requiring caution.

Sulfonylureas are primarily metabolized by the hepatic enzyme CYP2C9, as are about 100 other clinically used drugs. Drugs that induce CYP2C9, such as carbamazepine, rifampicin, and St John's wort, reduce sulfonylurea levels. Other drugs including amiodarone, ranitidine, and many antibiotics prolong sulfonylurea degradation and increase drug levels. Clarithromycin and verapamil can increase levels of glyburide by inhibiting the GI drug transporter P-glycoprotein.

Meglitinides are prone to pharmacokinetic interactions via the same mechanisms as sulfonylureas, but they are used far less frequently and interactions are of minor clinical importance.

Of the thiazolidinediones, pioglitazone is the only agent widely used in the U.S. Pioglitazone is metabolized by CYP2C8 and, to a lesser extent, by CYP3A4. Drugs including rifampicin, ketoconazole, and fluvoxamine inhibit CYP2C8, requiring close monitoring. Gemfibrozil administration requires halving of the pioglitazone dose.

Several drugs affect the efficacy of antidiabetic drugs in general. Thiazide diuretics decrease their efficacy by increasing insulin resistance and reducing potassium, which increases plasma glucose concentrations. Antimicrobials and glucocorticoids have negative effects on glucose metabolism. Drugs that induce weight gain, such as antipsychotics, may worsen glucose tolerance and seemingly decrease antidiabetic drug efficacy.

May M, Schindler C: Clinically and pharmacologically relevant interactions of antidiabetic drugs. *Therapeutic Advances in Endocrinology and Metabolism* 2016;7 (April):69–83. From Hannover Medical School, Germany. **This research was conducted without funding. The authors declared no competing interests.**

Common Drug Trade Names: amiodarone—*Cordarone*; carbamazepine—*Tegretol*; cephalexin—*Keflex*; cimetidine—*Tagamet*; clarithromycin—*Biaxin*; fluvoxamine—*Luvox*; gemfibrozil—*Lopid*; glyburide—*Glynase*; metformin—*Glucophage*; pioglitazone—*Actos*; ranitidine—*Zantac*; rifampicin—*Rifampin*; verapamil—*Calan*

Suicidal Behavior with Quinolones

Quinolone antibiotics were associated with suicidal behavior in a pharmacovigilance study of worldwide adverse-event reports.

Background: The reporting of several cases has raised concerns that exposure to quinolones may

be associated with suicidal behavior. To investigate further, the present study examined data from the World Health Organization's VigiBase database, which collects spontaneous adverse event reports from health professionals, pharmaceutical companies, and patients in 110 countries.

Methods: All adverse event reports involving antibiotic exposure between December 1970 and January 2015 were included in the analysis. Odds ratios* for suicidal behavior were compared between quinolone users and users of other antibiotics. The 4 most frequently prescribed quinolones—ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin—were also analyzed separately. Results were adjusted for both age and gender.

Results: Among nearly 1 million antibiotic-associated adverse events, there were 1627 reports of suicidal behavior. In quinolone users, 608 instances of suicidal behavior were reported, including 97 completed suicides. The majority of cases (93%) were reported after 2000, and most occurred in the U.S. and Europe (61% and 37%, respectively). Compared with other antibiotics, quinolones were associated with a higher risk of suicidal behavior (adjusted odds ratio, 2.78). Risks were significantly elevated for each of the 4 most commonly prescribed quinolones, with adjusted odds ratios ranging from 2.84 for moxifloxacin to 4.01 for ciprofloxacin. Compared with other antibiotics, quinolone exposure was also associated

with higher rates of depression (odds ratio, 4.15) and completed suicide (odds ratio, 1.56).

Quinolone-related suicidal adverse events were equally distributed across gender. The mean age of patients with suicidal behavior was 40 years, and half of cases occurred in patients aged 45–64 years. In patients aged <17 years, risk of suicidal behavior was slightly elevated and risk of completed suicide was significantly elevated (odds ratio, 8.96).

Discussion: It is unclear whether suicidal behavior is an independent adverse effect or secondary to these drugs' potential psychiatric effects. Quinolones inhibit GABA-mediated inhibitory neurotransmission, possibly leading to anxiety; and they cause neuroexcitation, perhaps by activating NMDA receptors. Some quinolones have been shown to decrease serotonin levels in the brain and induce oxidative stress. These drugs may also alter expression of microRNAs, which may be linked to depression.

Samyde J, Petit P, Hillaire-Buys D, Faillie J-L: Quinolone antibiotics and suicidal behavior: analysis of the World Health Organization's adverse drug reactions database and discussion of potential mechanisms. *Psychopharmacology* 2016; doi 10.1007/s00213-016-4300-3. From CHU Montpellier University Hospital and the University of Montpellier, France. **This study was conducted without funding. The authors declared no competing interests.**

Common Drug Trade Names: ciprofloxacin—*Cipro*; levofloxacin—*Levaquin*; moxifloxacin—*Avelox*; ofloxacin—*Floxin*

*See Reference Guide.

Reference Guide

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.

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.

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Melatonin for Migraine Prevention

In a randomized controlled trial, melatonin was well tolerated and effective for migraine prevention.

Methods: Study participants were adults with a ≥ 1 -year history of migraine who experienced ≥ 3 attacks or ≥ 4 migraine days per month. Those unable to discontinue other migraine medications were not enrolled. After a 4-week screening period, patients were randomly assigned to receive 3 mg/day melatonin, 25 mg/day amitriptyline (*Elavil*) as an active comparator, or placebo. Study medications were taken at bedtime. Patients recorded headaches in a diary for the 12-week study duration. The primary outcome measure was the change in migraine frequency from baseline to the last 4 study weeks.

Results: A total of 178 patients received study medication. The mean number of migraine days per month at baseline was 7. Both melatonin and amitriptyline significantly reduced the number of migraine days compared with placebo. During the last 4 study weeks, patients receiving placebo averaged 6.2 migraine days, compared with 4.6 migraine days in those receiving melatonin and 5 in those receiving amitriptyline ($p < 0.05$). In addition, melatonin was superior to both placebo and amitriptyline in the proportion of patients who met response criteria ($\geq 50\%$ decrease in headache frequency): 54% versus 20% and 39%, respectively. The 2 active treatments had similar effects on secondary outcomes: headache intensity, duration, and number of analgesics taken.

About 25–31% of each group discontinued treatment, usually as a result of adverse events. A total of 46 events were reported by patients taking amitriptyline, 16 by the melatonin group, and 17 by the placebo group. Daytime sleepiness was reported by 11 patients taking melatonin and 24 taking amitriptyline. Unexpectedly, patients in the melatonin group experienced a small weight loss (< 0.5 lb), while the placebo and amitriptyline groups gained small amounts.

Discussion: The investigators used the relatively low amitriptyline dose recommended in Brazil, where the study took place. A higher dose is usually prescribed in the U.S., which would provide greater efficacy but likely increase the dropout rate.

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

Goncalves A, et al: Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. *Journal of Neurology, Neurosurgery and Psychiatry* 2016; doi 10.1136/jnnp-2016-313458. From Albert Einstein Hospital, Sao Paulo, Brazil; and other institutions. **Funded by the Fundacao de Amparo a Pesquisa do Estado de Sao Paulo. The authors declared no competing interests.**

*See Reference Guide.

Buprenorphine Implants

The FDA has granted approval for the first buprenorphine implant (*Probuphine*) to be used as maintenance treatment for opioid dependence. The implant provides a low dose of buprenorphine over 6 months and should only be used in patients whose treatment is already stable with

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low-to-moderate oral doses. Potential advantages of this new formulation include improved convenience, as well as the impossibility of lost, forgotten, or stolen doses. *Probuphine* should only be used as part of a treatment program that also includes counseling and psychosocial support.

Probuphine consists of four, 1-inch-long rods that are implanted under the skin on the inside of the upper arm. If continued treatment is needed after 6 months, new implants may be inserted in the opposite arm for 1 additional course of treatment. Common adverse effects reported with *Probuphine* include implant-site pain, itching, and redness; headache; depression; constipation; nausea; vomiting; back pain; toothache; and oropharyngeal pain. The *Probuphine* label will carry a boxed warning about the possibility of implant migration, protrusion, expulsion, and nerve damage resulting from the implant itself or from the removal procedure. Because the implants contain a significant amount of drug that could be expelled or removed, the potential exists for accidental exposure or intentional misuse and abuse. Patients should be seen within 1 week of implantation and not less than monthly thereafter. *Probuphine* must be prescribed and dispensed under a Risk Evaluation and Mitigation Strategies (REMS) program.

FDA News Release: FDA approves first buprenorphine implant for treatment of opioid dependence. Available at <http://www.fda.gov/newsevents/newsroom/press-announcements/ucm503719.htm>.

Smoking-Cessation Product Safety

In a large safety trial mandated by the FDA and funded by the drug manufacturers, varenicline and bupropion were not associated with increased risk of neuropsychiatric adverse events compared with nicotine patches or placebo. The drugs were safe and effective for smoking cessation in patients with or without psychiatric disorders.

Background: The present multinational post-marketing trial was undertaken as a result of concern about reported neuropsychiatric events, such as suicidality and aggression, as well as the limitations and potential biases of earlier studies supporting the safety of smoking-cessation medications.

Methods: Study participants, aged 18–75 years (n=8144; mean age, 47 years; 44% men), smoked ≥ 10 cigarettes per day and were motivated to quit. Nearly half of participants had a diagnosis of a psychiatric disorder—i.e., mood disorder; anxiety

disorder; schizophrenia or schizoaffective disorder; or borderline personality disorder. Those with alcohol and other drug-use disorders, as well as those who were clinically unstable or at high risk of suicidal behavior, were excluded. Within non-psychiatric and psychiatric cohorts, participants were randomly assigned to treatment, with about 1000 patients per group. In the psychiatric cohort, treatment groups were balanced by illness category. Randomly assigned treatments were targeted to: 1 mg varenicline b.i.d.; 150 mg sustained-release bupropion b.i.d.; nicotine patches (21 mg/day); or placebo. In a triple-dummy design, all patients took 2 pills/day and used active or inactive patches. Participants set a quit date 1 week after randomization, received treatment for 12 weeks, and had an additional 12 weeks of follow-up. Neuropsychiatric adverse events were ascertained by self-report, clinical observation, and a semi-structured interview for psychiatric symptoms. Smoking cessation was defined as self-reported continuous abstinence for study weeks 9–12, confirmed by low exhaled carbon monoxide.

Results: More than three-fourths of the study cohort completed treatment. Among patients with psychiatric illness, the majority had a mood disorder (71%) or an anxiety disorder (19%). Half were taking psychotropic medications at baseline. One-third of the psychiatric cohort had a history of suicidal ideation, and 13% had a history of suicidal behavior.

The overall incidence of neuropsychiatric adverse events was 3.7% with placebo, 3.9% with nicotine patches, 4% with varenicline, and 4.5% with bupropion. Between-group differences were not statistically significant. The rate, combined across all treatments, was higher in the psychiatric cohort than in the non-psychiatric cohort (5.8% vs. 2.1%; $p < 0.0001$). Among the non-psychiatric cohort, varenicline was associated with a lower risk of adverse events than placebo, and bupropion did not differ from placebo. In the psychiatric cohort, there were no significant differences among treatments and placebo. Rates of severe aggression or suicidal behavior ranged from 0 to $< 0.1\%$ in the groups. There was 1 completed suicide, which occurred in a placebo-treated patient in the non-psychiatric cohort.

Patients who received varenicline had the highest rate of smoking cessation (34% for weeks 9–12 and 22% for weeks 9–24), significantly higher than the

other treatments. Bupropion and the nicotine patch had similar efficacy and were both superior to placebo.

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

Anthenelli R, et al: Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 2016; doi 10.1016/S0140-6736(16)30272-0. From the University of California, San Diego; and other institutions. **Funded by Pfizer; and GlaxoSmithKline. All study authors disclosed financial relationships with commercial sources including Pfizer and/or GlaxoSmithKline.**

Common Drug Trade Names: bupropion—*Zyban*; varenicline—*Chantix*

*See Reference Guide.

Loperamide Misuse

Use of loperamide at higher-than-recommended doses, including through abuse/misuse, or with other drugs that affect its metabolism has been linked to serious heart problems. QT interval prolongation, Torsades de pointes and other ventricular arrhythmias, syncope, and cardiac arrest can occur with loperamide toxicity. The majority of reported cases were in patients either misusing loperamide to self-treat opioid withdrawal or in patients using concomitant medications (e.g., cimetidine, ranitidine, and several antibiotics) that can increase loperamide absorption and/or inhibit its metabolism and enhance its euphoric effects. Maximum daily doses for the over-the-counter and prescription formulations are 8 and 16 mg/day, respectively.

FDA MedWatch Safety Alert: Loperamide (Imodium): Drug safety communication – serious heart problems with high doses from abuse and misuse. Available at <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm505303.htm>.

Common Drug Trade Names: cimetidine—*Tagamet*; loperamide—*Imodium*; ranitidine—*Zantac*

Strategies to Prevent NSAID GI Toxicity

The combination of a selective COX-2 inhibitor with a proton pump inhibitor (PPI) is the most effective strategy for preventing NSAID-induced gastrointestinal toxicity, according to a network meta-analysis of all available randomized controlled trials.

Methods: A comprehensive literature search identified all randomized controlled trials, published through May 2015, comparing gastroprotective

strategies for prevention of GI toxicity. Studies were conducted in healthy populations or patients with diseases requiring NSAID therapy and could be trials of primary or secondary prevention. The primary outcomes of interest, analyzed by network meta-analysis,* were ulcer complications (bleeding, perforation, and obstruction) and symptomatic ulcers. Secondary outcomes were endoscopic ulcers and adverse events. Studies were excluded if the duration was <4 weeks or if the evaluated agents have since been withdrawn from the market.

Results: The analysis included 82 trials conducted in >125,000 patients. Traditional nonselective NSAID therapy was used as the control or comparison treatment in most of the trials. The trials included 5 comparator strategies: selective COX-2 inhibitors; nonselective NSAIDs plus a PPI; nonselective NSAIDs plus misoprostol (*Cytotec*); nonselective NSAIDs plus a histamine-2 receptor antagonist (H2RA); selective COX-2 inhibitors plus a PPI.

In the analysis of ulcer complications, selective COX-2 inhibitors plus a PPI showed a large advantage over the other strategies and were associated with the lowest probability of an ulcer complication. (See table.)

Risk Ratios* (RRs) for Ulcer Complications	
Regimen	RR vs. Nonselective NSAIDs
Selective COX-2 inhibitors plus a PPI	0.07
Selective COX-2 inhibitors	0.25
Nonselective NSAIDs plus a PPI	0.28
Nonselective NSAIDs plus misoprostol	0.47
Nonselective NSAIDs plus an H2RA	0.84

The rankings for efficacy were similar for the other ulcer endpoints. This observation suggests that the comparisons are robust and also that endoscopic ulcer is a valid surrogate study endpoint for clinical ulcers.

Compared with nonselective NSAIDs, selective COX-2 inhibitors and nonselective NSAIDs plus PPIs were associated with a lower risk of withdrawal for adverse events. Nonselective NSAIDs plus misoprostol had a higher risk of discontinuation.

Discussion: To date no study has directly compared nonselective NSAIDs with COX-2 inhibitors plus PPIs, although the latter appears to be the most effective preventive strategy. It should be noted that specific adverse effects were often not reported in the studies, and the cardiovascular risks of these regimens were not analyzed.

Yuan J, et al: Systematic review with network meta-analysis: comparative effectiveness and safety of strategies for preventing NSAID-associated gastrointestinal toxicity. *Alimentary Pharmacology and Therapeutics* 2016;43:1262–1275. From the Chinese University of Hong Kong, and other institutions. **Source of funding not stated. The authors declared no competing interests.**

*See Reference Guide.

Treating Opioid Dependence in Pregnancy

Methadone is the standard treatment for opioid dependence in pregnancy. However, a review of the limited available evidence suggests buprenorphine (*Buprenex*) may be equally safe and effective.

A literature search identified 5 head-to-head comparisons of methadone and buprenorphine in pregnant women. Of these, 3 employed a randomized design, 1 compared a subset of patients from a single participating site in the largest, multicenter randomized trial with a clinical population, and the last used a retrospective

design to evaluate buprenorphine plus naloxone versus methadone.

Overall, methadone and buprenorphine were found to have similar efficacy and safety. Neonatal abstinence syndrome (NAS) developed in 40% of the buprenorphine-group infants and in 54% of the methadone-group infants. The total amount of morphine used to treat NAS and the duration of NAS symptoms were slightly lower in the buprenorphine group, but the difference reached significance only in a single large randomized trial. Length of infant hospital stay was 7–11 days with buprenorphine, compared with 8–18 days with methadone. No differences were found with other neonatal or maternal outcomes.

At present, methadone is the only FDA-approved treatment for opioid addiction during pregnancy. Buprenorphine has several advantages, including not requiring daily visits to a methadone treatment center, fewer drug interactions, and a better tolerability profile. However, acceptability of buprenorphine was the most common reason for its high discontinuation rate (33% of patients in the largest study, compared with 18% of the methadone group) and should be taken into account when choosing treatment. Patient dissatisfaction is likely the result of the drug's longer induction phase, its partial agonist activity, and the need for patients to be in mild-to-moderate withdrawal when starting therapy.

Noormohammadi A, et al: Buprenorphine versus methadone for opioid dependence in pregnancy. *Annals of Pharmacotherapy* 2016; doi 10.1177/1060028016648367. From the VA Outpatient Clinic, Corpus Christi, TX; and other institutions. **This review was conducted without funding. The authors declared no competing interests.**

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Network Meta-Analysis: A study design that can provide estimates of efficacy for multiple treatment regimens, even when direct comparisons are unavailable. This method extends the traditional meta-analytic technique to allow simultaneous comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common.

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.

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Antidiabetic Kidney Warnings Strengthened

Based on 101 confirmable postmarketing reports of acute kidney injury with the sodium-glucose cotransporter-2 (SGLT2) inhibitors canagliflozin and dapagliflozin, some of which required hospitalization and dialysis, the FDA has strengthened its existing warnings for these drugs. They now recommend that patients' kidney function be evaluated before canagliflozin or dapagliflozin is initiated and periodically after treatment is started. Conditions that could predispose patients to acute liver injury—e.g., decreased blood volume, congestive heart failure, chronic kidney insufficiency, and concomitant medications—should be factored into prescribing decisions. If signs or symptoms of acute kidney injury occur, the SGLT2 inhibitor should be stopped and kidney impairment addressed.

FDA MedWatch Alert: Canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR): drug safety communication – strengthened kidney warnings. Available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm506554.htm>

Common Drug Trade Names: canagliflozin—*Invokana, Invokamet*; dapagliflozin—*Farxiga, Xigduo XR*

Fluoroquinolone Adverse Effects

According to the FDA, fluoroquinolone use should be reserved for patients who have no other treatment options for acute bacterial sinusitis, acute exacerbation of chronic bronchitis, or uncomplicated urinary tract infections, because the risk of serious side effects generally outweighs the benefits in these patients.

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The product labels for fluoroquinolone antibiotics carry a Boxed Warning for tendinitis, tendon rupture, and worsening of myasthenia gravis, as well as warnings about the risks of peripheral neuropathy, central nervous system effects, and cardiac, dermatologic, and hypersensitivity reactions. Following a review that found peripheral neuropathy could be irreversible, the FDA evaluated post-marketing reports of disabling and potentially permanent adverse effects involving ≥ 2 body systems associated with systemic fluoroquinolone treatment. As a result of their findings, the FDA is now requiring the fluoroquinolone label warnings be updated to include disabling and potentially permanent effects on the tendons; muscles; joints; nerves; and central nervous system.

FDA MedWatch Alert: Fluoroquinolone antibacterial drugs for systemic use: drug safety communication—warnings updated due to disabling side effects. Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm513065.htm>.

Sildenafil for Resistant Hypertension

Patients with resistant hypertension had significant reductions in 24-hour ambulatory blood pressure (BP) measurements after receiving a single high dose of sildenafil (*Revatio*).

Background: Sildenafil and other phosphodiesterase type 5 (PDE5) inhibitors have vasodilatory effects and have been shown to produce office BP reductions in patients with untreated or resistant hypertension. Sildenafil improves hemodynamics by reducing peripheral vascular resistance and

improving diastolic function in patients with resistant hypertension. These drugs work by increasing levels of cyclic guanosine mono-phosphate, a pathway that is not shared by other antihypertensive drugs.

Methods: Study participants (n=26; aged ≥ 35 years) were recruited consecutively from specialized outpatient hypertension clinics and met American Heart Association criteria for resistant hypertension, defined as high BP despite the use of ≥ 3 antihypertensive drugs of different classes or controlled BP with the use of ≥ 4 agents at optimal doses. On a single occasion, patients received sildenafil doses of 37.5 mg, 50 mg, and 100 mg, 30 minutes apart (total sildenafil dose, 187.5 mg) after taking their usual BP medication. Following a 2-week washout, all patients received placebo administration in a similar manner. 24-hour ambulatory BP measurements were obtained before and after sildenafil and placebo administration, for a total of 4 days.

Results: All study participants were receiving diuretics, and $\geq 50\%$ of patients were also receiving calcium channel blockers, angiotensin II receptor antagonists, or beta-blockers. The addition of sildenafil resulted in reductions in systolic, diastolic, and mean BP on the day after treatment, which were statistically significantly different from placebo effects. Effects of sildenafil on day-time BP were larger than effects on BP at night. BP control ($<140/90$ mm Hg) was achieved following sildenafil and placebo administration in 30% and 4% of patients, respectively. No patients achieved a decrease of ≥ 10 mm Hg in systolic BP with placebo, while 46% did so following sildenafil. Patients did not report adverse effects of sildenafil treatment.

Discussion: Results of this preliminary study support sildenafil as a potential treatment for resistant hypertension. However, additional study is needed to investigate the effects of long-term PDE5 inhibitor use in a larger population in order to determine clinical relevance of this treatment.

Santa Catharina A, et al: Acute sildenafil use reduces 24-hour blood pressure levels in patients with resistant hypertension: a placebo-controlled, crossover trial. *Journal of Clinical Hypertension* 2016; doi 10.1111/jch.12850. From the University of Campinas, Brazil; and other institutions. **Funded by the Sao Paulo Research Foundation; and the National Council for Scientific and Technological Development. The authors declared no competing interests.**

New Anticoagulants: Efficacy and Safety

The non-vitamin K antagonist oral anticoagulants dabigatran, rivaroxaban, and apixaban are safe and effective alternatives to warfarin for treating atrial fibrillation, according to a Danish population-based study. In the study, all anticoagulant agents had similar efficacy in preventing ischemic stroke. Risks of death or bleeding were significantly lower with apixaban and dabigatran than with warfarin or rivaroxaban.

Methods: The analysis included patients with a first-time prescription for 1 of the 3 novel oral anticoagulants (NOACs) or who started treatment with warfarin during the study period. All patients had a diagnosis of atrial fibrillation and were naive to oral anticoagulants. Study endpoints were ischemic stroke, systemic embolism, and death. Bleeding events, categorized as major, gastrointestinal, intracranial, and traumatic intracranial, were also recorded.

Results: The study population included nearly 62,000 patients, of whom 57% received warfarin, 21% dabigatran, 12% rivaroxaban, and 10% apixaban. There was some evidence of preferential prescribing—e.g., patients starting dabigatran were, on average, younger than others and had fewer stroke risk factors—but outcome analyses were adjusted for these differences.

During the first year of anticoagulant therapy, there were 1702 instances of ischemic stroke or systemic embolism. Weighted rates of these outcomes were 3.3 per 100 person-years for warfarin and ranged from 2.9 to 3.9 for the NOACs. Apixaban and dabigatran did not differ from warfarin, but rivaroxaban was associated with a significantly lower risk (hazard ratio,* 0.83). After 2.5 years of treatment, risk for these events was still significantly lower with rivaroxaban than with warfarin. When the analysis was limited to ischemic stroke, none of the NOACs differed from warfarin.

Risk of bleeding events was comparable for rivaroxaban and warfarin (about 5 per 100 person years) and lower for apixaban and dabigatran (about 3 per 100 person years). Comparative risks of bleeding remained similar after 2.5 years of follow-up. Intracranial bleeding occurred less often with all of the NOACs than with warfarin. Risks of major bleeding and death were similar for warfarin and rivaroxaban and lower for apixaban

and dabigatran. Risk of the combined endpoint of ischemic stroke, systemic embolism, and death was lower for all of the NOACs than warfarin.

Larsen T, et al: Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ* 2016; doi 10.1136/bmj.i3189. From Aalborg University Hospital, Denmark; and other institutions. **Funded by the Obel Family Foundation; and other sources. Three study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

Common Drug Trade Names: apixaban—*Eliquis*; dabigatran—*Pradaxa*; rivaroxaban—*Xarelto*

*See Reference Guide.

Pseudoephedrine and Voiding Dysfunction

In an observational study of men with rhinitis, pseudoephedrine (taken as a nasal decongestant) was associated with subclinical voiding dysfunction in older men.

Background: Pseudoephedrine is labeled as requiring caution in men with benign prostatic hyperplasia, but there are no other warnings regarding urinary function or use in specific age groups. However, there have been reports of urinary retention in children and adults, and the drug is used to treat types of urinary incontinence. Pseudoephedrine is contraindicated in patients with urinary retention but is generally regarded as safe in patients with no history of voiding problems.

Methods: Study participants were 131 men (mean age, 42 years) seeking treatment for acute or chronic rhinitis who were prescribed 120 mg pseudoephedrine b.i.d. for 1 week. Urinary symptoms were assessed at baseline and after 1 week with the International Prostate Symptom Score (IPSS) questionnaire, an 8-item instrument that assesses urinary voiding and storage symptoms as well as quality of life.

Results: Average total scores on the IPSS and the subscales of voiding, storage, and quality of life worsened slightly after treatment. A total of 52 men (40%) reported worsened urinary function after treatment. These men were significantly older than those with unchanged or improved function and had significantly worse IPSS voiding scores before receiving pseudoephedrine. Overall IPSS scores and subscales for voiding and storage were significantly worse after treatment in men aged >50 years, and the magnitude of deterioration increased with age. Three patients, ages 29,

51, and 62 years, experienced symptomatic dysuria, but none had urinary retention. All of the symptoms improved after pseudoephedrine was discontinued.

Discussion: The probable mechanisms of the adverse urinary effects of pseudoephedrine are its effect on α -1A-adrenergic receptors, promoting contraction of the bladder neck, urethra, and prostate and enhancing bladder outlet resistance; and its effects on β -adrenergic receptors, which maintain the relaxation of smooth muscles in the bladder.

Shao I-H, et al: Voiding dysfunction in patients with nasal congestion treated with pseudoephedrine: a prospective study. *Drug Design, Development and Therapy* 2016;10:2333–2339. From Lotung Poh-Ai Hospital, Taiwan. **Funded by the Biostatistical Center for Clinical Research of Linkou Chang Gung Memorial Hospital. The authors declared no competing interests.**

*See Reference Guide.

Oral Docusate Recall

PharmaTech LLC is voluntarily recalling all non-expired lots of its docusate sodium solution (*Diocto Liquid*) because of contamination with *Burkholderia cepacia*. In addition, there have been several adverse-event reports of *B. cepacia* infections associated with liquid docusate sodium products manufactured by companies other than PharmaTech. The FDA and the CDC are investigating the extent of the contamination and suggest that clinicians refrain from recommending any liquid docusate sodium products.

FDA MedWatch Alert: Oral liquid docusate sodium by PharmaTech: Recall—Contaminated with *B. Cepacia*. Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm511528.htm>.

Escitalopram in Heart Failure

In patients with heart failure and depression, escitalopram did not influence mortality or cardiovascular morbidity, nor did it improve depressive symptoms to a greater degree than placebo.¹

Methods: Study subjects were adults attending outpatient heart-failure clinics who were screened for depression and underwent a DSM-IV structured clinical interview to confirm major depression diagnosis. Subjects were randomly assigned to receive 10–20 mg/day escitalopram or placebo for up to 24 months while receiving optimal heart-failure care. The primary endpoint was death from any cause or the first occurrence

of hospitalization. Secondary outcomes included depression, anxiety, and health-related quality of life. The study was terminated prematurely based on a determination of futility.

Results: The efficacy analysis was based on 372 patients, who participated for a median of about 18 months. Death or hospitalization occurred in 63% of the escitalopram group and 64% of the placebo group (p=ns). There were no statistically significant differences between groups in any time-to-event outcome, including cardiovascular or non-cardiovascular death or hospitalization for different causes, or in subgroups analyzed separately.

MADRS scores at 12 weeks were similar in the escitalopram and placebo groups. Depression and anxiety decreased to a similar extent in both groups, and cardiomyopathy-related quality of life at 12 months was significantly higher in the placebo group. An exploratory analysis suggested that remission of depression or marked improvement did not reduce the risk of death or hospitalization.

Discussion: Depression is common in patients with cardiovascular disease and is associated with poorer clinical outcomes. Results of previous randomized studies in patients with coronary

artery disease suggest that antidepressants may improve depression but do not affect the cardiovascular prognosis. Until now, a 12-week study of sertraline was the only randomized antidepressant trial in patients with heart failure; results of this study were also negative.² In the present study, escitalopram levels, obtained at weeks 6 and 12 and again at 6 and 12 months, were in the therapeutic range, indicating that the results likely confirm a lack of therapeutic efficacy in this sample.

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

¹Angermann C, et al: Effects of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression: the MOOD-HF randomized clinical trial. *JAMA* 2016;315 (June 28):2683–2693. From the University Hospital Wurzburg, Germany; and other institutions. **Funded by the German Ministry of Education and Research; and Lundbeck AS Denmark. Ten study authors disclosed potentially relevant financial relationships; the remaining 8 authors declared no competing interests.**

²O'Connor C, et al: Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. *Journal of the American College of Cardiology* 2010;56:692–699.

Common Drug Trade Names: escitalopram—*Lexapro*; sertraline—*Zoloft*

*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.

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.

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Alendronate Fracture Risk/Benefits

Long-term use of alendronate (*Fosamax*) was associated with a 30% reduction in risk of hip fracture, far outweighing any potential risk of drug-related atypical femoral fracture.

Methods: The study population consisted of nearly 62,000 patients from the Danish universal national health care registry, who were aged 50–94 years and first received a prescription for alendronate in 1996–2007. Continued alendronate use and fracture occurrence were tracked forward to 2013. Two separate case-control studies were conducted; for hip fractures and femoral subtrochanteric/shaft fractures. Each fracture case was matched with up to 3 controls (for hip fracture) or 5 controls (for femoral fracture) for age, gender, year of treatment start, and follow-up time. Treatment compliance was classified according to the proportion of prescribed daily doses of alendronate that were filled; a medication proportion ratio (MPR) of >80% was considered high. The analysis was adjusted for risk factors such as previous fractures, diabetes, and proton pump inhibitor exposure. In Denmark, alendronate is prescribed only for low bone mineral density or a previous low-trauma fracture, and 10 mg is the only available daily dose.

Results: The study subjects had a mean age of 72 years, and 83% were women. Nearly 30% completed 5 years of treatment with an MPR ≥80%; only 4% completed ≥10 years. For the first 10 years, rates of hip fracture declined in the population of alendronate users from an initial

36 per 1000 patient years to a stable 10–15 per 1000 patient years. The total rate of femoral fractures remained stable at 2.7–4.6 per 1000 patient years. There were a total of 1428 femoral fractures and 6784 hip fractures.

Risk of femoral fractures was reduced in patients with a high MPR, compared with those with poor compliance (MPR <50%). After adjustment for comorbid illnesses, the reduction was no longer statistically significant (adjusted odds ratio,* 0.90). Use of alendronate for >10 years was associated with reduced risk of subtrochanteric femur fracture (odds ratio, 0.43), but not shaft fractures. For hip fracture, high compliance was associated with reduced risk (odds ratio, 0.73; $p < 0.001$). Hip fracture risk was reduced by a similar ratio in compliant patients using alendronate for 5–10 years or for ≥10 years.

A long-term harm–benefit model was calculated by comparing the observed rate of hip fractures to the upper 95% confidence limit of femur fractures. For up to 13 years, the highest plausible rate of femur fractures was well below the observed rate of hip fractures in patients with high alendronate adherence.

Discussion: Due in part to fears of atypical femur fractures, prescription rates for bisphosphonates have fallen by 50% in the U.S. The results of this study suggest that prevention of hip fractures is a clear benefit of treatment, and any increase in atypical femur fractures is offset by prevention of non-atypical femur fractures. Even in a worst-case scenario, with atypical fractures representing 10%

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of all femur fractures, the incidence is still too low to offset the benefits of long-term alendronate use in preventing hip fracture.

Abrahamsen B, et al: Risk of hip, subtrochanteric, and femoral shaft fractures among mid and long term users of alendronate: nationwide cohort and nested case-control study. *BMJ* 2016; doi 10.1136/bmj.i3365. From the University of Southern Denmark, Odense; and other institutions. **This study was conducted without external funding. All study authors disclosed financial relationships with commercial sources.**

*See Reference Guide.

Liraglutide and Alzheimer's Progression

In patients with Alzheimer's disease, treatment with the GLP-1 analog liraglutide (*Victoza*) prevented the predicted decline of brain glucose metabolism, a marker for disease progression. Treatment did not affect cognition or amyloid deposition.

Background: Liraglutide is a GLP-1 receptor agonist used to treat type 2 diabetes. Common pathophysiological mechanisms for type 2 diabetes and Alzheimer's disease include deficient insulin and GLP-1 signaling and beta-cell toxicity. GLP-1 receptor agonists cross the blood-brain barrier and have been reported to be neuroprotective of several neurodegenerative disorders in animal models.

Methods: Study subjects were 38 patients with Alzheimer's disease, recruited from dementia clinics. Patients were required to be aged 50–80 years, able to give informed consent, and have mini-mental state examination scores of 18–21. Those with diabetes were excluded. In addition to existing medications (including cholinesterase inhibitors), participants were randomly assigned to treatment with either liraglutide (maintenance dose, 1.8 mg injected daily) or placebo for 26 weeks. Outcomes included beta-amyloid deposition and glucose metabolic rate, measured by PET scan, and cognitive function, measured using the Brief Cognitive Status Exam from the Wechsler Memory Scale.

Results: Participants had a mean age of about 65 years. By chance, the treatment groups were somewhat unbalanced; members of the group receiving liraglutide were older on average, were more likely to be female, and had a significantly longer mean duration of Alzheimer's disease—30 vs. 15 months ($p < 0.05$). Four patients did not complete liraglutide treatment: but only 1 for a drug-related reason, nausea and anorexia. The patients who

took liraglutide lost >10 pounds on average during the first 3 months, after which their weight stabilized. Fasting plasma glucose levels were lower during the study in the group receiving liraglutide.

Measures of amyloid deposits in different brain regions increased during the study, to a similar extent in both groups. In the placebo group, measures of glucose metabolism had statistically significant decreases over the course of treatment in the precuneus ($p = 0.009$); the parietal, temporal, and occipital lobes ($p = 0.04$, 0.046 , and 0.009 , respectively); and the cerebellum ($p = 0.04$). There were small, nonsignificant increases in glucose metabolism in the liraglutide group. Cognitive outcomes did not differ between the 2 groups.

Discussion: Current treatments for Alzheimer's disease target neurotransmission without addressing neurodegeneration or neuronal metabolism. Liraglutide potentially affects neurodegeneration, neuronal performance, and neuroinflammation, suggesting it could reduce intracerebral amyloid deposition and improve glucose metabolism in the CNS of patients with Alzheimer's disease, which would then improve cognition. In the present study, liraglutide prevented the decline of brain glucose consumption but had no effect on amyloid accumulation or cognition, possibly because the study lacked the statistical power to show positive effects of liraglutide on these outcomes.

Gejl M, et al: In Alzheimer's disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: randomized, placebo-controlled, double-blind clinical trial. *Frontiers in Aging Neuroscience* 2016; doi 10.3389/fnagi.2016.00108. From Aarhus University, Denmark; and other institutions. **Funded by Novo Nordisk Scandinavia; and Aarhus University. Three study authors declared financial relationships with commercial sources; the remaining 10 authors declared no competing interests.**

Opioid/Benzodiazepine Warning

Combined use of opioid pain and/or cough medications and benzodiazepines, which can lead to slowed or difficulty breathing and death, appears to be growing. Following a recent review, the FDA is now requiring that labels for prescription opioid pain and cough medicines, as well as benzodiazepines, carry Boxed Warnings about these risks. Physicians should limit prescribing of opioid medications with other CNS depressants including benzodiazepines. When combined use is necessary, the dosage and duration of treatment

should be limited and patients should be warned of the possibility that slowed or difficult breathing and/or sedation could develop. The FDA is also evaluating whether label changes are needed for central nervous system depressants.

FDA MedWatch Alert: Opioid pain or cough medicines combined with benzodiazepines: drug safety communication—FDA requiring boxed warning about serious risks and death. Available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm518710.htm>

Drugs Exacerbating Heart Failure

Polypharmacy is a significant concern in patients with heart failure, according to a scientific statement from the American Heart Association. The statement provides a comprehensive guide to drugs that can cause or exacerbate heart failure, including OTC agents and complementary and alternative medications (CAMs).

Polypharmacy is defined as the long-term use of ≥5 medications. By this criterion, polypharmacy is the norm in patients with heart failure, who take an average of nearly 7 prescription medications per day, in addition to OTC and CAM therapies.

Drugs may cause or exacerbate heart failure via direct myocardial toxicity, by negative inotropic, lusitropic, or chronotropic effects, by exacerbating hypertension, by delivering a high sodium load, or by interacting with other drugs. The list of drugs that cause myocardial toxicity is heavily weighted toward cancer chemotherapy agents. It also includes all stimulants, all TNF- α inhibitors, and many biologicals, as well as single representatives of other drug classes. (See table.)

OTC NSAIDs have the same risk of inducing heart failure as prescription NSAIDs, particularly at higher doses. Many OTC agents have a high sodium content or actions that can exacerbate heart failure—e.g., phenylephrine, pseudoephedrine, and nasal decongestants that contain vasoconstricting ingredients. Many CAMs can have significant interactions with cardiovascular medications, including St. John's wort, ginseng, and black cohosh. Others, such as garlic, ginkgo, and saw palmetto, have antiplatelet or anticoagulant effects and increase bleeding risk.

A complete medication reconciliation should be completed at every patient visit, including OTC agents and CAMs. Medications should be categorized as essential or optional, and consideration should be given to discontinuing optional ones. Combination medications should be considered to reduce the number of medications taken daily. Prescribing medications to treat adverse effects of other medications should be avoided.

Page R, et al: Drugs that may cause or exacerbate heart failure: a scientific statement from the American Heart Association. *Circulation* 2016; doi 10.1161/CIR.0000000000000426. From the University of Colorado, Aurora; and other institutions. **Two study authors disclosed financial relationships with commercial sources; the remaining 7 authors declared no competing interests.**

Common Drug Trade Names: albuterol—*Proventil*; bosentan—*Tracleer*; bromocriptine—*Parlodel*; carbamazepine—*Tegretol*; chloroquine—*Aralen*; citalopram—*Celexa*; clozapine—*Clozaril*; diltiazem—*Cardizem*; disopyramide—*Norpace*; dronedarone—*Multaq*; epoprostenol—*Flolan*, *Velettri*; flecainide—*Tambocor*; itraconazole—*Sporonox*; metformin—*Glucophage*; pramipexole—*Mirapex*; saxagliptin—*Onglyza*; sitagliptin—*Januvia*; sotalol—*Betapace*; verapamil—*Calan*

Common Prescription Drugs with a Major Association with Heart Failure Onset or Exacerbation	
Analgesics	NSAIDs, COX-2 inhibitors
Antidiabetics	metformin, thiazolidinediones, saxagliptin, sitagliptin
Antiarrhythmics	flecainide, disopyramide, sotalol, dronedarone
Antihypertensives	diltiazem, verapamil
Anti-infectives	itraconazole, amphotericin B
Neurologic/Psychiatric Medications	stimulants, carbamazepine, citalopram, clozapine, lithium
Antiparkinson Agents	bromocriptine, pergolide, pramipexole
Ophthalmics	topical beta-blockers
Pulmonary Medications	albuterol, bosentan, epoprostenol
Antirheumatics	TNF- α inhibitors
Antimalarials	chloroquine, hydroxychloroquine

Low-Dose Alteplase in Ischemic Stroke

In a randomized trial, low-dose alteplase (*Activase*) was as efficacious as standard-dose alteplase in preventing death and disability after an ischemic stroke and was associated with lower risk of intracerebral hemorrhage.

Background: Asian patients appear to be at high risk for intracerebral hemorrhage with standard-dose (0.9 mg/kg body weight) alteplase. The present study, conducted with a majority of Asian participants, was undertaken to evaluate safety and efficacy of the lower dose (0.6 mg/kg) which is approved in Japan.

Methods: The study included 3310 patients (mean age, 67 years; 63% of Asian ethnicity) experiencing an acute stroke who met guideline-recommended criteria for treatment with IV alteplase and could receive treatment within 4.5 hours of symptom onset. Patients were randomly assigned to receive either the standard dose or the reduced dose. Concomitant treatment followed practice guidelines. The primary efficacy outcome was the combined endpoint of death or disability at 90 days. Disability was defined as more-than-minimal residual neurologic symptoms. Intracerebral hemorrhage was the key secondary outcome.

Results: The mean time from stroke onset to administration of alteplase was 170 minutes. Post-randomization management, including rates of endovascular thrombectomy and recanalization,

was similar in the 2 groups. The primary outcome occurred in similar proportions of patients receiving standard-dose and low-dose alteplase (53% vs 51%). Relative efficacy of the 2 dosages was similar in patients who started treatment within 3 hours of symptom onset and those who began later, and also in those who did not receive aggressive BP-lowering treatment.

Major symptomatic intracerebral hemorrhage occurred in significantly fewer patients receiving low-dose versus standard-dose alteplase (1% vs. 2%; $p=0.01$; odds ratio,* 0.048), as did less severe symptomatic intracerebral hemorrhage (6% vs. 8%; $p=0.02$; odds ratio, 0.73). Treatment effects on intracerebral hemorrhage were similar in Asian and non-Asian patients and regardless of aggressive BP lowering. The overall risk of fatal cerebral hemorrhage events was 1.3% with low-dose alteplase and 2.5% with high-dose alteplase ($p=0.02$).

Discussion: These results suggest that a lower alteplase dose could improve intracerebral hemorrhage risk without sacrificing clinical efficacy.

Anderson C, et al: Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. *NEJM* 2016;374 (June 16):2313–2323. From the George Institute for Global Health and Sydney Medical School, Australia; and other institutions. **Funded by the National Health and Medical Research Council of Australia; and other sources. Twelve study authors declared financial relationships with commercial sources; the remaining 20 authors declared no competing interests.**

*See Reference Guide.

Reference Guide

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.

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Uncertainty About Rivaroxaban

Rivaroxaban (*Xarelto*) was FDA approved as an anticoagulant based on the large, multinational, phase III ROCKET trial, published in 2011, which found that the drug had similar clinical effects to warfarin.¹ In 2007, the drug's manufacturer became aware of an inaccuracy of a blood-testing device used to monitor patients receiving warfarin, which resulted in incorrect warfarin dosing for much of the study.² According to an investigative report, the manufacturer's failure to disclose these problems may undermine the validity of the ROCKET trial. However, both the FDA and the European Medicines Agency (EMA) have concluded that, for now, there is no reason to doubt the clinical benefit of rivaroxaban.

In ROCKET-trial patients who received warfarin, coagulation was measured with the INRatio, a point-of-care INR monitoring device. At the time it was discovered, information on the inaccuracy of the devices was not shared with the ROCKET safety monitoring board. In 2014, after publication of the ROCKET trial and approval of rivaroxaban, the FDA recalled the device because it generated INR results that could be clinically significantly lower than gold-standard laboratory results. Since the recall of the INRatio device, Janssen and Bayer have re-analyzed their data and published their results; the EMA has conducted a review concluding that the defective device would not have had an important effect on study results; and the FDA has launched its

own investigation while announcing that it has not changed its recommendations regarding use of rivaroxaban.

¹Patel M, et al: Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *NEJM* 2011;365:883–891.

²Cohen D: Manufacturer failed to disclose faulty device in rivaroxaban trial. *BMJ* 2016; doi 10.1136/bmj.i5131.

The author declared no competing interests.

Abaloparatide for Osteoporosis

An investigational anabolic treatment for osteoporosis, abaloparatide, prevented fractures in a placebo-controlled trial in women with osteoporosis.¹ Whether this agent offers additional benefit to teriparatide (*Forteo*), the first-in-class anabolic osteoporosis drug, remains to be seen.²

Background: Both abaloparatide and teriparatide act by binding the parathyroid hormone type 1 receptor. Biologic effects of the 2 drugs appear to differ, with abaloparatide offering more transient binding that could result in less bone resorption. The present study was designed to compare abaloparatide with placebo, not with teriparatide, which was included as an active control.

Methods: The multinational trial enrolled postmenopausal women, aged 49–86 years, with bone mineral density (BMD) T scores* between -2.5 and -5.0 at the lumbar spine or femoral neck and a history of vertebral fractures or low-trauma non-vertebral fracture. Women >65 years could have T scores between -3.0 and -5.0 and no fracture history. Study participants received treatment for 18 months with daily subcutaneous injections of

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randomly assigned 80 mcg abaloparatide, placebo, or 20 mcg teriparatide. All women were provided calcium and vitamin D supplements. Spinal x-rays were obtained at baseline and at the end of treatment. The primary efficacy outcome was the proportion of patients with a new morphometric vertebral fracture, comparing abaloparatide and placebo.

Results: Nearly 2500 women (mean age, 69 years) were randomly assigned to treatment. About 24% had a prevalent vertebral fracture, 31% had a history of nonvertebral fracture, and 37% had no prior fractures. Some 77% of the women completed all study visits and 86% had post-randomization radiographs that were analyzed for new fractures. Study withdrawal rates were similar across treatment groups.

New vertebral fractures occurred in 4 women (0.58%) who received abaloparatide and in 30 women (4.22%) who received placebo (relative risk,* 0.14; $p < 0.001$). In the teriparatide group, fracture risk was similar to the abaloparatide group. Abaloparatide was also superior to placebo with regard to change from baseline in total hip, lumbar spine, and femoral neck BMD (all $p < 0.001$). Rates of nonvertebral fracture were lower with abaloparatide than with placebo, but the difference was not statistically significant. Two hip fractures occurred in study subjects, both in the placebo group. Total hip and femoral neck BMD increases during the first 6 months were significantly larger with abaloparatide than with placebo. Markers of bone formation and resorption increased during the first 12 months for both of the anabolic drugs. After 3 months, the markers showed smaller increases in bone formation and bone resorption with abaloparatide relative to teriparatide. Abaloparatide was associated with a lower rate of hypercalcemia than teriparatide (3.4% vs. 6.4%), consistent with less bone resorption.

Discussion: The potential for greater efficacy in improving hip bone mass and reduced risk of hypercalcemia may be important distinguishing features of abaloparatide. However, there is a limit to the benefits of reducing bone resorption in the absence of stimulating bone formation. Use of teriparatide, currently the only approved anabolic treatment for osteoporosis, is limited by cost, the requirement for daily injection, and adverse effects including hypercalcemia. There is a need for new anabolic agents with improved safety, efficacy, ease of administration, and cost.

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

¹Miller P, et al: Effects of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. *JAMA* 2016;316 (August 16):722–733. From the Colorado Center for Bone Research, Lakewood; Radius Health, Waltham, MA; and other institutions. **Funded by Radius Health. All study authors disclosed financial relationships with commercial sources.**

²Cappola A, et al: Osteoporosis therapy in postmenopausal women with high risk of fracture [editorial]. *JAMA* 2016;316 (August 16):715–716. From the University of Pennsylvania, Philadelphia; and the University of California, San Francisco. **The authors declared no competing interests.**

*See Reference Guide.

Safety of Combined Asthma Treatments

In patients with moderate-to-severe asthma, combined therapy with budesonide plus formoterol was not associated with a higher rate of death or other serious adverse events than budesonide alone, according to a randomized postmarketing safety study.

Background: The FDA mandated a series of large studies to be conducted by the 4 manufacturers of long-acting β -agonist (LABA)-containing asthma products to investigate possibly increased rates of rare but serious adverse events in patients receiving inhaled glucocorticoid–LABA combined therapy.

Methods: This current study enrolled >11,500 participants from 25 countries. Patients were aged ≥ 12 years, receiving daily asthma medication, and currently receiving treatment with an inhaled glucocorticoid or a glucocorticoid–LABA combination, or they had severe enough disease to warrant such treatment. Based on symptom control and prior therapy, patients were stratified to 2 dose levels of budesonide and then randomly assigned to receive budesonide alone or budesonide–formoterol for 26 weeks. Dosages were 2 actuations of 80 or 160 mcg budesonide b.i.d and 4.5 mcg formoterol b.i.d. The primary study endpoint was serious asthma-related event, defined as a composite of asthma-related death, intubation, and hospitalization.

Results: Overall, 80% of participants completed the study with $\geq 80\%$ adherence to study medication. During the study, there were 43 serious asthma-related events in the budesonide–formoterol group, compared with 40 events in those taking budesonide alone (hazard ratio,* 1.07). There were 2 deaths, both in patients using combined

therapy: 1 in a patient who was intubated and died of cardiopulmonary failure and 1 from pneumonia secondary to bronchial asthma. All other serious events were asthma-related hospitalizations.

Treatment efficacy was also compared as a secondary study endpoint. Asthma exacerbation, the primary efficacy outcome, occurred in 9% of patients in the combined-therapy group and 11% in the budesonide-only group. The risk of exacerbation was 17% lower in the combined-therapy group (hazard ratio, 0.84; $p=0.002$).

Both the safety and efficacy findings of the study were consistent across all patient subgroups stratified by age, gender, race, and region.

Peters S, et al: Serious asthma events with budesonide plus formoterol vs. budesonide alone. *NEJM* 2016;375 (September 1):850–860. From Wake Forest School of Medicine, Winston-Salem, NC; and other institutions including AstraZeneca, Gothenburg, Sweden and Gaithersburg, MD. **Funded by AstraZeneca. Seven study authors disclosed financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

Common Drug Trade Names: budesonide—*Pulmicort*; budesonide-formoterol—*Symbicort*

*See Reference Guide.

Benefits and Risks of Statins

A panel of British and American epidemiologists undertook a comprehensive review in an effort to clarify for physicians, patients, and the public the risks and benefits of statin therapy. According to the review, statins are underutilized by patients at increased risk of cardiovascular events due to exaggerated claims about adverse effects. Large-scale evidence from randomized trials provides reliable estimates of the benefits of statin therapy, while claims that they commonly cause adverse effects reflect a failure to recognize the limitations of other sources of evidence.

Efficacy. High-quality evidence, in the form of randomized controlled trials, indicates that effective low-cost statin regimens reduce LDL cholesterol by >50% (i.e. ≥ 77 mg/dL) in individuals with LDL concentrations of ≥ 154 mg/dL. These results indicate that each annual incremental reduction in LDL of about 40 mg/dL with statin therapy produces a 25% reduction in major vascular events (i.e., coronary deaths, MIs, strokes, and coronary revascularizations) for an overall risk reduction of 45%. Lowering LDL cholesterol by 77 mg/dL with statins for about 5 years in 10,000 patients would prevent major

vascular events in 1000 (10%) high-risk patients and 500 (5%) low-risk patients.

Safety. A limited number of adverse events have been reliably attributed to statins. Based on clinical trial evidence, treatment of 10,000 patients for 5 years with a standard statin regimen is expected to result in about 5 cases of myopathy, 50–100 cases of new-onset diabetes, and 5–10 hemorrhagic strokes, for an overall adverse event incidence of 1–2% over 5 years. There is no evidence that statins cause other adverse events, and it is highly unlikely that any important adverse events remain undiscovered. In addition, any harmful effects of statins can usually be reversed without any residual problems by stopping treatment.

Discussion: Based on case series, adverse-event reports, and non-randomized observational studies, statins have been suspected of causing frequent intolerance, reflected as muscle pain and weakness. These reports describe an incidence of up to 20% and have fueled an increased reluctance of physicians to prescribe statins, reduced patient compliance, and increased likelihood of stopping statin therapy. However, in clinical trials, only about 0.1–0.2% of patients discontinued treatment because of muscle-related symptoms.

Collins R, et al: Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016; doi 10.1016/S0140-6736(16)31357-5. From the University of Oxford, U.K.; and other institutions. **The review was conducted with no external funding. Twenty-three study authors disclosed financial relationships with commercial sources; the remaining 5 authors declared no competing interests.**

Allergy Medications During Pregnancy

While allergen avoidance measures are the first choice for pregnant patients, when necessary, prescription of allergy medication for pregnant women should be based on the FDA's risk categories. Categories A and B are recognized to be safe, while Category C drugs (those with known adverse effects in animal studies but no adequate human studies) should be used on a case-by-case basis. Category D and E drugs should be avoided.

Intranasal steroids (e.g., fluticasone, budesonide, triamcinolone) are the drugs of choice for allergic rhinitis. Most are Category C, regarded as safe by current guidelines and appropriate to continue in pregnancy if they are working. Budesonide, the only Category B intranasal steroid with extensive evidence of safety in pregnancy, may be the best option in the class for pregnant patients.

Asthma / Allergy Medications to Avoid During Pregnancy	
Agent or Drug Class	Potential Complications
Oral decongestants	Potential to cause GI malformations in offspring, particularly during the first trimester
First Generation Oral Antihistamines	Potential to cause fetal malformations including cleft palate (diphenhydramine)
Intranasal antihistamines	Intranasal azelastine should be avoided because it has been associated with minor adverse effects in fetal animals and there is no safety data in humans. It is also costly and associated with sedation.
Immunologic Agents	Mycophenolate mofetil, methotrexate, cyclosporine, and azathioprine are contraindicated in pregnancy.
Humanized Monoclonal Antibodies	Omalizumab is not recommended because of the black box warning regarding anaphylaxis, which can be life-threatening to both mother and fetus.

Oral antihistamines are used to treat pruritus and rhinorrhea. First-generation oral antihistamines (e.g., brompheniramine, hydroxyzine, diphenhydramine) are not recommended for pregnant women. However, second-generation agents (e.g., loratadine or cetirizine) have an excellent safety profile, and the latter drug has the additional benefit of relieving nausea and vomiting. Fexofenadine and desloratidine have been associated with low birth weight in animal models and are classified as Category C.

Systemic steroids may increase risk of low birth weight, intrauterine growth restriction, preterm birth, and preeclampsia. However, the benefits of controlling asthma during pregnancy outweigh these risks.

Asthma and allergic rhinitis are commonly treated with montelukast or zafirlukast, which are

considered safe for use in pregnancy. In addition, for patients with asthma, albuterol appears to be the safest short-acting β -agonist and salmeterol the preferred long-acting bronchodilator.

Gonzalez-Estrada A, et al: Allergy medications during pregnancy. *The American Journal of the Medical Sciences* 2016;352 (September):326–331. From Quillen College of Medicine, East Tennessee State University, Johnson City, TN. **Source of funding not stated. The authors declared no competing interests.**

Common Drug Trade Names: albuterol—*Proventil, Ventolin*; azathioprine—*Azasan, Imuran*; azelastine—*Astelin, Astepro*; brompheniramine—*Respa-BR*; budesonide, inhaled—*Symbicort*; cetirizine—*Zyrtec*; desloratidine—*Clarinex*; diphenhydramine—*Benadryl*; fexofenadine—*Allegra*; fluticasone—*Flonase*; hydroxyzine—*Vistaril*; loratadine—*Claritin*; methotrexate—*Rheumatrex, Trexall*; montelukast—*Singulair*; mycophenolate mofetil—*Cellcept, Myfortic*; omalizumab—*Xolair*; salmeterol—*Serevent*; triamcinolone—*Nasacort*; zafirlukast—*Accolate*

Reference Guide

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.

Relative Risk: 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.

T Score: A statistical measurement of the number of standard deviations that a value is above or below the group average.

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Generic Olmesartan

The FDA recently granted approval for a generic version of the angiotensin II receptor blocker olmesartan (*Benicar*). Also available will be generic versions of 3 olmesartan combination medications: *Benicar HCT*, which combines olmesartan and hydrochlorothiazide; *Azor*, which combines olmesartan and amlodipine; and *Tribenzor*, which combines all 3 agents.

FDA gives green light to first olmesartan generics. *Medscape*. October 27, 2016.

Tamoxifen, SSRIs, and Mortality

According to results of a large cohort study, selective serotonin reuptake inhibitor-associated inhibition of CYP2D6, the enzyme that converts tamoxifen to its most important active metabolite, does not increase risk of death.¹

Methods: This study compared mortality in women concomitantly treated with tamoxifen and fluoxetine or paroxetine, which are potent inhibitors of CYP2D6, versus any of the other SSRIs, which are not potent inhibitors. The analysis included data from 5 large U.S. electronic healthcare databases covering privately insured women and those insured by Medicare or Medicaid. The study cohort included all women simultaneously receiving tamoxifen and an SSRI between 1995 and 2013. The analysis was adjusted for a large number of covariates using propensity scores* for the probability of being prescribed fluoxetine or paroxetine instead of another SSRI.

Results: The study cohort comprised 6067 women who began using tamoxifen before starting an SSRI (of whom 2268 received fluoxetine or paroxetine) and 8465 who received the SSRI first (3531 who used the high-potency CYP2D6 inhibitors). The study women had a mean age of about 55 years at the start of follow-up, which lasted a median of 2.2 years. More than half had a diagnosis of stage 0 or I breast cancer.

Fluoxetine and paroxetine were not associated with increased mortality compared with the other SSRIs (hazard ratio,* 0.96). Mortality was not increased either in women who started tamoxifen before the SSRI (hazard ratio, 0.91) or in those who began SSRI treatment first (hazard ratio, 1.02). Results did not differ when the analysis was stratified by the length of concomitant exposure, when the analysis was limited to fluoxetine or paroxetine as individual agents, or when it included only women who had received a diagnosis of stage 0-IV breast cancer within 180 days before receiving a tamoxifen prescription.

Discussion: Tamoxifen is a prodrug that is converted to 2 active metabolites. It is possible that the lack of an effect of CYP2D6 inhibition may be attributable to the other metabolite, or to the usual practice of administering tamoxifen at much higher doses than are required to be clinically active. A previous study found increases in mortality with paroxetine but not fluoxetine, but in women who were on average 20 years older than those in the present study.² Menopausal

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status might affect the relationship among tamoxifen, CYP2D6 inhibition, and mortality. An important limitation of this study was the lack of information on breast cancer-specific mortality.

¹Donneyong M, et al: Risk of mortality with concomitant use of tamoxifen and selective serotonin reuptake inhibitors: multi-database cohort study. *BMJ* 2016; doi: 10.1136/bmj.i5014. From Brigham and Women's Hospital and other institutions, Boston, MA. **Funded by the Agency for Healthcare Research and Quality. Two study authors declared financial relationships with commercial sources; the remaining 6 authors declared no competing interests.**

²Kelly C, et al: Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. *BMJ* 2010; doi 10.1136/bmj.c693.

Common Drug Trade Names: fluoxetine—*Prozac*; paroxetine—*Paxil*; tamoxifen—*Nolvadex*

*See Reference Guide.

Romozosumab in Osteoporosis

In a phase III clinical trial, the anti-sclerostin antibody romozosumab was associated with a reduced incidence of vertebral fracture in women with osteoporosis, both after 1 year of placebo-controlled treatment and after a second year of treatment with open-label denosumab.

Background: Romozosumab is a monoclonal antibody that binds and inhibits sclerostin, an inhibitor of bone formation, resulting in increased bone formation and reduced bone resorption. Denosumab is an FDA-approved antiresorptive biologic agent.

Methods: This multinational study was carried out in postmenopausal women, aged 55–90 years, with osteoporosis, defined as a T-score* of -2.5 to -3.5 at the total hip or femoral neck. For the first study year, the women were randomized to double-blind treatment with monthly subcutaneous injections of 210 mg romozosumab or placebo. In year 2, romozosumab or placebo was stopped and all participants received open-label subcutaneous 60-mg injections of denosumab every 6 months. Lateral spinal radiographs were obtained at baseline and after 6, 12, and 24 months of treatment. Bone mineral density was evaluated at 6-month intervals in a subset of women. The primary study endpoint was the cumulative incidence of new vertebral fracture at 12 and 24 months.

Results: A total of 7180 women (mean age, 71 years) were randomized; 89% completed 1 year of treatment and 84% completed 2 years.

New vertebral fractures in women treated with romozosumab or placebo, followed by denosumab		
	Romozosumab to denosumab	Placebo to denosumab
1-year outcomes		
number of patients	3321	3322
number of fractures	16	59
incidence	0.5%	1.8%
risk ratio;* p value	0.27; p<0.001	—
2-year outcomes		
number of patients	3325	3327
number of fractures	21	84
incidence	0.6%	2.5%
risk ratio; p value	0.25; p<0.001	—

Compared with placebo, romozosumab was associated with a 73% lower rate of new vertebral fracture after 1 year. (See table.) After the second year, women who had received romozosumab in phase 1 had a 75% lower cumulative incidence of vertebral fracture. Risk of nonvertebral fracture was lower at 1 and 2 years with romozosumab, but the difference was not statistically significant.

In a subset of women in whom markers of bone turnover were measured, there was evidence of increased bone mineral density by 6 and 12 months, continuing to increase after the transition to denosumab. Levels of the bone-formation marker P1NP increased during the first 2 weeks of romozosumab and had returned to baseline levels at 9 months. Levels of the bone resorption marker β -CTX decreased by day 14 of romozosumab treatment and remained below levels in the placebo group throughout the study.

Osteonecrosis of the jaw occurred in 2 women in the romozosumab group: 1 who had ill-fitting dentures and 1 following a tooth extraction after receiving her first dose of denosumab. Another patient had an atypical femoral fracture 3.5 months after starting romozosumab.

Editorial.² Concern over osteonecrosis of the jaw and atypical femoral fractures has led to a decrease in the use of bisphosphonates to treat osteoporosis and an urgent need for new treatments. Sequential therapy with 2 biologic agents

represents a promising new approach. Results of the present study can be viewed as a success in terms of vertebral-fracture prevention, but the nonsignificant reduction in nonvertebral fractures is a disappointment. One case of jaw osteonecrosis might be attributed to the use of denosumab, but the other 2 bony complications were unexpected, and it is not clear how frequent these adverse events might be with greater use of the drug.

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

¹Cosman F, et al: Romosozumab treatment in postmenopausal women with osteoporosis. *NEJM* 2016; doi 10.1056/NEJMoa1607948. From Helen Hayes Hospital, West Haverstraw, NY; and other institutions including Amgen, Thousand Oaks, CA, and UCB Pharma, Brussels, Belgium. **Funded by Amgen; and UCB Pharma. Sixteen study authors disclosed financial relationships with commercial sources, including Amgen or UCB Pharma; the remaining 1 author declared no competing interests.**

²Rosen C, Ingelfinger J: Building better bones with biologics—a new approach to osteoporosis [editorial]? *NEJM* 2016; doi 10.1056/NEJMe1611863. From Maine Medical Center Research Institute, Scarborough, ME. **The authors declared no competing interests.**

*See Reference Guide.

Investigational Alzheimer's Drug

In a randomized clinical trial, the investigational $\alpha 7$ nicotinic acetylcholine receptor agonist ABT-126 failed to show efficacy in patients with Alzheimer's disease. In view of the present results, phase III trials of the drug have been put on hold and the agent has been withdrawn from clinical development. Future development of this class of drugs is uncertain.

Methods: The trial was conducted in patients, aged 55–90 years, with mild-to-moderate Alzheimer's dementia. Patients were randomly assigned to 1 of 3 different doses of ABT-126, placebo, or the active control donepezil (*Aricept*), and received treatment for 24 weeks. After the first 100 patients were enrolled, subsequent patients were randomized with a higher probability to receive the more effective doses of ABT-126. In the second study phase, also 24 weeks, patients were randomly assigned to receive the most effective ABT-126 dose or placebo. The primary efficacy measure was change from baseline to week 24 in the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog).

Results: A total of 438 patients received treatment in the first study phase. The second phase population included 124 patients who completed the first phase and 88 newly enrolled patients. No statisti-

cally significant improvement from baseline in ADAS-Cog score was observed in any of the ABT-126 dosage groups, relative to placebo. In contrast, the donepezil group showed significant improvement in ADAS-Cog scores, indicating the study design was adequate to show an effect. By the end of the second study phase, ABT-126 had some modest treatment effects, but these did not exceed those of donepezil.

Gault L, et al: ABT-126 monotherapy in mild-to-moderate Alzheimer's dementia: randomized double-blind, placebo and active controlled adaptive trial and open-label extension. *Alzheimer's Research and Therapy* 2016; doi 10.1186/s13195-016-0210-1. From AbbVie, Inc., Chicago, IL; and other institutions. **Funded by AbbVie, Inc. All study authors declared financial relationships with commercial sources.**

Antidepressants and Falls in Older Women

Prescribers may avoid selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) in frail elderly patients out of concern that these agents increase risk of falls. However, an analysis of data from a clinical trial suggests that other antidepressants, with the possible exception of bupropion, may not be any safer with regard to falls.

Methods: Data from a 2-year clinical trial of a bisphosphonate in frail women, aged ≥ 65 years, living in long-term care facilities were analyzed to determine the risk of recurrent falls with antidepressant use. Participating women ($n=181$; mean age, 85 years) had a history of osteoporosis or vertebral/hip fracture and a life expectancy of ≥ 2 years. Rates of recurrent falls (i.e., ≥ 2 within 6 months) were compared among groups of women receiving SSRIs or TCAs, other antidepressants, or no antidepressant. The "other" category included duloxetine, venlafaxine, mirtazapine, trazodone, and bupropion. Because bupropion is the only one of these agents with low effect on serotonin, a separate analysis was carried out for bupropion only.

Results: The majority of participants (72%) were cognitively intact, while 28% were moderately-to-severely cognitively impaired. At baseline, 33% of women were taking an SSRI or tricyclic, and 18% were taking another antidepressant, including 5 women (3%) receiving bupropion. Depression/anxiety was the most common indication for antidepressant use. Average prescribed doses of non-SSRI/non-tricyclic antidepressants were 67–73% higher than for the minimum effective geriatric dose for depression.

A total of 18% of the study women had recurrent falls during the first 6 months of follow-up, and 16% during the second 6 months. After adjustment for cognitive status, comorbidity, anxiety/depression symptoms, and other medications that may increase falls, women receiving non-SSRI/non-TCAs had a 2-fold increased incidence of recurrent falls compared with women not receiving any antidepressant (adjusted odds ratio,* 2.14; p=0.05). SSRI/TCAs were associated with a smaller increase that was not statistically significant (adjusted odds ratio, 1.46). There was no meaningful change in the odds ratios when the analysis was controlled for the use of bisphosphonate.

When the women taking bupropion were removed from the "other" category, risk for recurrent falls was further increased (adjusted odds ratio, 2.73; p=0.01). Bupropion was associated

with a 60% lower risk of fractures than no antidepressant use, but the number of exposed women was too small to determine statistical significance.

Discussion: These observations are consistent with findings of previous research associating non-SSRI/non-TCAs with hip fracture.

Naples J, et al: Non-tricyclic and non-selective serotonin reuptake inhibitor antidepressants and recurrent falls in frail older women. *American Journal of Geriatric Psychiatry* 2016; doi 10.1016/j.jagp.2016.08.008. From the University of Pittsburgh and the VA Pittsburgh Healthcare System, PA. **Funded by the National Institutes on Aging; and other sources. One study author disclosed financial relationships with commercial sources; the remaining 4 authors declared no competing interests.**

Common Drug Trade Names: bupropion—*Wellbutrin*; duloxetine—*Cymbalta*; mirtazapine—*Remeron*; trazodone—*Oleptro*; venlafaxine—*Effexor*

*See Reference Guide.

Reference Guide

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.

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.

T Score: A statistical measurement of the number of standard deviations that a value is above or below the group average.

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NSAIDs and Heart Failure

According to a population-based cohort study, the known NSAID-associated increase in heart-failure risk extends to conventional agents as well as COX-2 inhibitors, it varies among individual NSAIDs, and is dose-dependent.

Methods: Study data were extracted from 4 large electronic health-record databases containing information on NSAIDs prescribed and dispensed, hospitalizations, and outpatient diagnoses. The study cohort consisted of all adults who received ≥ 1 NSAID prescription or dispensation after ≥ 1 year without NSAID treatment and who had not been admitted for heart failure in the previous year. Patients admitted for heart failure during the follow-up period were identified as cases and were each matched with up to 100 controls according to age, gender, and date of cohort entry. The analysis included 23 traditional NSAIDs and 4 selective COX-2 inhibitors. Cohort members were categorized as current NSAID users (within 14 days before hospitalization), recent users (within 15–183 days), and past users.

Results: The study cohort consisted of >92,000 persons (average age, 77 years; 45% men) hospitalized for heart failure and >8 million controls. Within the cohort, 17% of case patients and 14% of controls were current users of NSAIDs. No individual NSAID was used by >3% of patients.

A total of 6 NSAIDs marketed in the U.S. were associated with increased risk of heart-failure hospitalization, which remained statistically significant after correction for multiple compar-

isons. These NSAIDs, in declining order of risk, were ketorolac (odds ratio [OR],* 1.83), indomethacin (OR, 1.51), piroxicam (OR, 1.27), diclofenac (OR, 1.19), ibuprofen (OR, 1.18), and naproxen (1.16). In addition, risk estimates were elevated for sulindac (OR, 1.32) and several other less commonly used NSAIDs not available in the U.S, but these associations were not statistically significant. A dose-response analysis showed that risk of heart-failure hospitalization was increased more than 2-fold in current users of high doses of diclofenac, indomethacin, and piroxicam.

Compared with past NSAID use, current use was associated with a 20% increased risk of heart-failure hospitalization (OR, 1.19). There was no evidence that recent use of any NSAID was associated with increased risk of heart failure. Celecoxib was the most frequently prescribed COX-2 inhibitor. Current use of celecoxib was not associated with increased risk of heart-failure hospitalization, either compared with past NSAID use or with current use of the other NSAIDs, and even when celecoxib was used at high doses.

Arfe A, et al: Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. *BMJ* 2016; doi 10.1136/bmj.i4857. From the University of Milano-Bicocca, Milan, Italy; and other institutions. **Funded by the European Community. Eleven study authors declared financial relationships with commercial sources; the remaining 9 authors declared no competing interests.**

Common Drug Trade Names: celecoxib—*Celebrex*; diclofenac—*Voltaren*; indomethacin—*Indocin*; ketorolac—*Toradol*; naproxen—*Naprosyn*; piroxicam—*Feldene*; sulindac—*Clinoril*

*See Reference Guide.

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New Drugs for Treating Osteoporosis

Advances in understanding bone pathophysiology have led to the development of several new classes of drugs to treat osteoporosis, according to a review. For the first time, agents are coming online that uncouple the stimulation of bone formation from that of bone resorption, favoring increases in bone mineral density (BMD). Unfortunately the new drugs' effects appear limited to the lumbar spine; there is not yet an ideal agent that equally reduces risk of vertebral and non-vertebral fractures and has minimal long-term adverse effects.

Remodeling of bone involves 2 processes, bone resorption mediated by osteoclasts and bone formation mediated by osteoblasts. A challenge in treating osteoporosis is that these 2 processes are coupled. Bisphosphonates, currently the mainstay of osteoporosis prevention and treatment, inhibit the genesis of osteoclasts, leading to low bone turnover and reduced coupled activity of osteoblasts for bone formation, with the possible long-term consequence of defective bone microarchitecture and atypical fractures. These fractures are now a recognized complication of bisphosphonate use, and patient reassessment is recommended after using these agents for 3–5 years. Recent clinical trials have examined combinations of currently available treatments—for example, combining anabolic therapy such as teriparatide with an antiresorptive therapy such as a bisphosphonate or denosumab, which inhibits the maturation of osteoclasts. These combinations favorably affect BMD, particularly at the hip, but there have not yet been clinical trials with enough statistical power to show a reduction in fractures.

Three novel therapies that uncouple bone formation and resorption are currently in late-phase clinical trials. Odanacatib is an inhibitor of cathepsin K, an enzyme produced by osteoclasts that degrades type I collagen, the major component of bone matrix. This agent, which is dosed once a week, showed dose-related efficacy in increasing lumbar spine, total hip, femoral neck, trochanter, and one-third radius BMD in postmenopausal women treated for 12 months. The drug was related to decreases in levels of bone resorption markers and only modest, transient decreases in markers of bone formation, consistent with the uncoupling hypothesis. Extension studies out to 5 years show a continuing increase in BMD at multiple sites with ongoing treatment and a

return of BMD to baseline after discontinuation. Early results of an ongoing Phase III clinical trial suggest these findings may translate to reduced rates of fracture at several sites, although increases in atypical femoral fractures also occurred.

Romosozumab is a monoclonal antibody that blocks sclerostin, a protein that inhibits osteoblast proliferation and function. It increases bone formation markers and decreases a bone resorption marker, again suggesting uncoupling. A phase II study showed a significant increase in lumbar spine BMD, which appeared to be transient even with continued treatment. Phase III studies are ongoing.

Endogenous parathyroid hormone-related protein (PTHrP) is associated with increases in spine BMD with no accompanying increase in bone resorption markers, and it is better tolerated than the related teriparatide. In a phase II trial, abaloparatide, a novel synthetic analogue of PTHrP, was associated with increases in lumbar spine, femoral neck, and total hip BMD. Phase III trials are underway.

Chan C, et al: Novel advances in the treatment of osteoporosis. *British Medical Bulletin* 2016;119 (September):129–141. From Southampton General Hospital, UK. **Source of funding not stated. The authors declared no competing interests.**

Common Drug Trade Names: denosumab—*Prolia, Xgeva*; teriparatide—*Forteo*

Cranberry Capsules and Urinary Health

In a placebo-controlled trial, daily cranberry capsules did not prevent bacteriuria with pyuria in women living in nursing homes.¹

Methods: Study participants were female long-term nursing home residents, aged ≥ 65 years, with a clean-catch urine specimen at baseline. An indwelling bladder catheter was grounds for exclusion. Randomized, double-blind active treatment consisted of 2 daily cranberry capsules containing a total of 72 mg proanthocyanidins, a dose equivalent to 20 oz. cranberry juice. During 1 year of active or placebo treatment, urinary specimens were obtained every 2 months and tested for bacteriuria or pyuria.

Results: A total of 185 women were randomized to treatment. At baseline, the average age was 86 years, about one-third had bacteriuria plus pyuria, and two-thirds had urinary incontinence. About one-third had experienced a urinary tract infection (UTI) in the past year. A total of 147 patients completed 1 year of surveillance, and 33 died. The proportion of urinary samples that met criteria for

bacteria/pyuria over 12 months did not differ between treatments, with rates of 26% in the women receiving cranberry capsules and 30% in the placebo group. Rates of bacteriuria were somewhat lower with cranberry use in the first 6 months, but at no point was the difference statistically significant. There were 10 symptomatic UTIs in 9 patients in the active treatment group and 12 in 9 patients in the control group. The 2 treatment groups did not differ in rates of adverse events, antibiotic use for suspected UTI, hospitalization, or death.

Discussion: The study was conducted in a group of patients with a high prevalence of bacteriuria. Capsules were used instead of juice to obtain a standardized dose and for better tolerance. Proanthocyanidins in cranberry juice reportedly inhibit binding of *E. coli* to uroepithelial cells, but there is no evidence this mechanism has a role in preventing human UTI.² This and numerous other clinical trials of cranberry products in multiple populations have failed to provide support for the continuing promotion of cranberry products for urinary tract health in the popular media.

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

¹Juthani-Mehta M, et al: Effect of cranberry capsules on bacteriuria plus pyuria among older women in nursing homes: a randomized clinical trial. *JAMA* 2016; doi: 10.1001/jama.2016.16141. From Yale School of Medicine and Yale School of Public Health, New Haven, CT. **Funded by the National Institute on Aging. The authors declared no competing interests.**

²Nicolle L: Cranberry for prevention of urinary tract infection? Time to move on [editorial]. *JAMA* 2016; doi: 10.1001/jama.2016.16140. From the University of Manitoba, Canada. **The author declared no competing interests.**

*See Reference Guide.

Breast Cancer and GLP-1 Analogues

Elevated breast cancer incidence has been observed in some clinical trials of glucagon-like peptide-1 analogues. However, in a large population-based study of women with diabetes, the agents were not associated with increased breast cancer risk, suggesting the increase might be attributable to increased breast cancer detection in GLP-1 analogue users.

Methods: The study was conducted using the U.K. Clinical Practice Research Datalink, which includes data from about 700 general practices. The study cohort comprised all women aged ≥ 40 years who were given a prescription for a new non-insulin glucose-lowering drug between 1988

and mid-2015. Within this cohort, patients were selected who started a new glucose-lowering drug class in 2007, when the first incretin-based drugs were introduced, or later. Patients with a previous diagnosis of breast cancer were excluded, as were those with < 1 year of follow-up after the prescription and those who received a diagnosis of breast cancer within the first year. The reference group for the comparison of breast cancer incidence consisted of women using dipeptidyl peptidase-4 (DPP-4) inhibitors, another class of incretin-based drugs that were also introduced in 2007 and that have not previously been associated with breast cancer risk.

Results: The cohort included nearly 45,000 women, who were followed for a mean of 3.5 years. Nearly 2500 women were given a prescription for a GLP-1 analogue: liraglutide (43%), exenatide (32%), lixisenatide (4%), or multiple agents (21%). The entire patient cohort had a mean age of 65 years, and the majority of women had a body mass index of ≥ 30 .

During follow-up, there were 31 incident cases of breast cancer in women using GLP-1 analogues and 68 in those using DPP-4 inhibitors. Compared with DPP-4 inhibitor use, use of GLP-1 analogues was not associated with increased risk of breast cancer (adjusted hazard ratio,* 1.40). Similar hazard ratios were observed when each of the 2 most commonly used GLP-1 analogues, liraglutide and exenatide, were analyzed separately. In secondary analyses, breast cancer risk was increased in women who had used GLP-1 analogues for 2–3 years (hazard ratio, 2.66), but the incidence returned to background levels after 3 years. No association was revealed when cases occurring during the first year of use were included in the analysis. The rate of mammographic screening was higher in women who took GLP-1 analogues than in those who took DPP-4 inhibitors. Risk of breast cancer was higher in women with no history of mammographic screening in the 3 years before cohort entry.

Hicks B, et al: Glucagon-like peptide-1 analogues and risk of breast cancer in women with type 2 diabetes: population based cohort study using the UK Clinical Practice Research Datalink. *BMJ* 2016; doi: 10.1136/bmj.i5340. From Jewish General Hospital and McGill University, Montreal, Canada. **Funded by the Canadian Institutes of Health Research. One study author disclosed financial relationships with commercial sources; the remaining 5 authors declared no competing interests.**

Common Drug Trade Names: exenatide—*Byetta*; liraglutide—*Saxenda, Victoza*; lixisenatide—*Adlyxin*

*See Reference Guide.

Opioid Poisoning

Hospitalizations for prescription opioid poisoning among children and adolescents increased nearly 2-fold from 1997 to 2012, according to nationwide cohort data. This trend mirrors a similar increase in adults, which has been attributed to the rise in prescription of opioids to treat chronic pain.

Methods: The Kids' Inpatient Database is a U.S. database of pediatric hospitalizations maintained by the Agency for Healthcare Research and Quality, which releases data every 3 years. The present study was an examination of hospitalizations for prescription opioid poisonings in patients, aged 1–19 years, at 3-year intervals spanning 1997 to 2012. The present analysis is based on about 6–7 million hospital discharges. Incidence estimates were for the entire U.S. population, weighted and based on the at-risk population in each age group during each risk period.

Results: More than 13,000 hospitalizations for prescription opioid poisoning were identified, of which 176 cases were fatal. The annual incidence of hospitalizations for prescription opioid poisoning increased over the study years, from 1.40 per 100,000 to 3.71 per 100,000, a weighted increase of 165%. The largest proportional

increase, 205%, occurred in children aged 1–4 years, and the largest absolute increase, occurring in adolescents aged 15–19 years, was from 3.69 to 10.17 per 100,000 (a weighted 176% increase). When poisonings were examined by intent, only 16 were attributed to attempts at suicide or self-injury in children under age 10 years during the entire study period. In those aged 10–14 years, the incidence of self-poisoning increased 37% over the study period, and accidental poisonings increased 82%. In older adolescents, these trends were more marked, with increases of 140% for self-inflicted poisoning and 303% for accidental poisoning.

Discussion: This study provides important details about the consequences for children and adolescents of widespread opioid availability. The increased use of these agents for self-harm and suicide attempts in older adolescents is of particular concern, as is the increase in accidental poisonings, which is probably driven by misuse and abuse, rather than by therapeutic errors or the drugs' adverse effects.

Gaither J, et al: National trends in hospitalizations for opioid poisonings among children and adolescents, 1997 to 2012. *JAMA Pediatrics* 2016; doi 10.1001/jama-pediatrics.2016.2154. From Yale School of Medicine, New Haven, CT; and other institutions. **Funded by the National Institute on Drug Abuse. The authors declared no competing interests.**

Reference Guide

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.

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.

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