PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Crisaborole for Atopic Dermatitis

The phosphodiesterase 4 (PDE-4) inhibitor crisaborole (*Eucrisa*) ointment has received FDA approval as treatment for mild-to-moderate atopic dermatitis in patients aged ≥2 years. Although the mechanism of action in atopic dermatitis is unknown, patients who received crisaborole in clinical trials had greater response, indicated by clear or almost clear skin in 28 days, than those who received placebo. Common adverse effects of crisaborole include application site pain, including burning and stinging. Serious hypersensitivity reactions have also occurred.

FDA News Release: FDA approves Eucrisa for eczema. Available at http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm533371.htm.

Pioglitazone Cancer Warning

Based on results of an updated review, the FDA has issued a new warning about increased risk of bladder cancer in patients receiving treatment with pioglitazone (*Actos* and others). An initial warning was issued in 2010 based on interim results of an epidemiological study. Labels for all pioglitazone-containing drugs were updated to reflect the risk in 2011. Labels will again be updated to reflect the new research confirming the association.

Patients with active bladder cancer should not be given pioglitazone, and the risk–benefit ratio should be carefully considered before prescribing pioglitazone-containing products to patients with a history of bladder cancer. In addition, patients taking the drug should be counseled to contact a healthcare professional if they experience blood or red-colored urine, new or worsening urge to urinate, or pain when urinating.

FDA Drug Safety Communication: Pioglitazone-containing Medicines: Updated FDA Review, Increased Risk of Bladder Cancer. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm532772.htm.

Analgesic Use and Hearing Loss

Long-term regular use of either acetaminophen or NSAIDs, but not aspirin, was associated with an increased rate of hearing loss in women participating in a longitudinal study.

Background: Results of previous studies indicate high doses of NSAIDs or salicylates can cause hearing loss. Mechanisms for this effect include impairment of outer hair cell function, reduced vascular supply to the cochlea, and inhibition of cyclooxygenase. Acetaminophen may deplete cochlear glutathione, which protects the cochlea from noise-induced damage.

Methods: Data were collected from the Nurses' Health Study's biannual questionnaires, beginning in 1990 when questions about analgesic use began to appear. The analysis excluded women with a history of cancer because of the ototoxicity of many chemotherapeutic drugs. Regular analgesic use was defined as use on ≥2 days per week, and duration of medication use was characterized as <1 year, 1–2 years, 3–4 years, 5–6 years, and >6 years. Women who used analgesics <2 days a

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week and those with <1 year of regular use were classified as unexposed for that questionnaire cycle. The primary study outcome was self-reported hearing problems between 1990 and 2012.

Results: Nearly 56,000 women (mean age, 54 years in 1990) were included in the analysis, of whom 16% reported regular aspirin use, 11% reported regular NSAID use, and 8% reported regular acetaminophen use. A total of 18,663 women experienced hearing loss during follow-up. Both NSAIDs and acetaminophen were associated with rates of hearing loss that increased progressively with years of exposure ($p<0.01$ for trend with both types of medication in adjusted analyses). In women exposed to NSAIDs for >6 years, the relative risk* for hearing loss was 1.10 compared with women with no exposure. In women exposed to acetaminophen for >6 years, the relative risk was 1.09 compared with unexposed women. Longer durations of use were correlated with increased risk for hearing loss. Assuming a causal relationship for regular use of analgesics, the proportion of all hearing loss attributable to regular use of NSAIDs and acetaminophen was 5.5%.

Discussion: The magnitude of the increase in risk for hearing loss was modest in the study, but given the high prevalence of analgesic use, public health implications could be large. It should be noted that while the results support an association between regular analgesic use and hearing loss, whether or not the association is causal could not be established based on the study design.

Lin B, et al: Duration of analgesic use and risk of hearing loss in women. *American Journal of Epidemiology* 2016; doi 10.1093/aje/kww154. From Massachusetts Eye and Ear Infirmary, Boston; and other institutions. **Funded by the NIH. The authors declared no competing interests.**

***See Reference Guide.**

Antipsychotic Safety in COPD

According to a population-based study, antipsychotic drugs are associated with increased risk of acute respiratory failure (ARF) in patients with chronic obstructive pulmonary disease.

Methods: Data from the Taiwan Longitudinal Health Insurance Database were analyzed for patients with COPD between 2000 and 2011. Case patients were those admitted to the hospital or receiving emergency care for ARF. With each patient serving as his or her own control, use of antipsychotics was compared between the 14 days preceding ARF treatment and the 75–88 days before ARF. The 14-day exposure period is based on previous case reports, in which ARF usually developed within 10 days of taking an antipsychotic, and the 75–88 days represents the half-life of depot antipsychotics.

Results: Nearly 12,000 cases of ARF were identified among >60,000 patients with COPD. After applying exclusion criteria, such as previous ARF, the analysis was limited to 5032 incident cases. More than three-fourths were men, and the average age was 73 years.

Among the patients with ARF, 593 (12%) had filled ≥1 antipsychotic prescription during the 14-day antipsychotic-exposure window, compared with 443 patients (9%) during the control period (adjusted odds ratio,* 1.66; $p<0.001$). Risks were increased by a similar amount whether the antipsychotic was a conventional agent or an atypical and whether it was given orally or by injection. Risks were increased even at the lowest antipsychotic dosages (≤25% of the defined daily dose), although they were highest in patients receiving the defined daily dose or more (adjusted odds ratio, 3.74; $p=0.001$).

Discussion: This study was prompted by 12 case reports of ARF in patients taking a variety of antipsychotics, and the results highlight a life-threatening adverse respiratory effect of antipsychotic treatment that is not usually considered clinically. According to the case reports, ARF may occur shortly after increasing the dose or after an overdose, and stopping the antipsychotic leads to resolution of symptoms within 48 hours. Antipsychotics may inhibit the respiratory pattern generator in the brainstem via their effects on serotonin, dopamine, and histamine. Other potential mechanisms include dystonia in the larynx due to dopamine blockade and serotonin-related collapse of upper airway muscles.

Wang M-T, et al: Association between antipsychotic agents and risk of acute respiratory failure in patients with chronic obstructive pulmonary disease. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2016.3793. From the National Defense Medical Center, Taipei, Taiwan; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

***See Reference Guide.**

Cholinesterase Inhibitors in Alzheimer's

Patients who do not experience response to cholinesterase inhibitors after 3 months may still benefit from more prolonged treatment, according

to the results of a naturalistic longitudinal study. This observation contradicts some guidelines that recommend discontinuing these agents after 3 or 6 months in patients without an initial response.

Methods: This retrospective longitudinal study included 628 patients who received treatment with a cholinesterase inhibitor at 2 memory clinics in Italy. Patients were aged ≥65 years, had a diagnosis of Alzheimer's disease according to standard criteria, and initially had mild-to-moderate dementia. Patients were evaluated after 3 months of treatment and then at 6-month intervals for up to 3 years, while still receiving treatment. After 3 months of treatment, those whose Mini-Mental State Examination (MMSE) scores were increased or unchanged were considered responders and those whose MMSE scores decreased were considered nonresponders. Based on population averages, the investigators defined disease progression as a loss of ≥2 points per year on the MMSE. Functional status was evaluated at every visit using the Katz Index of Independence in Activities of Daily Living (ADL) and the Lawton-Brody Instrumental Activities of Daily Living (IADL). Patients were classified as either young-old (≤75 years) or old-old (≥76 years). The 3 available cholinesterase inhibitors (i.e., donepezil, rivastigmine, galantamine) were evaluated as a class because they are believed to have equivalent efficacy.

Results: After 3 months of cholinesterase-inhibitor treatment, 56% of patients met response criteria. The responder group was predominantly female (67%) and younger than the nonresponders (mean ages, 74 and 78 years, respectively). Responders had a significantly earlier age of onset of the disease ($p<0.0001$), a higher level of education ($p<0.001$), and lower baseline MMSE scores ($p=0.004$), but higher ADL ($p<0.0001$) and IADL scores ($p=0.017$). Outcomes did not differ among the 3 cholinesterase inhibitors.

The effect of initial response on the longitudinal disease course was assessed in 247 patients who had 6 follow-up evaluations over the 3 years. In these patients, MMSE scores remained lower in initial nonresponders than in responders, but the average course of decline was slower in nonresponders: 1.0 versus 1.6 points per year ($p<0.0001$). Initial response did not influence scores on the ADL or IADL evaluations of functional status.

The old-old patients had a slower annual rate of MMSE decline than the younger patients: 1.0 versus 1.32 points ($p=0.004$). They also had sig-nificantly slower rates of decline on the 2 measures of function. Old age was associated with a lower probability of progression of disease (odds ratio,* 0.948; $p=0.003$). Patients who initially had response to treatment had a higher likelihood of disease progression (odds ratio, 3.733; $p<0.0001$).

Discussion: There have been few other studies of the long-term effects of cholinesterase inhibitors in Alzheimer's disease. This study shows that, in terms of cognitive impairment, patients with a positive initial response have better long-term outcomes, but those without initial response also benefit via a slower rate of decline. In addition, functional impairment is the primary cause of nursing home placement in patients with dementia, and as suggested by these results, continuing treatment could also slow functional decline.

Boccardi V, et al: Short-term response is not predictive of long-term response to acetylcholinesterase inhibitors in old age subjects with Alzheimer's disease: a "real world" study. *Journal of Alzheimer's Disease* 2016; doi 10.3233/JAD-160904. From the University of Perugia; and the Regional Neurogenetic Centre, Catanzaro, Italy. **Source of funding not stated. The authors declared no competing interests.**

Common Drug Trade Names*: donepezil—*Aricept*; galantamine—*Razadyne*; rivastigmine—*Exelon

***See Reference Guide.**

Loperamide Abuse

The over-the-counter antidiarrheal opioid loperamide is being used increasingly to self-medicate for opioid withdrawal and, less frequently, to achieve opioid psychoactive effects, according to a brief review. Once a Schedule V drug, loperamide is now widely and legally available, with the indication of decreasing the frequency of diarrhea.

At the recommended doses, loperamide acts mainly on intestinal opioid receptors, but high doses result in entry into the central nervous system (CNS). Cardiotoxicity is its main risk. Loperamide has not been recognized as a drug of abuse and has been the subject of few reports in the literature. It is also not tracked by national surveys or surveillance programs.

At the recommended antidiarrheal dosage range of 2–16 mg/day, loperamide is actively pumped out of the CNS at the blood-brain barrier by the P-glycoprotein transporter protein. At higher doses, this system is saturated and loperamide

enters the CNS. Loperamide is metabolized by the cytochrome P450 system. Bioavailability is only about 10–20%. The onset of action is about 1 hour after ingestion, and the half-life is between 7 and 19 hours.

Before 2013, there were no published reports of loperamide misuse. Reports of recreational use that described dosages in the range of 70–100 mg/day began appearing in social media in 2013. These were accompanied by drug and poison control agencies' reports of increases of 71% in presentations due to loperamide overdose. Social-media discussions suggest it is mainly used to treat opioid withdrawal symptoms. Prior use of opioids is a predisposing factor, and there are no reports or mentions of loperamide being a gateway drug. Some persons who use loperamide to treat withdrawal describe effects similar to buprenorphine, but without the cravings that result from discontinuation. Some recreational users describe a euphoric effect. There are no analgesic benefits.

High loperamide doses have been associated with cardiotoxicity: QT-interval prolongation and widening of the QRS interval. Because use is usually short term, there have been few reports of tolerance. Most users have been able to taper the drug successfully, with few or mild symptoms.

It can be difficult to detect misusers of loperamide. Overdose has been associated with drowsiness, vomiting, and abdominal pain. Patients who have taken a supratherapeutic dose may present with cardiac arrhythmias, and management should be aimed at reversing cardiotoxicity. Loperamide intoxication can be managed with naloxone. Identification of loperamide misuse should prompt a discussion of the underlying reason for use and possible treatment for opioid addiction.

Stanciu C, Gnanasegaram S: Loperamide, the "poor man's methadone": brief review. *Journal of Psychoactive Drugs* 2016; doi 10.1080/02791072.2016.1260188. From East Carolina University, Greenville, NC. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

Common Drug Trade Names*: buprenorphine—*Subutex*; loperamide—*Imodium A-D*; naloxone—*Narcan

Unauthorized Lithium Products

Health Canada has issued a warning regarding the safety of 3 products—*Lithium Plus*, *Serotonin Support*, and *Brain Support*—as they may contain lithium orotate. The products, which can pose serious health risks, are marketed by Cutting Edge Naturals.

MedEffect e-Notice: Unauthorized products "Lithium Plus, Serotonin Support, and Brain Support" may pose serious health risks. Available at http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/61608a-eng.php.

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.

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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Oral Pharmacotherapy for Type 2 Diabetes

The American College of Physicians (ACP) has updated its guideline on oral drug treatment of type 2 diabetes based on studies performed after the 2012 guideline was released and to include agents that received FDA approval since that time. Recommendations from the 2012 guideline were carried forward in areas where there was no new evidence.

Recommendation 1: Unless contraindicated, metformin should be prescribed as first-line oral pharmacotherapy for patients with type 2 diabetes who need to improve glycemic control. Metformin effectively reduces glycemic levels, is associated with weight loss, causes fewer hypoglycemic episodes, and is priced lower than most other pharmacologic options. It may also have an advantage over sulfonylureas in terms of cardiovascular mortality.

Recommendation 2: Adding a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin should be considered to improve glycemic control when a second oral therapy is needed. Although the evidence for specific combinations was considered weak, combining metformin with another therapy was more effective than metformin monotherapy at reducing HbA_{1c} levels, weight, and BP. However, the risk–benefit profiles differ between the potential combinations, and cost should also be factored into the choice. Although not specifically recommendations, the ACP did offer some guidance for choosing between options for add-on therapy:

- Sulfonylureas are the least expensive option as an add-on to metformin, but they are associated with increased risk for hypoglycemia and with weight gain.
- SGLT-2 inhibitors are preferred over sulfonylureas in terms of cardiovascular mortality, HbA_{1c}, weight, systolic BP, and heart rate.
- SGLT-2 inhibitors are preferred over DPP-4 inhibitors in terms of weight and systolic BP.
- DPP-4 inhibitors are preferred over sulfonylureas for long-term, all-cause, and cardiovascular mortality and morbidity.
- DPP-4 inhibitors are preferred over pioglitazone for short-term cardiovascular morbidity.
- DPP-4 inhibitors are preferred over sulfonylureas or thiazolidinediones for weight.

Comparing adverse effects, metformin monotherapy was associated with less risk of hypoglycemia than other monotherapies. Sulfonylureas increased risk for hypoglycemia, thiazolidinediones for congestive heart failure, and SGLT-2 inhibitors for genital mycotic infections. Thiazolidinediones and sulfonylureas were associated with more weight gain than the other drug classes.

Qaseem A, et al: Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians. *Annals of Internal Medicine* 2017; doi 10.7326/M16-1860. From the American College of Physicians, Philadelphia, PA; and other institutions. **Funded by the American College of Physicians. The authors disclosed no relationships with commercial sources.**

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Testosterone and Thromboembolism

Both the FDA and Health Canada recently required the addition of warnings regarding venous thromboembolism (VTE) risk to the labeling of testosterone products. Results of a population-based study support the association, which is of particular concern given the recent growth in off-label prescribing.

Methods: Study subjects were nearly 3-million men aged 20–89 years who were registered with the primary care-based U.K. Clinical Practice Research Datalink. Cases were defined as men who experienced a first pulmonary embolism or deep vein thrombosis between January 2001 and May 2013. Each case patient was matched with up to 50 controls for age, history of primary hypogonadism, and presence or absence of VTE risk factors (e.g., cancer, surgery, trauma, certain medical conditions) within the 90 days before the index event, or a history of cancer in the more remote past.

Results: During follow-up, >19,000 cases of VTE occurred, for an incidence of 15.8 per 10,000 person-years. The rate of testosterone use in patients with VTE was 0.36%, compared with 0.14% in the control group (adjusted rate ratio* of VTE associated with current testosterone, 1.25). The risk increase was limited to men who did not have pathological hypogonadism.

Martinez C, et al: Testosterone treatment and risk of venous thromboembolism: population based case-control study. *BMJ* 2016; doi 10.1136/bmj.i5968. From the Institute for Epidemiology, Statistics and Informatics, Frankfurt, Germany; and other institutions. **This research was conducted without external funding. Four study authors declared financial relationships with commercial sources; the remaining 3 authors declared no competing interests.**

***See Reference Guide.**

Relative Safety of Celecoxib

In a trial mandated by the FDA following the market withdrawal of the selective COX-2 inhibitor rofecoxib, the other available drug in this class, celecoxib (*Celebrex*), had cardiovascular safety similar to the nonselective NSAIDs naproxen and ibuprofen, in patients with arthritis.

Methods: The multicenter study enrolled >24,000 patients who required daily treatment with an NSAID for rheumatoid arthritis or osteoarthritis and who had cardiovascular disease or were at increased cardiovascular risk. Patients were randomly assigned to 100 mg celecoxib b.i.d., 600 mg ibuprofen t.i.d., or 375 mg naproxen b.i.d. Dosage increases were permitted within limits. The primary study endpoint was a composite of death from cardiovascular causes (including hemorrhagic death), nonfatal MI, or nonfatal stroke. A secondary outcome included both the primary outcome and other major adverse cardiovascular events: coronary revascularization or hospitalization for unstable angina or transient ischemic attack.

Results: Patients were followed for an average of 3–4 years. A total of 69% of patients stopped taking their assigned drug during follow-up, about one-fourth did not complete follow-up, and 2.5% died during the study. The primary composite cardiovascular endpoint occurred during follow-up in 2.3% of patients who received treatment with celecoxib, and the secondary endpoint, major cardiovascular events, in 4.2%. Similar proportions of patients who received naproxen or ibuprofen experienced these effects. Risks of adverse cardiovascular outcomes were somewhat lower with celecoxib than the other NSAIDS, but the differences were not statistically significant. (See table.) Relative hazards for these events were well within the study's prespecified noninferiority threshold. Rates of GI adverse events were significantly lower with celecoxib than the other 2 NSAIDs. Celecoxib was associated with significantly fewer serious renal adverse events than ibuprofen.

Comparison of primary and secondary outcomes in patients treated with celecoxib vs a nonselective NSAID

Outcome	Adjusted Hazard Ratio*
Primary Endpoint	
Celecoxib vs naproxen	0.93
Celecoxib vs ibuprofen	0.85
Major Adverse Cardiovascular Events	
Celecoxib vs naproxen	0.97
Celecoxib vs ibuprofen	0.87
Serious GI Events	
Celecoxib vs naproxen	0.71
Celecoxib vs ibuprofen	0.65
Renal Events	
Celecoxib vs naproxen	0.79
Celecoxib vs ibuprofen	0.61

Discussion: These results provide some reassurance about the safety of moderate-dose celecoxib

(dose was kept within the regulatory threshold of 200 mg/day for most patients), but not the safety of higher dosages. In addition, the observations do not reflect the relative safety of celecoxib compared with the >2 dozen other members of the NSAID drug class.

Nissen S, et al: Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *NEJM* 2016; doi 10.1056/NEJMoa1611593. From the Cleveland Clinic, OH; and other institutions. **Funded by Pfizer. Eleven study authors declared financial relationships with commercial sources; the remaining 7 authors declared no competing interests.**

***See Reference Guide.**

Warfarin/SSRIs, and Bleeding

Concomitant use of selective serotonin reuptake inhibitors increases risk of bleeding in patients taking warfarin because of the combination of anticoagulant action of warfarin and SSRIs' antiplatelet effects. Results of a cohort study suggest that bleeding risk is not further increased with use of fluoxetine or fluvoxamine, SSRIs that inhibit the enzyme that metabolizes warfarin.

Background: Because cardiovascular and cerebrovascular diseases often co-occur with depression, it is common for patients to receive anticoagulant and antidepressant therapy concomitantly. Numerous studies have found increased rates of bleeding associated with concomitant use of warfarin and SSRIs, assumed to be related to cytochrome (CYP) P450 metabolism. In addition to increased bleeding risk, there is also a presumed protective effect in terms of thromboembolic and ischemic events. However, the differential effects of SSRIs with and without strong CYP2C9 activity have not previously been investigated.

Methods: The study cohort was selected from 5 U.S. claims databases covering 1994–2013 and included all patients who started warfarin and then received an SSRI prescription during warfarin treatment. Patients were followed for ≤180 days from the beginning of concomitant treatment. Outcomes were compared between patients receiving 1 of the 2 antidepressants with high CYP2C9 activity (i.e., fluoxetine and fluvoxamine) and those receiving any other SSRI. The outcomes of interest were hospitalization for composite bleeding events (upper gastrointestinal [GI] bleeding, lower GI bleeding, hemorrhagic stroke, major urogenital bleeding, and other major bleeding), hospitalization for composite ischemic or thromboembolic events (acute myocardial infarction [MI], ischemic stroke, systemic embolism, transient ischemic attack, or venous thromboembolism), and all-cause mortality.

Results: The cohort comprised >52,000 patients (mean age, 54 years; 28% men) who received an SSRI while taking warfarin. The large majority of patients received an SSRI that was not a potent CYP2C9 inhibitor; 15% of patients received fluoxetine and <1% received fluvoxamine. For the major outcome comparisons, patients in the 2 SSRI groups were matched according to a propensity score* for receiving fluoxetine or fluvoxamine, resulting in a final cohort of 8000 patients receiving these SSRIs and nearly 42,000 receiving other SSRIs.

Average follow-up was 52 days of concomitant treatment. During this time, there was no significant increase in risk of any of the composite study outcomes between patients taking fluoxetine/fluvoxamine versus those taking other SSRIs. (See table). Among individual outcomes, there was a numerically higher risk of upper GI bleeding in patients receiving these SSRIs, but the difference was not statistically significant. Event rates did not differ between groups in various subgroup analyses or in sensitivity analyses limited to follow-up times of continuous warfarin use before SSRI prescription (7,14, 28, or 56 days), intended to rule out the effects during warfarin stabilization.

Hazard ratio* comparing SSRIs that are potent CYP2C9 inhibitors with other SSRIs

Outcome	Events in Total Cohort	Adjusted Hazard Ratio
Bleeding events	822	1.14
Ischemic or thromboembolic events	1169	1.03
Mortality	766	0.90

Dong Y-H, et al: Clinical outcomes of concomitant use of warfarin and selective serotonin reuptake inhibitors: a multidatabase observational cohort study. *Journal of Clinical Psychopharmacology* 2017; doi 10.1097/JCP.0000000000000658. From Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and other institutions. **Funded by the Agency for Healthcare Research and Quality; and other sources. Three study authors declared financial relationships with commercial sources; the remaining 5 authors declared no competing interests.**

Common Drug Trade Names*: fluoxetine—*Prozac*; fluvoxamine—*Luvox

***See Reference Guide.**

Antidepressants and Hyponatremia

A population-based cohort study found that second-generation antidepressants were associated with increased risk of hospitalization for hyponatremia in elderly patients.

Methods: The study was conducted using healthcare databases in Ontario, Canada. Exposed individuals were patients aged >65 years who had a mood or anxiety disorder and were given a prescription for any of 9 second-generation antidepressants in 2003–2012. Those receiving >1 antidepressant concurrently were excluded; however, patients receiving a concurrent mood stabilizer were not excluded. Each exposed patient was individually matched with a control subject based on index date and a propensity score* for being prescribed a second-generation antidepressant that included >100 factors, including age, gender, chronic kidney disease, and diuretic use. The primary outcome of interest was hospitalization for hyponatremia within 30 days of the index date. The secondary outcome was hospitalization for concomitant hyponatremia and delirium.

Results: The study cohort comprised >138,000 matched pairs of exposed patients and controls. Patients had a mean age of 76 years, and 68% were women. Nearly half of all antidepressant users (46%) received a prescription for citalopram. Although absolute risks were small (<2%), antidepressants were associated with a >5-fold increase in risk of hospitalization for hyponatremia, and a 4-fold greater risk of hospitalization with hyponatremia and delirium. The association was robust in numerous alternative analyses and sensitivity analyses and in different subgroups: patients using different antidepressants or dosages, those with or without chronic kidney disease or congestive heart failure at baseline, and diuretic users and non-users. Venlafaxine was associated with no hospitalizations, but all other antidepressants including mirtazapine, the only other non-SSRI, were associated with increased risk.

Discussion: Although the excess absolute risk of hyponatremia with antidepressants is small, the widespread use of these drugs suggests thousands of cases may occur each year and there are no guidelines for serum sodium monitoring in this situation.

Gandhi S, et al: Second-generation antidepressants and hyponatremia risk: a population-based cohort study of older adults. *American Journal of Kidney Disease* 2017;69 (January):87–96. From Western University, London; and St. Michael's Hospital, Toronto, Canada. **Funded by the Canadian Institutes of Health Research; and other sources. The authors declared no competing interests.**

Common Drug Trade Names*: citalopram—*Celexa*; mirtazapine—*Remeron*; 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.

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.

Rate Ratio: A comparison of the rates of a disease/event in 2 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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Eluxadoline and Pancreatitis

The FDA has issued a warning that eluxadoline (*Viberzi*) should not be used to treat irritable bowel syndrome with diarrhea in patients without a gallbladder. These patients are at increased risk of developing pancreatitis, which could be caused by spasms of digestive system muscle located in the small intestine and can lead to hospitalization and/or death. Symptoms of pancreatitis—new or worsening stomach-area or abdominal pain, or upper right-sided abdominal pain that can move to the back or shoulder and can include nausea/vomiting—have developed after as few as 1 or 2 doses of eluxadoline in patients without a gallbladder. Patients should be cautioned to discontinue eluxadoline use and seek emergency care if these symptoms occur.

FDA Drug Safety Communication: Viberzi (eluxadoline)–Increased risk of serious pancreatitis in patients without a gallbladder. Available at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm546771.htm.

Solifenacin and Donepezil Dosing

In a first-in-patients study, co-administration of solifenacin, a peripheral anticholinergic approved for treatment of overactive bladder, allowed patients to tolerate increased doses of donepezil. The increased donepezil doses resulted in better clinical outcomes.

Background: It has been suggested that profound underdosing contributes to the lack of efficacy of donepezil and other cholinesterase inhibitors in Alzheimer's disease. However, dose-limiting adverse effects are a major factor contributing to underdosing. A 23-mg strength of donepezil was introduced in 2010 but has found limited acceptance due mainly to GI intolerance.

Methods: This single-blind, dose-escalation, crossover study recruited patients, aged 50–89 years, with a diagnosis of probable Alzheimer's dementia, according to standard criteria. All had Mini-Mental State Examination (MMSE) scores of 10–20, indicating moderate impairment. All patients had received treatment with 10 mg/day donepezil for ≥12 weeks before study entry. Those taking memantine at stable doses for ≥8 weeks were allowed to continue.

All patients received 6 tablets of single-blind study medication per day throughout the study. At entry, patients received 10 mg/day donepezil plus placebo for 2 days. On day 3, 10 mg/day solifenacin was introduced and then increased to 15 mg/day after 1 week. Remaining placebo tablets were subsequently replaced with donepezil, increasing in weekly 5-mg increments to 25 mg/day and then at biweekly intervals until the patient's first intolerable dose or the protocol-specified maximum of 40 mg/day. When titration was completed, patients were continued on maintenance with 15 mg/day solifenacin and the maximum tolerated dose of donepezil for 12 weeks. The primary study outcome was the maximum tolerated dose of donepezil during coadministration of solifenacin. Cognitive effects were a secondary study outcome.

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Results: The 41 study participants had a mean age of 73 years, and 54% were women. The mean baseline MMSE score was 16.5. The average duration of donepezil treatment before study entry was >2 years, and 61% of patients were also taking memantine. Of the 11 patients who did not complete the study, none withdrew because of a drug-related adverse effect.

Solifenacin was not associated with observable cognitive decline, neuropsychological dysfunction, or other evidence of centrally mediated adverse effects. Of the 33 patients who completed donepezil titration, all reached a maximum tolerated dosage of ≥25 mg/day and all but 4 tolerated 40 mg/day. In all patients who completed the study, the maximum titrated dose was maintained throughout the final 3 months of the study. GI intolerance was the dose-limiting adverse effect in 3 of the 4 patients whose maximum tolerated dose was 25 mg. No clinically meaningful changes in vital signs, electrocardiogram, or laboratory findings occurred.

Mean scores on the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog) improved during the study period, reaching a peak at 18 weeks (following completion of donepezil titration), after which scores declined but remained higher than baseline averages at the 26-week endpoint. Final scores averaged about 2.5 points better than would be expected with 10 mg/day donepezil. A total of 14 patients (61%) were judged to be responders, based on stable or improved ADAS-cog scores. In the 16 patients with evaluable Clinical Global Impression–Improvement ratings at 26 weeks, both study clinician and caregiver ratings indicated substantial global improvement ($p<0.01$).

Chase T, Farlow M, Clarence-Smith K: Donepezil plus solifenacin (CPC-201) treatment for Alzheimer's disease. *Neurotherapeutics* 2017; doi 10.1007/s13311-016-0511-x. From Chase Pharmaceuticals, Inc., Washington, DC; and Indiana University School of Medicine, Indianapolis. **Funded by Chase Pharmaceuticals Corporation. The authors did not include disclosure of potential conflicts of interest.**

Common Drug Trade Names*: donepezil—*Aricept*; memantine—*Namenda*; solifenacin—*VESIcare

Brodalumab for Psoriasis

The FDA has approved brodalumab (*Siliq*) injection for treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Treatment should be reserved for patients whose psoriasis has not responded to other systemic therapies or whose response was not maintained. Brodalumab efficacy, demonstrated in several clinical trials, is based on the agent's binding to a protein that causes inflammation, thus inhibiting the inflammatory response that underlies psoriasis. Patients receiving brodalumab may be at greater risk of infection or allergic or autoimmune reactions. Patients with Crohn's disease or active tuberculosis infection should not receive treatment with brodalumab, and immunization with live vaccines should be avoided. Common adverse effects of brodalumab include arthralgia, headache, fatigue, diarrhea, throat pain, nausea, myalgia, injection site reactions, influenza, neutropenia, and fungal infections. Although a causal association has not been confirmed, suicidal ideation and behavior (including completed suicides) did occur with brodalumab in clinical trials and the agent will carry a boxed warning about the increased risk. The drug will be available only through a risk evaluation and mitigation strategy (REMS) program.

FDA News Release: FDA approves new psoriasis drug. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm541981.htm.

Diabetic Neuropathy

Early recognition and treatment of diabetic neuropathy is crucial for prevention of foot injuries and the sequelae of autonomic neuropathies. There are treatments to relieve symptoms of diabetic neuropathies; however, according to a position statement from the American Diabetes Association, research has not identified treatments that target the natural history of these complications.

Two types of diabetic neuropathy are most commonly seen in clinical practice: distal symmetric polyneuropathy (DSPN) and cardiovascular autonomic neuropathy (CAN). Tight glucose control can dramatically reduce the incidence of both types of neuropathy in patients with type 1 diabetes, but the effects of glucose control are small in patients with type 2 diabetes, many of whom experience these complications despite adequate glucose control.

The American Diabetes Association recommends annual screening for DSPN beginning with the diagnosis of type 2 diabetes and beginning 5 years after the diagnosis of type 1 diabetes. Patients with prediabetes may also benefit from screening tests if they have symptoms of peripheral

neuropathy. Electrophysiological testing or referral to a neurologist is rarely indicated.

Tight glucose control and lifestyle modifications are recommended as preventive strategies for diabetic neuropathy. Pregabalin and duloxetine are FDA-approved for treating neuropathic pain in diabetes. Tapentadol, an opiate, is also approved, but the evidence supporting its use is weaker. Gabapentin has shown promise in clinical trials, although results have not been uniformly positive. Symptoms of CAN are less specific but generally occur upon standing and include lightheadedness, weakness, palpitations, faintness, and syncope. As with DSPN, available treatments are only symptomatic, generally targeting orthostatic hypotension.

Pop-Busui R, et al: Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care* 2017;40 (January):136–154. From the University of Michigan, Ann Arbor; and other institutions. **Funded by the American Diabetes Association. The authors declared no competing interests.**

Common Drug Trade Names*: duloxetine—*Cymbalta*; gabapentin—*Neurontin*; pregabalin—*Lyrica*; tapentadol—*Nucynta

Liraglutide and Diabetes Onset

In a manufacturer-sponsored, placebo-controlled trial, treatment with liraglutide (*Victoza*) resulted in reduced onset of diabetes and greater weight loss in overweight patients with prediabetes.

Methods: This multinational study was conducted as part of the clinical development program for liraglutide. Participants, enrolled in a larger study of long-term treatment, were adults with a body mass index of ≥30, or ≥27 with treated or untreated dyslipidemia, hypertension, or both. Those included in the present analysis were also required to meet American Diabetes Association criteria for prediabetes. All participants received standard lifestyle counseling, with monthly follow-up. Patients also received randomly assigned 3 mg/day liraglutide or placebo in prefilled pens for subcutaneous injection. Study medication was withdrawn after 160 weeks of randomized treatment, with additional follow-up after 12 weeks off drug. The study had 4 prespecified primary outcomes: time to onset of type 2 diabetes, weight loss, and proportion of patients losing ≥5% and >10% of their initial weight.

Results: A total of 2254 patients were randomized, of whom 53% in the liraglutide group and 45% in the placebo group completed 160 weeks of treatment. A greater proportion of patients in the liraglutide group withdrew because of adverse events (13% vs 6%), while more patients in the placebo group withdrew because of lack of efficacy (2% vs 5% for placebo) or withdrew consent (22% vs 31% for placebo).

Type 2 diabetes developed during treatment in 26 patients in the liraglutide group, compared with 46 patients in the placebo group (2% vs 6%; hazard ratio,* 0.21). During the 12-week off-treatment follow-up, diabetes was diagnosed in 5 additional patients in the liraglutide group and 1 in the placebo group. Weight-based outcomes also favored liraglutide, with a mean weight loss of 14.3 lbs versus 4.4 lbs with placebo ($p<0.0001$). Weight loss of ≥5% occurred in 50% of the liraglutide group and in 24% of the placebo group (odds ratio,* 3.2). A loss of 10% occurred in 25% and 10% of the groups, respectively (odds ratio, 3.1). More patients who received liraglutide than placebo regressed from prediabetes to normoglycemia (66% vs 36%; odds ratio, 3.6). Liraglutide was also associated with greater improvement in measures of insulin resistance and beta-cell function and in health-related quality of life.

Gastrointestinal problems were the most common adverse effect in the liraglutide group and the most frequent cause for discontinuation (8% vs 2% of the placebo group). Gallbladder-related adverse events were also more frequent with liraglutide (5% vs 2%).

Discussion: Liraglutide appears to be effective at preventing progression to type 2 diabetes. Regression from prediabetes to normoglycemia has also been observed in clinical trials with other GLP-1 receptor agonists.

le Roux C, et al: 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet* 2017; doi 10.1016/S0140–6736(17) 30069–7. From University College Dublin, Ireland; and other institutions including Novo Nordisk A/S, Soeborg, Denmark. **Funded by Novo Nordisk. All study authors disclosed financial relationships with commercial sources.**

***See Reference Guide.**

Nasal Spray for Nocturnal Polyuria

Desmopressin acetate nasal spray (*Noctiva*) has received the first FDA approval for treatment of adults with nocturnal polyuria (overproduction of urine leading to ≥2 awakenings per night to urinate). Because nocturia can be caused by many medical conditions (e.g., congestive heart failure,

diabetes, diseases of the bladder or prostate) and by medications, the underlying condition should be identified and treatment optimized. A 24-hour urine collection should be undertaken to confirm overproduction before considering *Noctiva* use. The agent is taken once daily, before bed, and works by increasing water absorption through the kidneys, leading to less urine production. *Noctiva* is not safe for use in patients with congestive heart failure, uncontrolled hypertension, or polydipsia and should not be used by pregnant women or children. Because *Noctiva* can cause hyponatremia, serum sodium levels should be assessed before starting treatment and periodically thereafter. Common adverse effects include nasal discomfort, nasopharyngitis, congestion, sneezing, increased blood pressure, back pain, nosebleeds, bronchitis, and dizziness.

FDA News Release: FDA approves first treatment for frequent urination at night due to overproduction of urine. Available at: www.fda.gov/newsevents/newsroom/pressannouncements/ucm544877.htm.

Options for Urinary Incontinence

The bladder is rich with sympathetic alpha-adrenergic receptors, parasympathetic muscarinic receptors, and sympathetic beta-adrenergic receptors. In women with urinary incontinence, stimulation of the parasympathetic system leads to activation of the muscarinic receptors causing detrusor contraction and bladder emptying. Strategies to treat urinary incontinence include beta-alpha adrenergic receptor agonism and inhibition of parasympathetic receptors. The American College of Physicians recommends against drug treatment for stress urinary incontinence (i.e., associated with physical exertion or increased abdominal pressure), but in favor of drug therapy for urge incontinence, if bladder training has failed.

Six oral anticholinergic drugs are available—oxybutynin, tolterodine, fesoterodine, solifenacin, trospium, and darifenacin—all with similar effectiveness. Extended-release formulations may produce fewer adverse effects. Overall, the effect of these drugs is small, and nonadherence is common. These agents should be used cautiously in older women because of potential adverse effects on memory and other central nervous system effects. Mirabegron is a new, selective beta-3 adrenoreceptor agonist that improves continence, but can cause hypertension and urinary tract infection. The antidepressant duloxetine had very modest benefit in a clinical trial and is not recommended unless the patient has psychiatric comorbidity. Local vaginal estrogen preparations, including the estrogen ring for vaginal atrophy, can relieve urinary incontinence and other vaginal symptoms associated with menopause. Systemic estrogen is not recommended for urinary incontinence and can actually worsen symptoms.

Shih E, et al: Medical management of urinary incontinence in women. *Cleveland Clinic Journal of Medicine* 2017;84 (February):151–158. From the Cleveland Clinic, OH; and other institutions. **Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.**

Common Drug Trade Names*: darifenacin—*Enablex*; duloxetine—*Cymbalta*; estrogen vaginal ring—*Estring*; fesoterodine—*Toviaz*; mirabegron—*Myrbetriq*; oxybutynin—*Ditropan*; solifenacin—*VESIcare*; tolterodine—*Detrol*; trospium—*Sanctura

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

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

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Medication Reminder Devices

Although many patients cite forgetfulness as the main explanation for medication noncompliance, in a randomized trial, simple, inexpensive reminder devices did not improve adherence in poorly compliant patients with chronic illnesses.

Methods: Study subjects, aged 18–64 years, were >53,000 enrollees in a large pharmacy-benefits program. Patients had prescriptions for 1–3 maintenance medications for a chronic medical or psychiatric illness and had suboptimal adherence, defined as a medication possession ratio (MPR) of 30–80% during the prior 12 months. MPR is the proportion of days for which a patient has obtained the prescribed medication; a perfect MPR is 100%. Patients were randomly assigned to receive 1 of 3 reminder devices—a pill bottle with toggles that can be slid after each day's dose is removed, a pill bottle cap with a digital timer displaying the time elapsed since the most recent dose, and a pill box with 1 compartment for each day of the week—or to a control group that received no reminder device. The primary outcome was the MPR during the 12 months following receipt of the devices, with optimal adherence defined as an MPR ≥80%.

Results: Baseline MPRs ranged from about 40% for medications dosed more than once per day to 44% with once-daily medications. During follow-up, optimal adherence was achieved by 15–16% of patients with no significant differences between the groups including the no-intervention control. There was no clinically meaningful, statistically significant differences in pairwise comparisons between the interventions or in subgroup analyses.

Discussion: In surveys of patients with poor medication adherence, up to 60% cited forgetfulness as the main reason. Data on the usefulness of relatively costly electronic-alert devices are limited and inconsistent. The present study results suggest that inexpensive reminder devices may do no better. The larger-than-expected improvement in the control group suggests that nonadherence is a fluctuating target, regardless of intervention. Reminder devices may work better in multicomponent interventions designed to promote both their use and the filling of prescriptions.

Choudhry N, et al: Effect of reminder devices on medication adherence: the REMIND randomized clinical trial. *JAMA Internal Medicine* 2017; doi 10.1001/ jamainternmed.2016.9627. From Brigham and Women's Hospital, Boston, MA; and CVS Health, Woonsocket, RI. **Funded by CVS Health. Five study authors disclosed financial relationships with commercial sources; the remaining 5 authors declared no competing interests.**

Sirukumab for Rheumatoid Arthritis

In a phase III trial, sirukumab, a monoclonal antibody that targets interleukin-6, improved symptoms of rheumatoid arthritis (RA) that had been refractory to other biological treatments.

Background: IL-6 is one of the key pathways in the pathophysiology of RA. Monoclonal antibodies that target the IL-6 receptor have shown efficacy. Sirukumab takes an alternative approach, selectively targeting the IL-6 cytokine itself.

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Methods: The study, conducted in 20 countries, enrolled patients with active RA of ≥3 months duration. Participants were required to have ≥4 tender joints, ≥4 swollen joints, elevated C-reactive protein, and other markers of active disease that had been refractory to previous anti-tumor necrosis factor (TNF) therapy or had been unable to tolerate these drugs. Continuation of background therapy with conventional disease-modifying agents such as methotrexate (*Rheumatrex*) was permitted. Patients were randomly assigned to receive, by subcutaneous injection, 100 mg sirukumab every 2 weeks, 50 mg sirukumab every 4 weeks, or placebo. At week 18, patients in the placebo group who did not experience response were allowed to switch to a randomly assigned dose of sirukumab. At week 24, all patients receiving placebo were re-randomized to a dose regimen of sirukumab. The primary efficacy outcome was American College of Rheumatology 20 (ACR20) response at 16 weeks (≥20% improvement from baseline). Blinded treatment was continued for a total of 52 weeks.

Results: A total of 878 patients were randomized. Of 294 in the placebo group, 32% met criteria at 18 weeks for reassignment to sirukumab. Patients had discontinued their previous anti-TNF therapy because of lack of efficacy (88%), intolerance (4%), or both/other reasons (8%). In addition, 39% received previous treatment with other ineffective biological agents.

Primary efficacy outcome: ACR20 response at 16 weeks		
Treatment	**Responders**	**Significance vs Placebo**
Sirukumab 100 mg/2 weeks	132/292 (45%)	p<0.0001
Sirukumab 50 mg/4 weeks	117/292 (40%)	p<0.0001
Placebo	71/294 (24%)	—

After administration of sirukumab, trough steady-state drug concentrations were achieved by week 12 and C-reactive protein levels were completely suppressed by week 2. At week 16, response rates were similar in the 2 sirukumab groups and superior to placebo. (See table above.) Patients who received sirukumab experienced greater responses than the placebo group on all secondary study endpoints, including various categories of ACR response, remission, and other measures of disease activity, symptoms, health status, and quality of life. Improvements were observed as early as weeks 2–8 and were maintained through week 24.

Adverse events at 24 weeks were similar in the active medication and placebo groups. Infections were the most common event leading to discontinuation at week 24 (12 patients in the combined sirukumab dosage groups) and week 52 (24 patients combined).

Discussion: The ACR20 response rate in this study is consistent with other agents used to treat RA that is refractory to multiple earlier-stage treatments.

Aletaha D, et al: Efficacy and safety of sirukumab in patients with active rheumatoid arthritis refractory to anti-TNF therapy (SIRROUND-T): a randomised, double-blind, placebo-controlled, parallel-group, multinational, phase 3 study. *Lancet* 2017; doi 10.1016/S0140-6736(17)30401-4. From the Medical University of Vienna, Austria; and other institutions. **Funded by Janssen Research & Development, LLC; and GlaxoSmithKline. All study authors declared financial relationships with commercial sources.**

Alendronate for Osteoporosis in Men

According to a meta-analysis, alendronate is an effective treatment to increase bone mineral density (BMD) in men with osteoporosis.

Background: The importance of osteoporosis and osteoporotic fractures in men is being recognized increasingly. An estimated 1 in 8 men over age 50 years will experience an osteoporotic fracture. Alendronate is the first bisphosphonate to be studied extensively in men.

Methods: A literature search identified all randomized controlled trials comparing alendronate with placebo or another active treatment in men with osteoporosis (i.e., BMD T-score of -2 standard deviations [SD] at the femoral neck and -1 SD at the lumbar spine or -1 SD at the femoral neck and a previous vertebral deformity or osteoporotic fracture). Outcome measures were BMD of the lumbar spine, femoral neck, total hip, trochanter, and total body and the incidence of vertebral fractures.

Results: A total of 8 studies, with a population of 988 patients, were included in the meta-analysis; 7 were conducted in men with primary osteoporosis and 1 in men with hypogonadism-induced osteoporosis. Alendronate dosage was 10 mg/day in 6 studies and 70 mg/week in 2 studies. Follow-up ranged from 6 months to 3 years. Control treatments included placebo, salmon calcitonin plus calcium, zoledronic acid, and alfacalcidol. There was no evidence of publication bias.

All 8 studies reported significantly higher BMD values with alendronate than with comparison

treatments at both the lumbar spine and femoral neck (p<0.001 for all comparisons). The advantage of alendronate for these outcomes persisted at 6, 12, 24, and 36 months. In the 4 studies that reported additional BMD outcomes, BMD was significantly higher with alendronate at the total hip, but not the trochanter or total body. In the 4 studies that reported vertebral fracture, rates were markedly reduced with alendronate (risk ratio,* 0.46; p=0.003). Treatment with 10 mg/day alendronate was more effective than with 70 mg once a week.

Discussion: Although positive, the findings are based on a small number of studies highly heterogeneous with regard to dosage, length of treatment and follow-up, comparison treatments, and the causes for osteoporosis, all of which might affect the results of the analysis.

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

Xu Z: Alendronate for the treatment of osteoporosis in men: a meta-analysis of randomized controlled trials. *American Journal of Therapeutics* 2017;24:e130–e138. From the Central Hospital of Zaozhuang Mining Group, Zaozhuang, China. **Source of funding not stated. The author declared no competing interests.**

Common Drug Trade Names*: alendronate—*Fosamax*; zoledronic acid—*Zometa

***See Reference Guide.**

5-α Reductase Inhibitors and Suicide

Despite concerns based on pharmacovigilance sources, use of 5-α-reductase inhibitors (5-ARIs) was not associated with an increased rate of suicide in a large cohort of older men with benign prostatic hyperplasia (BPH). The drugs were, however, associated with a temporary increase in depression and self-harm.

Background: The potential adverse neurologic effects of 5-ARIs are a growing concern. There have been postmarketing reports of self-harm, suicidal ideation, and suicide in men taking these drugs, and depression is now included as an adverse event in the product monographs. There are also multiple lines of evidence supporting plausible biological mechanisms, including the role of 5-α reductase in production of neuroactive steroids and the involvement of testosterone in depression via the neuroendocrine stress response.

Methods: A cohort of men, aged ≥66 years, who received treatment with dutasteride or finasteride for BPH between 2003 and 2013, was identified from Canadian healthcare databases. Each patient was matched with a control, selected from the general population, based on index date, history of depression or self-harm, and a 44-item propensity score.* The index date for cases was the date of prescription filling and for controls, a date was randomly selected. Risk was assessed for the period of continuous drug usage from the index date until 12 months after discontinuing the medication. The primary study outcome was suicide. Secondary outcomes were self-harm and new onset of depression.

Results: The study population consisted of >93,000 pairs of exposed and unexposed men with a mean age of 75 years. About half of patients took dutasteride and half finasteride. Baseline rates of psychotropic use, which ranged from <1% for mood stabilizers to about 15% for antidepressants, did not differ between exposed and unexposed men.

The absolute risk of suicide was low—0.04% in both patients and controls. Use of a 5-ARI was not associated with suicide risk (hazard ratio,* 0.88). However, in the treated group, the absolute rate of self-harm was 0.18% and of depression 1.95%. Compared with unexposed men, their risk of self-harm was increased during the first 18 months of 5-ARI use (hazard ratio, 1.88), but not afterward. Risk of depression was increased throughout the period of 5-ARI use, up to >3 years, although the highest risk was in the first 18 months (hazard ratio, 1.94, dropping to 1.22 afterward).

Discussion: These results suggest that neither finasteride nor dutasteride is associated with increased suicide risk in older men with BPH and that the potential benefits of treatment likely outweigh the small increase in risk of self-harm and depression. However, discontinuation of these drugs may be appropriate if self-harm or depression occurs, and the associations should be evaluated in younger men receiving treatment for alopecia.

Welk B, et al: Association of suicidality and depression with 5α-reductase inhibitors. *JAMA Internal Medicine* 2017; doi 10.1001/jamainternmed.2017.0089. From Western University, Canada; and other institutions. **Funded by Western University; and other sources. One study author disclosed a financial relationship with a commercial source; the remaining 5 authors declared no competing interests.**

Common Drug Trade Names*: dutasteride—*Avodart*; finasteride—*Propecia, Proscar

***See Reference Guide.**

Updated Drug Safety Signals

Based on FDA Adverse Event Reporting System (FAERS) database reports from the last quarter of 2016, the FDA has identified potential safety issues with several commonly used drugs. (See table.) A causal relationship has not been confirmed, but the FDA is investigating the possibility. If the agency determines that the drug is associated with the risk, changes to the labeling or development of a Risk Evaluation and Mitigation Strategy may be required.

Selected FAERS Safety Signals		
Drug Name(s)	**Potential Signal of Serious Risk / New Safety Information**	**Additional Information**
Naltrexone–bupropion (*Contrave*)	Loss of consciousness	Need for regulatory action is under evaluation
Methylprednisolone acetate injection (*Depo-Medrol*)/medroxy-progesterone acetate injection (*Depo-Provera*)	Medication errors	Labeling and packaging have been revised to avoid potential name confusion
Glyburide (*Diabeta*)	Skin reactions	Label updated to include bullous reactions, erythema multiforme, and exfoliative dermatitis as adverse reactions
Sodium nitroprusside (*Nitropress*)	Carboxyhemoglobinemia	Need for regulatory action is under evaluation
Apremilast (*Otezla*)	Diarrhea, nausea, and vomiting	Need for regulatory action is under evaluation

Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS): October - December 2016 Report. Available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm549834.htm.

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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.

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.

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Abaloparatide Approval

The new injectable anabolic agent abaloparatide (*Tymlos*) recently received FDA approval for treatment of postmenopausal osteoporosis in women who are at high risk for fracture, including those with a history of osteoporotic fracture, multiple risk factors for fracture, or who have failed or are intolerant to other available therapies. Abaloparatide is expected to be available in the U.S. in June.

The approval is based on studies that showed rapid and significant reductions in the risk of vertebral and nonvertebral fractures regardless of age, time since menopause, presence or absence of prior fracture, and baseline bone mineral density (BMD). In the studies, abaloparatide also increased BMD and a marker of bone formation. In the phase III Abaloparatide Comparator Trial in Vertebral Endpoints, abaloparatide produced an 86% reduction in the relative risk of new vertebral fractures and a 43% reduction in the relative risk of nonvertebral fractures compared with placebo. Absolute risk reductions were 3.6% and 2.0%, respectively.

The most common adverse effects of abaloparatide include hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, and vertigo. However, orthostatic hypotension, hypercalcemia, hypercalciuria, and urolithiasis have also occurred. Animal studies also indicate that abaloparatide may have a dose-dependent association with osteosarcoma. Although it is not known whether the agent increases osteosarcoma risk in humans, its use is not recommended for patients at increased risk.

FDA approves Radius Health's TYMLOS™ (abaloparatide), a bone building agent for the treatment of postmenopausal women with osteoporosis at high risk for fracture [press release]. Waltham, MA: Radius Health; April 28, 2017. Available at http://ir.radiuspharm.com/releasedetail.cfm?ReleaseID=1023557.

Guideline for Cervical Cancer Prevention

According to a new, globally applicable, resource-stratified guideline from the American Society of Clinical Oncology (ASCO), primary prevention of cervical cancer depends on human papillomavirus (HPV) vaccination of all girls, beginning as early as age 9 years, with 2 doses of vaccine in most cases. Although vaccination should not replace cervical cancer screening, there is no preventive strategy that can substitute for vaccination.

The primary clinical concerns of the updated ASCO guideline, which is based on a review of all current guidelines and systematic reviews published between 1966 and 2015, are the number and timing of vaccine doses and the age and gender of target populations. According to their findings, girls should be vaccinated routinely, with the target age range being as early as possible, starting at ages 9–14 years. A 2-dose regimen is recommended for immunocompetent girls, and the doses should be separated by at least 6 and up to 12–15 months. Young women who are first vaccinated at age ≥15 years should receive 3 doses. For those who have received only 1 dose and are aged ≥14 years, catch-up doses should be offered

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up to age 26 years. In settings where coverage of the target female population is <50%, vaccination of boys should be considered to increase herd immunity and prevent HPV-related illnesses in boys. The benefit of vaccinating boys is marginal if more than half of girls are vaccinated.

Arrossi S, et al: Primary prevention of cervical cancer: American Society of Clinical Oncology resource-stratified guideline. *Journal of Global Oncology* 2017; doi 10.1200/JGO.2016.008151. From the Instituto Nacional del Cancer, Buenos Aires, Argentina; and other institutions. **Source of funding not stated. Ten study authors disclosed financial relationships with commercial sources; the remaining 9 authors declared no competing interests.**

Antibiotics and Colorectal Adenoma Risk

According to an analysis of data from the longitudinal Nurses' Health Study, prolonged use of antibiotics in early or mid-adulthood is associated with increased risk of colorectal adenoma in women aged ≥60 years. This observation supports the increasing evidence linking antibiotics with colorectal cancer and the mediating role of the gut microbiome in carcinogenesis.

Methods: The population for the present analysis was limited to 16,642 Nurses' Health Study respondents, aged ≥60 years in 2004, who reported history of earlier antibiotic use and who underwent ≥1 colonoscopy in 2004–2010. Eligible participants did not have a pre-2004 history of cancer, ulcerative colitis, or colorectal polyps. The women were asked about use of antibiotics at ages 20–39 years, 40–59 years, and during the preceding 4 years. The primary outcome of interest was colorectal adenoma. Adenomas were classified as indicating high or low risk of future advanced cancer, based on histology, size, and number.

Results: A total of 1195 women received a new diagnosis of adenoma. Increasing total antibiotic exposure at ages 20–39 years was associated with significantly increased risk of adenoma, as was increasing antibiotic exposure at ages 40–59 years. (See table.) Associations with duration of antibiotic use were similar for high-risk and low-risk adenomas. Recent antibiotic use, in the 4 years before colonoscopy, was not associated with risk of adenoma. None of the indications for antibiotic use appeared to be significantly associated with adenoma risk.

Discussion: This report strengthens evidence from previous studies, which were limited by short follow-up duration and lack of control for factors that might influence both antibiotic use and development of colorectal cancer. Because colorectal cancer typically develops over a decade, studies require long follow-up to show an association.

Antibiotic use and risk of colorectal adenoma after age 60 years

	Number of cases	Multivariable odds ratio*
Exposure (ages 20–39 years)		
None	141	1 (referent)
1–14 days	653	1.12
15 days to 2 months	296	1.41
>2 months	105	1.36
Exposure (ages 40–59 years)		
None	66	1 (referent)
1–14 days	637	1.32
15 days to 2 months	357	1.51
>2 months	135	1.69

The biological plausibility of the association rests on the alteration of the gut microbiota to alternative microbe populations. The microbiota may react with mucosal immune and epithelial cells to initiate or promote colorectal carcinogenesis. The link with antibiotics was strongest for adenomas in the proximal colon, a site of higher bacterial concentration and fermentation. Pathogens that necessitate antibiotic use may induce inflammation, a known risk factor for colorectal cancer.

Cao Y, et al: Long-term use of antibiotics and risk of colorectal adenoma. *Gut* 2017; doi 10.1136/gutjnl-2016-313413. From Massachusetts General Hospital; and Harvard Medical School, Boston, MA. **Funded by the NIH; and other sources. One of the 14 study authors disclosed relationships with commercial sources.**

***See Reference Guide.**

Canagliflozin Safety

In 2016, the FDA issued a warning, based on interim results from the ongoing Canagliflozin Cardiovascular Assessment Study, about a potentially increased risk of leg and foot amputations in patients with diabetes who receive the sodium-glucose cotransporter-2 (SGLT2) inhibitor canagliflozin (*Invokana, Invokamet*).[1] At that time, a causal association was not confirmed. An updated review now indicates that amputations of the leg and foot occur about twice as often in patients

taking canagliflozin than those assigned to placebo, and the agent will now carry a Boxed Warning regarding the risk.[2]

In clinical studies, amputations of the toe and middle of the foot were the most common; however, amputations involving the leg, both above and below the knee, also occurred. Before prescribing canagliflozin, physicians should consider factors that may predispose patients to the need for amputations, including prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. Canagliflozin should be discontinued in patients who experience any of these conditions or symptoms.

[1]FDA MedWatch Alert: Canagliflozin (Invokana, Invokamet): Drug Safety Communication - Clinical Trial Results Find Increased Risk of Leg and Foot Amputations. Available at www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm501565.htm. See *Primary Care Drug Alerts* 2016;37 (June):21.

[2]FDA MedWatch Alert: Canagliflozin (Invokana, Invokamet): FDA Drug Safety Communication: FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). Available at www.fda.gov/Drugs/DrugSafety/ucm557507.htm.

Safety of Cough/Cold Medicines in Children

Adverse events associated with over-the-counter cough and cold medicines in children are rare and most often involve accidental ingestion rather than intended therapeutic use, according to an analysis of nationwide data.

Background: Concerns raised to the FDA in 2007 resulted in voluntary relabeling of cough and cold preparations as not for use in children aged <4 years, despite limited data available at the time. The present study was undertaken to assess the risks of current use in children.

Methods: The Pediatric Cough and Cold Safety Surveillance System, funded by the national trade association of healthcare product manufacturers and marketers, collects data from the National Poison Data System, the FDA Adverse Event Reporting System, the medical literature, news reports, and manufacturers' postmarketing safety databases. The investigators identified adverse events reported in children aged <12 years, occurring in the U.S. in 2009–2014, and related to the 8 most common ingredients in cough and cold preparations. Autopsy reports were sought for all fatal events.

Results: A total of 3251 cases were determined to be at least potentially related to a cough and cold medication ingredient. Accidental unsupervised ingestion accounted for 67% of exposures, 13% were medication errors, and the rest were undetermined. Nearly half (46%) of the cases occurred in children aged 2–4 years, of which nearly 90% were accidental ingestions. Medication errors were more common in children aged 6–11 years. The drug was self-administered in more than 99% of accidental ingestions, while with medication errors, the agent was usually administered by a parent (44%) or another caregiver (42%). Diphenhydramine and dextromethorphan accounted for 97% of exposures. Cases usually involved liquid, pediatric formulations rather than solid, adult formulations.

The most common adverse events were tachycardia, somnolence, hallucinations, ataxia, mydriasis, and agitation. While most cases involved transient, non-life-threatening effects, 20 were fatal: 2 cases were accidental ingestions, 2 were medication errors, 6 were homicides, 3 occurred for other reasons, and 7 were unknown. Most of the fatal occurrences (70%) were in children aged <2 years. Several cases (n=6) involved a cough and cold medication with a prescription opioid combination. The dose was often not reported, but in no case with available information was a fatality associated with a therapeutic dose.

The reported adverse-event rate was 0.573 cases per million units sold. Rates per unit sold were higher for accidental ingestions than for medication errors and higher for liquid pediatric formulations and single-ingredient products than other types.

Discussion: Although the data suggest that cough and cold medications, when used as directed, are generally safe in children, availability of medication in the home and unsafe storage practices most often lead to adverse events. Efforts that focus on preventing unintentional ingestion and medication errors in younger children should also include manufacturing controls—e.g., child-resistant packaging and flow restrictors on liquid medication bottles—and caregiver education on safe storage and supervision.

Green J, et al: Safety profile of cough and cold medication use in pediatrics. *Pediatrics* 2017; doi 10.1542/peds.2016–3070. From Rocky Mountain Poison and Drug Center, Denver, CO; and other institutions.
Funded by the Consumer Healthcare Products Association Pediatric Cough Cold Task Group. Four study authors disclosed financial relationships with commercial sources; the remaining 5 authors declared no competing interests.

Antidepressants and Stroke Risk

In a population-based study, new users of a serotonin norepinephrine reuptake inhibitor (SNRI) had an elevated risk of nonfatal stroke compared with new users of a selective serotonin reuptake inhibitor (SSRI).

Methods: The study was a retrospective analysis of health care data from the Canadian province of Manitoba. It included all patients who received a new prescription for an SSRI or an SNRI in 1998–2014, after ≥1 year free of antidepressant therapy. Hospitalized patients and those with a recent cardiovascular or cerebrovascular event were excluded. The primary study outcome was a composite of hospital admission for acute myocardial infarction, fatal or nonfatal stroke, or other cardiovascular illness. Patients were followed until the first occurrence of a study outcome or 1 year after the new prescription because these effects are known to occur early in treatment.

Results: The study population consisted of >225,000 patients given a prescription for an SSRI and nearly 55,000 given an SNRI. The most frequently prescribed drugs in either class were citalopram (42% of SSRI prescriptions) and venlafaxine (94% of SNRI prescriptions).

After propensity score matching* to adjust for baseline differences between those receiving an SSRI or an SNRI, new users of SNRIs had a significantly higher risk of the primary composite outcome than users of an SSRI (propensity-weighted hazard ratio,* 1.13). This increase was entirely due to increased risk of nonfatal stroke (hazard ratio, 1.20). Among nonfatal stroke events, ischemic stroke incidence was elevated in SNRI users (hazard ratio, 1.32); hemorrhagic stroke was not.

When the analysis was stratified into 2 age groups, the nonfatal stroke risk increase with SNRIs was confined to patients aged >40 years. Drug-related differences in some outcomes were significant in different risk groups: All-cause and cardiovascular-related deaths were more frequent in SNRI users without a history of mood and anxiety disorders, but nonfatal strokes were elevated regardless of this history. Risks of the composite outcome, nonfatal stroke, and cardiovascular-related hospitalizations were increased in SNRI users with a history of cardiovascular disease, but not in those without such a history.

Discussion: SNRIs increase norepinephrine levels and related sympathetic activity, which can induce hypertension, tachycardia, and cardiotoxicity when these drugs are taken in high doses or in overdose. The present study extends the limited existing epidemiologic data on adverse clinical outcomes by examining risk in new users, regardless of treatment indication, and in a wide age range of patients. The authors note that while this study was designed to compare 2 classes of antidepressants, the vast majority of patients in the SNRI group received venlafaxine (94%), and further study to investigate the risk associated with individual SNRIs is needed.

Leong C, et al: Cerebrovascular, cardiovascular, and mortality events in new users of selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors: a propensity score-matched population-based study. *Journal of Clinical Psychopharmacology* 2017; doi 10.1097/JCP.0000000000000701.
From the University of Manitoba, Canada. **Funded by the university. The authors declared no competing interests.**

Common Drug Trade Names*: citalopram—*Celexa*; 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.

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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New ADHD Treatments Approved

The FDA has approved the first generic atomoxetine (*Strattera*) products to treat ADHD in adults and children.[1] The generics, manufactured by 4 pharmaceutical companies, will be available in multiple strengths and carry the same Medication Guide requirement as the branded product.

Also approved is a new extended-release orally disintegrating methylphenidate formulation (*Cotempla XR-ODT*).[2] In clinical trials, *Cotempla XR-ODT* had onset of action at 1 hour post-dose and lasted through 12 hours. Adverse effects were consistent with the known profile for other extended-release methylphenidate products. The new formulation, as with other CNS stimulants, has high abuse and dependence potential and is approved as a controlled substance.

[1]FDA News Release: FDA approves first generic Strattera for the treatment of ADHD. Available at www.fda.gov/newsevents/newsroom/pressannouncements/ucm561096.htm.

[2]Neos therapeutics announces FDA approval of Cotempla XR-ODT™ (methylphenidate) extended-release orally disintegrating tablets for the treatment of ADHD in patients 6 to 17 years old [press release]. Dallas and Fort Worth, TX: Neos Therapeutics Inc.; June 19, 2017. Available at http://investors.neostx.com/phoenix.zhtml?c=254075&p=RssLanding&cat=news&id=2281776.

Opana Market Withdrawal Requested

The FDA has requested that Endo Pharmaceuticals remove their reformulated oxymorphone hydrochloride (*Opana ER*) from the market because of unintended consequences of the reformulation; the benefits of the new formulation no longer outweighing its risks. The opioid pain reliever *Opana ER* was first approved in 2006 for the management of moderate-to-severe pain when continuous analgesia is needed for an extended period of time. In 2012, the original formulation was replaced with a new formulation intended to reduce abuse potential by making the drug resistant to physical and chemical manipulation for use by snorting or injecting. A review of postmarketing data indicates a significant shift in the route of *Opana ER* abuse from nasal to injection following the reformulation. Injection abuse of the new product has been associated with outbreaks of HIV and hepatitis C, as well as cases of thrombotic microangiopathy. If the product is not voluntarily withdrawn, the FDA plans to withdraw its approval.

FDA News Release: FDA requests removal of *Opana ER* for risks related to abuse. Available at www.fda.gov/newsevents/newsroom/pressannouncements/ucm562401.htm.

Cholinesterase Inhibitor for Alzheimer's

A novel synthesized acetylcholinesterase (AChE) inhibitor, octohydroaminoacridine, improved cognitive function with few adverse effects in a phase-II study in patients with Alzheimer's disease. The drug is more highly selective for centrally active acetylcholinesterase (the peripheral enzyme that may be related to the side effects of many members of this drug class) than other AChE inhibitors.

Methods: The study, conducted in China, enrolled patients, aged 50–85 years, with a diagnosis of mild-to-moderate probable Alzheimer's disease,

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according to standardized criteria. Patients underwent brain imaging, and were excluded if they had evidence of other forms of dementia or a history of significant systemic or psychiatric conditions or traumatic brain injury. After a 4-week screening/washout period, they were randomly assigned to 16 weeks of double-blind treatment with 1 of 3 different octohydroaminoacridine dosage groups (3, 6, or 12 mg/day) or placebo. The primary efficacy outcome was change from baseline in the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog).

Results: A total of 284 patients were randomized, and 79–81% of each treatment group completed the study. Patients had an average age of about 72 years and mean baseline ADAS-Cog scores of 28–31.

After 16 weeks, changes in ADAS-Cog scores differed significantly among the groups ($p<0.001$ for each active treatment group vs placebo). The placebo group demonstrated a 1.4-point increase in ADAS-Cog score, while active treatment produced 2.1, 2.2, and 4.2-point decreases with low, middle, and high doses, respectively. Some secondary outcome measures also favored the active drug: the Clinician's Interview-Based Impression of Change Plus ($p=0.011$) and activities of daily living scores, which were superior to placebo in the middle- and high-dosage groups ($p<0.01$). The Neuropsychiatric Inventory, which measures behavioral disturbances, showed no differences among groups.

Adverse events did not occur more frequently with octohydroaminoacridine than with placebo, and laboratory abnormalities were found more often in the placebo group. The rate of adverse events with octohydroaminoacridine was not dose-dependent, unlike other cholinesterase inhibitors. The most common adverse events were gastrointestinal (GI) and cardiovascular in nature. These effects usually followed a dose increase and were mild and transient. There was no evidence that the drug compromised cardiovascular function in the study patients, many of whom had cardiovascular disease. Serious adverse events occurred in 2.9% of the placebo group, compared with 2.9% of the low-dose group and 4.6% of the middle-dose group; there were no serious adverse events in the high-dose group.

Discussion: AChE inhibitors are widely used to improve cognitive function in Alzheimer's disease. However, the agents are associated with dose-dependent adverse effects, primarily in the GI tract. These results suggest that octohydroaminoacridine improves both cognitive function and behavior without dose-dependent adverse effects. The highest dose of the medication will be investigated in upcoming phase III trials.

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

Xiao S, et al: Efficacy and safety of a novel acetylcholinesterase inhibitor octohydroaminoacridine in mild-to-moderate Alzheimer's disease: a phase II multicenter randomised controlled trial. *Age and Ageing* 2017; doi 10.1093/ageing/afx045. From Shanghai Jiao Tong University School of Medicine, China; and other institutions. **Funded by Changchun Huayang High-Science and Technology Co, Ltd.; and other sources. The authors declared no competing financial interests.**

***See Reference Guide.**

Cetirizine Eye Drops

The first topical ocular formulation of the antihistamine cetirizine, a second-generation H_1 receptor antagonist that binds competitively to histamine receptor sites to reduce swelling, itching, and vasodilation, (cetirizine ophthalmic solution 0.24%; *Zerviate*) has received FDA approval for the treatment of ocular itching associated with allergic conjunctivitis. In clinical trials, the drops produced significant reductions in ocular itching compared with placebo beginning at 15 minutes and lasting 8 hours after instillation. The recommended dose of *Zerviate* is 1 drop in each affected eye twice per day, separated by approximately 8 hours. The most commonly reported adverse reactions of *Zerviate*, occurring in 1–7% of patients, are ocular hyperemia, instillation site pain, and reduction in visual acuity.

Nicox receives FDA approval of Zerviate (cetirizine ophthalmic solution) 0.24% [press release]. Sophia Antipolis, France: Nicox S.A.; May 31, 2017. Available at http://www.nicox.com/assets/files/ZERVIATE_FDA_Approval_20170531_EN.pdf.

Antibiotics: Fetal Safety

According to results of a population-based cohort study, use of quinolones, tetracyclines, sulfonamides, most macrolides, and metronidazole during pregnancy is associated with increased risk of spontaneous abortion.

Methods: The study cohort, identified from a national database, comprised all women, aged 15–45 years, giving birth in Quebec, Canada, in 1998–2009. Pregnancies with known exposure to

teratogenic drugs were excluded. Case patients were women with a clinically detected spontaneous abortion before the 20th gestational week. Each case was matched with 10 controls who did not have a spontaneous abortion. To account for potential bias due to the underlying indication, 2 antibiotics with an established record of safety in pregnancy—penicillins and cephalosporins—were chosen as active comparators.

Results: The analysis included >180,000 pregnancies, of which 8702 (4.7%) ended in a spontaneous abortion. Antibiotics were used before the 20th week by 16% of case patients and 13% of controls. After adjustment for potential confounders, most classes of antibiotics were associated with increased risk of spontaneous abortion, compared with pregnancies with no antibiotic exposure. (See table.) Risks were also elevated for these antibiotic classes when compared with penicillins and cephalosporins. When individual antibiotics were analyzed, risks were increased for all members of the implicated drug classes except erythromycin. Risks were also not elevated for the class of urinary anti-infectives, mainly represented by nitrofurantoin.

Risk of spontaneous abortion with antibiotic use during pregnancy

Drug class	Number (%) of spontaneous abortions	Adjusted odds ratio*
No antibiotic use	7274 (84%)	1.00 (reference)
Penicillins	500 (6%)	0.86
Cephalosporins	60 (<1%)	0.90
Macrolides	264 (3%)	1.61
Quinolones	1.60 (2%)	2.72
Sulfonamides	30 (<1%)	2.01
Tetracyclines	67 (<1%)	2.59
Metronidazole	53 (<1%)	1.70

Discussion: Previous studies suggested a link between antibiotics and spontaneous abortion but were limited by small sample size and the possibility of recall or indication bias. The present study tried to avoid these limitations, notably by including the 2 active comparator antibiotic classes in order to avoid confounding by infection severity. While confounding by severity cannot fully explain the findings, neither can it be ruled out completely.

Muanda F, et al: Use of antibiotics during pregnancy and risk of spontaneous abortion. *Canadian Medical Association Journal* 2017; doi 10.1503/cmaj.161020. From the Université de Montréal; and the Centre hospitalier universitaire Sainte-Justine, Montréal, Canada. **Funded by the Fonds de la recherche en santé du Québec; and the Réseau Québécois de recherche sur l'usage des médicaments. One study author disclosed a relevant financial relationship; the remaining 2 authors declared no competing interests.**

***See Reference Guide.**

Ticagrelor Samples Recalled

AstraZeneca has voluntarily recalled a single lot of professional sample bottles containing 90 mg ticagrelor (*Brilinta*) following a report that a bottle also contained 200 mg lesinurad (*Zurampic*) tablets. The affected lot, JB5047, comprises only professional sample bottles containing 8 tables distributed to physicians in the U.S. in March and April 2017. Other forms and dosage strengths of ticagrelor, including those obtained in retail or mail order pharmacies, are not affected. Inadverently missed ticagrelor doses, due to incorrect medication ingestion, can increase patients' risk of blood clots, heart attack, and death. Ingestion of lesinurad has the potential to cause adverse renal effects, including acute renal failure.

FDA MedWatch Alert: Brilinta (ticagrelor 90 mg tablets, 8 count physician sample bottles: recall of lot # JB5047 - due to report of another medicine in one bottle. Available at www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm560786.htm.

New GLP-1 Analogue for Diabetes

Semaglutide, an investigational once-weekly injected GLP-1 analogue, was superior to the DPP-4 inhibitor sitagliptin in improving glycemic control and inducing weight loss in a 1-year clinical trial. Semaglutide had similar safety and tolerability to other agents in its class.

Methods: The multicenter trial enrolled >1200 patients with type 2 diabetes and insufficient glycemic control (HbA_{1c} value, 7.0–10.5%) while receiving metformin, a thiazolidinedione, or both. Participants were randomized to double-blind add-on therapy with subcutaneous semaglutide at 0.5 or 1.0 mg once weekly with a sitagliptin placebo, or 100 mg/day oral sitagliptin with

subcutaneous placebo injections. Background medications were continued at the pre-trial dose. Patients with unacceptable hyperglycemia during the trial could receive rescue medications at their clinician's discretion. The primary efficacy outcome was change in HbA_{1c} from baseline to week 56. Change in body weight was the confirmatory secondary outcome.

Results: Mean baseline HbA_{1c} was 8.1%. At week 56, HbA_{1c} decreases were significantly larger with both doses of semaglutide than with sitagliptin (endpoint A_{1c} values, 6.8, 6.5, and 7.6, respectively). Semaglutide was also associated with larger reductions in fasting glucose and other markers of glycemic control. Mean body weight reduction was greater with both semaglutide doses than with sitagliptin (10–13 lbs vs 4 lbs). Semaglutide was associated with higher likelihood of losing both ≥5% and ≥10% of initial weight and with greater reductions in body mass index and waist circumference. The proportion of patients achieving response (i.e., HbA_{1c} <7.0% without symptomatic hypoglycemia and with no weight gain) was 63% with 0.5 mg/week semaglutide, 74% with 1.0 mg/week semaglutide, and 27% with sitagliptin (p<0.0001).

Rescue medication was provided to 5% of patients who received 0.5 mg semaglutide, 2% who received 1.0 mg semaglutide, and 20% of the sitagliptin group. Adverse events with semaglutide were similar to those observed with other GLP-1 analogues and were mainly gastrointestinal. Confirmed hypoglycemia occurred in 2%, <1%, and 1% of patients receiving 0.5 mg semaglutide, 1.0 mg semaglutide, and sitagliptin, respectively.

Discussion: First-generation GLP-1 receptor antagonists must be taken once or twice a day. Three GLP-1 analogues with once-weekly dosing have been FDA-approved for treating type 2 diabetes: exenatide extended-release, albiglutide, and dulaglutide. Head-to-head comparisons are not available, but based on indirect comparisons, semaglutide may result in better glycemic control than other GLP-1 analogues or DPP-4 inhibitors.

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

Ahren B, et al: Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet* 2017;5 (May):341–354. From Lund University, Sweden; and other institutions including Novo Nordisk A/S, Seborg, Denmark. **Funded by Novo Nordisk. All 7 study authors disclosed financial relationships with commercial sources, including Novo Nordisk.**

Common Drug Trade Names*: albiglutide—*Tanzeum*; dulaglutide—*Trulicity*; exenatide, extended-release—*Bydureon*; metformin—*Glucophage*; sitagliptin—*Januvia

***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.

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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PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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New Combination for Hepatitis C

A new, fixed-dose combination of sofosbuvir, velpatasvir, and voxilaprevir (*Vosevi*) has received fast-track FDA approval for treatment of adults with chronic hepatitis C virus (genotypes 1–6) and no more than mild cirrhosis that had not been responsive to previous treatment with sofosbuvir or other drugs for the virus. Safety and efficacy of *Vosevi* were demonstrated in 2 clinical trials, in which 96–97% of patients had no virus detected in their blood 12 weeks after treatment. Common adverse effects of *Vosevi* in these trials were headache, fatigue, diarrhea, and nausea. In addition, treatment can reactivate hepatitis B virus in coinfected patients. Recommendations for *Vosevi* administration differ based on viral genotype and prior treatment history, but the agent is contraindicated in all patients taking rifampin.

FDA News Release: FDA approves Vosevi for hepatitis C. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm567467.htm.

Common Drug Trade Names*: rifampin—*Rifadin*; sofosbuvir—*Sovaldi*; sofosbuvir/velpatasvir/voxilaprevir—*Vosevi

Cholesterol Lowering with Inclisiran

The injected anti-RNA therapy inclisiran, an investigational drug that interferes with the synthesis of PCSK9, was well tolerated and produced large reductions in LDL cholesterol in a phase II clinical trial.

Background: Inclisiran is a synthetic small interfering RNA (siRNA) that silences the RNA that synthesizes PCSK9, the enzyme that degrades LDL cholesterol receptors on cell membranes, resulting in increased removal of LDL cholesterol from circulation.

Methods: Study participants (n=497) had baseline LDL-cholesterol levels of >70 mg/dL and a history of atherosclerotic cardiovascular disease, or >100 mg/dL without cardiovascular disease. They were required to have received the maximum possible dose of a statin for ≥30 days, with or without additional lipid-lowering therapy, but without any anti-PCSK9 monoclonal antibody treatment. Patients were randomly assigned to 1 of 8 treatment groups: a single injection of placebo or inclisiran at 200, 300, or 500 mg on day 1; or 2 injections of placebo or inclisiran at 100, 200, or 300 mg, on days 1 and 90. The primary efficacy endpoint was change in LDL cholesterol from baseline to day 180.

Results: Mean baseline LDL-cholesterol levels ranged from 118 to 139 mg/dL across the treatment groups. Nearly 70% of participants had a history of cardiovascular disease, 73% were receiving statins, and 31% were receiving second-line treatment with ezetimibe (*Zetia*).

After 180 days, participants in the single-dose inclisiran groups had mean reductions in LDL cholesterol ranging from 28% to 42%. Patients who received the 2-dose regimen had reductions ranging from 36% to 53% ($p<0.001$ vs placebo for all comparisons). Levels increased slightly with placebo. Significantly reduced LDL-cholesterol levels continued at day 240 in the inclisiran

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groups. The lowest LDL-cholesterol levels were reached at day 30 for single-dose inclisiran and day 150 for the 2-dose regimens.

Injection-site reactions occurred in about 5% of the combined inclisiran groups and in no placebo patients. Other adverse events with inclisiran were generally similar to those experienced by the placebo group. Hepatic enzymes were transiently elevated in 4 inclisiran patients. No patients developed antidrug antibodies.

Discussion: These results suggest inhibiting the translation of PCSK9 messenger RNA in the liver may be an effective alternative to targeting circulating PCSK9 with monoclonal antibodies and would almost certainly involve a lower injection burden, compared with monthly or biweekly injections. Consistency in LDL-cholesterol reduction may be an additional advantage of therapies that target PCSK9. Maintaining consistent LDL-cholesterol reductions over time with statins is often hindered by nonadherence.

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

Ray K, et al: Inclisiran in patients at high cardiovascular risk with elevated cholesterol. *NEJM* 2017;376 (April 13): 1430–1440. From Imperial College London, U.K.; and other institutions. **Funded by the Medicines Company. All study authors disclosed financial relationships with commercial sources.**

***See Reference Guide.**

GI Effects of Methylphenidate

According to a meta-analysis, methylphenidate (*Ritalin*) was associated with increased risks of decreased appetite, weight loss, and abdominal pain, but not other gastrointestinal side effects in children and adolescents with ADHD.

Methods: Randomized controlled trials of methylphenidate, either parallel-group or crossover, with a majority of participants aged <19 years, were identified from a recent Cochrane review. Methylphenidate dosing forms could be either oral (immediate- or extended-release) or transdermal, and the control condition was either placebo or no treatment. Information on GI adverse events from the 61 trials (n=5983) were ascertained using rating scales, spontaneous reports, or regular interviews by investigators.

Results: Methylphenidate was associated with a >3-fold increase in risk of reduced appetite in both parallel-group and crossover trials. The drug was also associated with decreased weight in parallel-group trials and with abdominal pain in the crossover studies. In neither of the analyses was methylphenidate associated with risk of diarrhea, dyspepsia, increased appetite, nausea, or vomiting. Risk of any GI adverse event did not differ according to the type of methylphenidate preparation, dosage, or duration of treatment.

Discussion: Guidelines for prescribing methylphenidate suggest that the risk of decreased appetite may be controlled by dosage reduction. The meta-analysis contradicts this advice, but the findings were based on only 10 studies, of generally low quality, comparing different dosages.

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

Holmskov M, et al: Gastrointestinal adverse events during methylphenidate treatment of children and adolescents with attention deficit hyperactivity disorder: a systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *PLOS One* 2017; doi 10.1371/journal.pone.0178187. From Region Zealand Psychiatry, Slagelse, Denmark; and other institutions. **Funded by the Region Zealand Research Foundation. Two of the 12 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

Adjuvant Neratinib in Breast Cancer

The kinase inhibitor neratinib has received FDA approval as extended adjuvant treatment following acute trastuzumab to reduce risk of recurrence in patients with early-stage HER2-positive breast cancer. Neratinib blocks several enzymes that promote cell growth; the treatment reduced rates of recurrence and death compared with placebo over 2 years in a clinical trial. Common adverse effects of neratinib treatment include: diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, liver enzyme increases, nail disorders, dry skin, abdominal distention, weight loss, and urinary tract infection. Diarrhea is common, so antidiarrheal prophylaxis should be provided during the first 2 cycles (56 days) of treatment and as needed thereafter.

FDA News Release: FDA approves new treatment to reduce the risk of breast cancer returning. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm567309.htm.

Common Drug Trade Names*:** **neratinib—*Nerlynx*; trastuzumab—*Herceptin

Statins for Primary Prevention

According to a secondary analysis of clinical-trial data, statin therapy given as primary prevention did not reduce mortality or cardiovascular events in older adults with moderate hyperlipidemia and hypertension.

Methods: The ALLHAT study was a comparative trial of antihypertensive medications. A subset of participants were included in the ALLHAT-LLT (lipid-lowering therapy) cohort. These patients were aged ≥55 years; had hypertension and 1 additional coronary heart disease (CHD) risk factor; were not currently receiving lipid-lowering therapy; and had LDL-cholesterol levels between 120 and 189 mg/dL. ALLHAT-LLT participants were randomly assigned to open-label treatment with either 40 mg/day pravastatin or usual care. The present post-hoc analysis included ALLHAT-LLT patients aged ≥65 years at enrollment who had no evidence of atherosclerotic cardiovascular disease (i.e., CHD, peripheral vascular disease, or cerebrovascular disease). The primary efficacy outcome was all-cause mortality at 6 years.

Results: The analysis included 2867 patients (mean age, 71 years), followed for a mean of nearly 5 years. Of those randomly assigned to receive pravastatin, 78% were still receiving treatment with the drug after 6 years; 29% of the usual-care group were given a prescription for a statin by year 6. Mean LDL-cholesterol levels by year 6 were 109 mg/dL in the pravastatin group and 129 mg/dL in the usual-care group. There were more deaths in patients assigned to receive pravastatin than in controls, although the differences were not statistically significant. In participants aged ≥75 years, there were 92 deaths in the pravastatin group and 65 deaths in controls (p=ns). The adjusted hazard ratio* for mortality was higher with pravastatin than usual care but did not reach significance. Rates of CHD events, stroke, heart failure, and cancer did not differ between the 2 treatment groups. There was no statistical interaction between patient age and treatment group.

Discussion: The other major primary prevention trial with a substantial older population, the JUPITER trial, showed a modest, nonsignificant beneficial effect of rosuvastatin on mortality in patients aged ≥70 years, but that trial may have been biased. Another large trial, HOPE-3, showed rosuvastatin was effective for primary prevention of cardiovascular events in older individuals, but had no effect on mortality. The ALLHAT-LLT results suggest that statins may adversely affect the function or health of older adults, possibly offsetting any cardiovascular benefits.

Study Rating*—15 (88%): This study met most criteria for a randomized controlled trial; however, neither patients nor evaluators were blinded to treatment assignment.

Han B, et al: Effect of statin treatment vs usual care on primary cardiovascular prevention among older adults: the ALLHAT-LLT randomized clinical trial. *JAMA Internal Medicine* 2017; doi 10.1001/jamainternmed.2017.1442. From New York University School of Medicine, NY; and other institutions. **Funded by the National Heart, Lung, and Blood Institute; and Pfizer, Inc. The authors declared no competing interests.**

Common Drug Trade Names*: pravastatin—*Pravachol*; rosuvastatin—*Crestor

***See Reference Guide.**

Metformin in Alzheimer's Disease

Treatment with metformin (*Glucophage*) showed promising effects on cognition and biomarkers of Alzheimer's disease in a placebo-controlled pilot study.

Background: Insulin resistance has been associated with Alzheimer's-like biomarkers, reduced activation of cerebrocortical insulin receptors, and decreased cerebral glucose metabolism that correlates with memory impairment. Clinical trials with intranasal insulin and other antidiabetic drugs have had mixed results. Treatment with metformin, an insulin sensitizer, is a promising alternative approach, avoiding the risks of chronic insulin administration.

Methods: Study participants were patients aged 55–80 years with a diagnosis of mild cognitive impairment or early dementia due to Alzheimer's disease, and with no history of diabetes or prediabetes. Eligibility criteria included fasting glucose <110 mg/dL or HbA1c <6.0, at least 1 positive biomarker for Alzheimer's disease, a lack of evidence for vascular dementia, and a baseline Mini-Mental State Examination (MMSE) score >19. Patients taking a cholinesterase inhibitor were allowed to continue on a stable dose. Study treatment consisted of 8 weeks of randomly assigned metformin (titrated to 1000 mg b.i.d. or maximum tolerated dose) or placebo, followed by

8 weeks of the crossover treatment. Outcome measures in this exploratory trial included cerebrospinal fluid (CSF) sampling, magnetic resonance imaging (MRI) to assess cerebral blood flow in specified regions, and testing with the Alzheimer's Disease Assessment Scale-cognitive subscale, computerized neuropsychological assessments, the Geriatric Depression Scale, and the Dementia Severity Rating Scale.

Results: Study participants (n=20; 9 women) had a mean age of 70 years and baseline MMSE scores averaging 26. After 8 weeks of active treatment, metformin was detectable in CSF at average levels of about 10% of mean fasting plasma levels. There were no changes in CSF markers of Alzheimer's disease. Functional MRI studies showed no statistically significant treatment effect in any of the predefined regions of interest, but a subset analysis of patients who completed scans before and after both metformin and placebo exposure showed a significant increase in superior and middle orbitofrontal cerebral blood flow with metformin but not placebo ($p<0.05$ for both regions).

Cognitive testing showed a statistically significant improvement in 1 measure of executive function after metformin treatment ($p<0.05$). Statistical trends favoring metformin were observed on measures of learning and memory, but not language or motor speed.

Common adverse effects of metformin were anorexia, diarrhea, nausea, hypoglycemia, and weight loss. Transient lactic acidosis developed in 2 patients. Metformin was not associated with changes in plasma glucose or insulin, depression, or functional status.

Discussion: Regardless of important limitations, including the small sample and crossover without a washout period, results of this study indicate that metformin crosses the blood-brain barrier and may improve executive function in patients with Alzheimer's dementia. Additional studies appear to be warranted.

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

Koenig A, et al: Effects of the insulin sensitizer metformin in Alzheimer disease: pilot data from a randomized placebo-controlled crossover study. *Alzheimer Disease and Associated Disorders* 2017;31 (April–June):107–113. From the University of Pennsylvania, Philadelphia. **Funded by the BrightFocus Foundation; the NIMH; and other sources. The authors declared no competing interests.**

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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.

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Triple-Bead Mixed Amphetamine Salts

A new once-daily triple-bead mixed amphetamine salts formulation (*Mydayis*) has received FDA approval for the treatment of ADHD in adults and adolescents aged ≥13 years. In clinical trials, the agent was shown to significantly improve symptoms beginning at 2–4 hours and lasting for up to 16 hours postdose. Common adverse effects were similar to those with other amphetamine formulations and included insomnia, decreased appetite, and weight loss in adults and adolescents; dry mouth, increased heart rate, and anxiety in adults; and irritability and nausea in adolescents. Mydayis is expected to become available in the U.S. later this year at strengths of 12.5, 25, 37.5, and 50 mg.

U.S. FDA approves Mydayis ™ (mixed salts of a single-entity amphetamine product)—a new once-daily option for ADHD symptom control in patients 13 years and older [press release]. Lexington, MA; Shire PLC: June 20, 2017. Available at https://www.shire.com/en/newsroom/2017/june/w6x937.

Safety of Proton Pump Inhibitors

There is growing concern about how PPIs are used in the U.S. as a consequence of over-the-counter availability of some agents, off-label prescribing, and inappropriate dosing. To make sense of the many reports of adverse consequences of PPI therapy, a group of researchers applied the Hill criteria—a list of 9 considerations that can help determine whether a statistical association represents a causal relationship—to commonly reported PPI adverse effects. The Hill criteria include such items as strength of association, temporal association, biological plausibility, and consistency of observed results.

The evidence regarding PPI adverse effects consists largely of observational studies, which can trigger false alarms because of various biases. Overzealous interpretations of these associations can lead to inappropriate discontinuation of a needed medication. On the other hand, the observational evidence has led to appropriate scrutiny of PPI therapy and questioned its overuse for non-approved indications. After applying the criteria, the authors determined that most of the evidence linking PPIs to serious long-term adverse effects is weak and insubstantial and should not alter prescription of the agents at the lowest effective dosages for patients with a proven indication.

Vaezi M, et al: Complications of proton pump inhibitor therapy. Gastroenterology 2017; doi 10.1053/j.gastro.2017.04.047. From Vanderbilt University Medical Center, Nashville, TN; and other institutions. **Source of funding not stated. Two of 3 study authors disclosed financial relationships with commercial sources; the remaining author declared no competing interests.**

Beta-Blockers and Post-MI Mortality

In a large cohort study, beta-blocker therapy did not reduce mortality in patients without heart failure or left ventricular systolic dysfunction who survived an acute myocardial infarction. Beta-blockers are routinely prescribed in this patient group, in part out of uncertainty created by conflicting guidelines.

Methods: The study cohort was derived from the U.K. national heart attack register and consisted of

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nearly 180,000 persons admitted to hospitals for an MI between 2007 and mid-2013. Eligible subjects were discharged following acute MI without a diagnosis of heart failure or left ventricular dysfunction and were followed until the end of 2013. Patients with a history of beta-blocker use or a condition for which they may have received beta-blockers were excluded. The primary outcome was all-cause mortality at 1 year after hospitalization, compared between patients who did and did not receive beta-blocker therapy.

Results: Nearly all cohort members (95%) received beta-blockers. Overall mortality at 1 year was significantly lower in patients who received the drugs than in those who did not (5% vs 11%; p<0.001). However, in a propensity-score* analysis adjusted for selection bias and confounders, there was no difference in mortality between those who received or did not receive the agents. There was no survival difference for beta-blockers at 1 month, 6 months, or 1 year or in patient subsets with ST-segment elevation MI or non-ST-segment elevation MI.

Discussion: In the U.S., beta-blockers are recommended for all patients after MI, regardless of heart failure class or ejection fraction, and many patients are prescribed the drugs indefinitely. However, beta-blockers are associated with adverse effects and potential harms, and medication adherence is reduced as the number of medications is increased. Because beta-blockers do not appear to confer any survival benefit, these results suggest that they should not be routinely prescribed following MI in patients without heart failure who have preserved ejection fraction.

Dondo T, et al: Beta-blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. *Journal of the American College of Cardiology* 2017;69 (June 6):2710–2720. From the University of Leeds, U.K.; and other institutions.
Funded by the British Heart Foundation; and other sources. Six of 12 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.

***See Reference Guide.**

New HCV Treatment

The combination of glecaprevir and pibrentasvir (*Mavyret*) has received fast-track FDA approval to treat chronic hepatitis C virus (HCV) genotypes 1–6 in adults without cirrhosis or with mild cirrhosis, including patients with moderate-to-severe kidney disease and those receiving dialysis. *Mavyret* is also approved for adult patients with HCV genotype-1 infection who have previously received treatment with either an NS5A inhibitor or an NS3/4A protease inhibitor but not both. *Mavyret* is the first approved agent with an 8-week treatment duration; previous options required ≥12 weeks of treatment. In clinical trials, 92–100% of patients who received *Mavyret* had no virus detected in their blood 12 weeks after completing treatment, suggesting the infection had been cured. Common adverse effects were headache, fatigue, and nausea. *Mavyret* is not recommended in patients with moderate cirrhosis and is contraindicated in patients with severe cirrhosis and in those receiving atazanavir and rifampin. Hepatitis B virus (HBV) reactivation has been reported in coinfected patients; all patients should be screened for current or past HBV infection before being started on *Mavyret*.

FDA News Release: FDA approves Mavyret for Hepatitis C. Available at https://www.fda.gov/newsevents/ newsroom/pressannouncements/ucm570038.htm.

Common Drug Trade Names*: atazanavir—*Reyataz*; glecaprevir–pibrentasvir—*Mavyret*; rifampin—*Rifadin

Quarter-Dose Antihypertensives

According to a meta-analysis, quarter-dose antihypertensive therapy may be more tolerable than standard-dose monotherapy. Limited evidence suggests quarter-dose regimens that combine antihypertensive agents from multiple classes may have superior efficacy to single-dose regimens, with fewer adverse effects.

Methods: The authors identified randomized controlled trials (either parallel-group or crossover designs), published up until June 2016, as well as trials from online registries and other sources. Trials compared quarter-dose therapy with either placebo or standard doses of antihypertensive agents, with ≥2 weeks of treatment and follow-up. All trials included antihypertensive agents from >1 of the 5 major classes: calcium channel blockers, beta-blockers, angiotensin receptor II antagonists, angiotensin-converting enzyme inhibitors, and thiazide diuretics. Efficacy was assessed as the mean change from baseline in systolic and diastolic blood pressure (BP) from baseline to end of study.

Results: The analysis included 42 studies with >20,000 patients, who received treatment for a mean of 7 weeks (range, 4–12 weeks) and with mean baseline BPs of 154/101 mm Hg. Single quarter-dose regimens, the most commonly eval-

uated strategy, were superior to placebo (see table), but not to standard-dose monotherapy. All of the antihypertensive drug classes had similar efficacy. Dual quarter-dose regimens were also superior to placebo and had comparable effects to standard-dose therapy. There were no trials of triple quarter-dose therapy. Quadruple quarter-dose therapy was associated with substantially greater effects than either placebo or standard-dose monotherapy in 2 separate trials.

Meta-analysis: BP-lowering from baseline with quarter-dose regimens		
Comparison	**# of Studies (patients)**	**Systolic/Diastolic BP Decrease**
Single quarter-dose vs placebo	36 (n=4721)	4.7/2.4
Dual quarter-dose vs placebo	6 (n=312)	6.7/4.4
Quadruple quarter-dose vs placebo	1 (n=19)	22.4/13.1
Quadruple quarter-dose vs standard dose monotherapy	1 (n=108)	13.1/7.9

Single and dual quarter-dose therapy had similar adverse-effect profiles to placebo. Adverse effects were not reported in detail in the quadruple therapy trials, but the combinations were reported as well tolerated, although only 40 patients received these regimens for only 4 weeks.

Discussion: The meta-analysis suggests low-dose antihypertensive drugs should have a broader clinical role. Dual quarter-dose therapy may have comparable efficacy and superior tolerability to standard-dose monotherapy, and adding a quarter dose of a new agent to existing therapy may be preferable to doubling the dose of the existing agent. More research is needed to determine the role of triple or quadruple quarter-dose regimens in patients with resistant hypertension.

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

Bennett A, et al: Efficacy and safety of quarter-dose blood pressure-lowering agents: a systematic review and meta-analysis of randomized controlled trials. *Hypertension* 2017; doi 10.1161/HYPERTENSIONAHA.117.09202. From the University of Sydney, Australia; and other institutions. **Funded by the National Health and Medical Research Council.**

***See Reference Guide.**

Pravastatin Recall

Due to mislabeling, a single lot of 40-mg pravastatin tablets has been recalled by International Laboratories. While the product is labeled as pravastatin, bottles actually contain 300-mg extended-release bupropion tablets. Common adverse effects of bupropion—e.g., nausea, vomiting, dry mouth, headache, constipation, sweating, sore throat, diarrhea, dizziness, restlessness, blurry vision—are generally mild and reversible. However, bupropion lowers the seizure threshold and poses a substantial risk to patients with epilepsy. In addition, hypertensive crisis is possible as a result of a drug interaction in patients taking monoamine oxidase inhibitors. Patients with the affected lot (#115698A) should be advised not to take the medication.

FDA MedWatch Alert: Pravastatin sodium tablets by International Laboratories: recall – mislabeling. Available at https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm571066.htm.

Common Drug Trade Names*: bupropion, extended-release—*Budeprion XL, Wellbutrin XL*; pravastatin—*Pravachol

Dabigatran Reversal

Idarucizumab, a monoclonal antibody fragment that binds dabigatran and reverses its anticoagulant activity, received accelerated FDA approval in 2015 based on an interim analysis of the first 90 patients in an open-label clinical trial.[1,2] Results of the full sample analysis, presented here, support the early findings.[3]

Methods: The study enrolled 503 patients receiving dabigatran therapy who required urgent reversal because of uncontrollable or life-threatening bleeding (group A) or the need to undergo surgery that could not be delayed for ≥8 hours and required normal hemostasis (group B). All patients were given 5 g of intravenous idarucizumab in 2 doses of 2.5 g, ≤15 minutes apart. The primary study endpoint was the maximum percentage reversal of the anticoagulant effect of dabigatran, measured at any time within 4 hours of the second infusion. Anticoagulation was measured using the diluted thrombin time or the ecarin clotting time.

Results: A total of 301 patients were enrolled in group A, and 202 in group B. Patients had an average age of 78 years, and >95% were receiving dabigatran for stroke prevention in the context of atrial fibrillation. Of the patients in group A, 88% were experiencing major or life-threatening

bleeding: GI bleeding (46%), intracranial hemorrhage (33%), or bleeding from trauma (26%). In group B, 98% received the intended surgery, a median of 1.6 hours after the first idarucizumab infusion.

The median peak reversal of anticoagulation was 100%. Reversal was rapid and occurred independently of patients' age, gender, renal function, and baseline concentration of dabigatran. After the administration of idarucizumab, measured levels of dabigatran were below the threshold of anticoagulant activity in all but 3 patients and remained below this threshold for 24 hours in 77%.

In patients with bleeding, the median time to cessation of bleeding was 2.5 hours in those in whom this could be measured, excluding patients with intracranial hemorrhage and those whose bleeding stopped before treatment. Among the patients requiring surgery, hemostasis was normal in 93%; no patient continued to have severely abnormal homeostasis. Mortality at 30 days was 14% in group A and 13% in group B. Thrombotic events occurred in about 6% of patients, and anti-idarucizumab antibodies developed in nearly 6%. Most of the adverse events were worsening of the index event or a coexisting condition.

Discussion: This trial was designed to replicate routine emergency care and avoid delays in treatment. Thus some proportion of patients received treatment before baseline coagulation tests could be performed, and some had normal clotting times when treated. The results suggest that idarucizumab can be used safely even in patients with little or no circulating dabigatran.

[1]Pollack C Jr, et al: Idarucizumab for dabigatran reversal. *NEJM* 2015;373 (August 6):511–520. See *Primary Care Drug Alerts* 2015;36 (September):33–34.

[2]FDA News Release (October 16, 2015): FDA approves Praxbind, the first reversal agent for the anticoagulant Pradaxa. Available at http://www.fda.gov/newsevents/newsroom/pressannouncements. See *Primary Care Drug Alerts* 2015;36 (October):37–38.

[3]Pollack C Jr, et al: Idarucizumab for dabigatran reversal—full cohort analysis. *NEJM* 2017; doi 10.1056/NEJMoa1707278. From Thomas Jefferson University, Philadelphia, PA; and other institutions. **Funded by Boehringer Ingelheim. Nineteen of 21 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names*: dabigatran—*Pradaxa*; idarucizumab—*Praxbind

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

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

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Mortality Increase with PPI Use

According to results of a longitudinal cohort study, use of proton pump inhibitors is associated with a 25% increase in mortality over 6 years, compared with use of H2 blockers.

Methods: Using administrative data from the US Department of Veterans Affairs, all outpatients who received a first prescription for a PPI or an H2 blocker between October 2006 and September 2008 were identified. Patients who first received an H2 blocker and later switched to a PPI entered the PPI cohort at that time. Patients were followed through September 2013. The primary study outcome was time to death from any cause, comparing the PPI cohort of 276,000 patients with the H2 inhibitor cohort of more than 73,000. Mortality was also compared between PPI users vs nonusers, and PPI users vs those with no acid-suppressive therapy.

Results: At baseline, PPI users were older and more likely to have comorbid illnesses including diabetes, hypertension, cardiovascular disease, and hyperlipidemia than those prescribed an H2 blocker. They also were more likely to have upper GI pathology including bleeding, ulcer disease, *H. pylori* infection, Barrett's esophagus, achalasia, stricture, and esophageal cancer.

After adjusting for multiple factors, PPI use was associated with an increased risk of death compared with H2 blocker use (hazard ratio,* 1.25). Adjustment for a high-dimensional propensity score* reduced the difference somewhat, but the excess mortality with PPI use was still statistically significant. Differences in mortality were also observed between PPI users and nonusers (total 3.3 million patients; adjusted HR, 1.15), and between those receiving PPIs and no acid suppression therapy (total 2.9 million patients; adjusted HR, 1.23). Longer cumulative exposure to PPIs was associated with a graded increase in mortality.

Discussion: Recent studies have established associations of PPI therapy with acute interstitial nephritis, chronic kidney disease, end-stage renal disease, onset of dementia, hypomagnesemia, *C. difficile* infections, and fractures. PPIs increase oxidative stress, endothelial dysfunction, telomere shortening, and accelerated senescence in endothelial cells, likely to be common mechanisms for these effects. These results add increased mortality to the risks associated with PPIs and support more conservative use of the agents, which are widely used for non-labeled indications and for inappropriately long periods.

Xie Y, et al: Risk of death among users of proton pump inhibitors: a longitudinal observational cohort study of United States veterans. *British Medical Journal* 2017; doi 10.1136/bmjopen-2016-015735. From the VA Saint Louis Health Care System, MO; and other institutions. **Source of funding not stated. The authors declared no competing interests.**

***See Reference Guide.**

Flu Vaccination for Children

Vaccination against seasonal influenza is recommended for children aged ≥6 months, adolescents, and the general population, especially healthcare and daycare providers, according to the American Academy of Pediatrics (AAP). In recent years,

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percentages of vaccinated children have been in the mid-to-high 50s and adults in the low-to-mid 40s.

In the 2016–2017 flu season, there were 104 laboratory-confirmed flu-related pediatric deaths, according to the AAP. Historically, 80–85% of flu-related pediatric deaths have occurred in unvaccinated children, about half of whom had high-risk conditions. For the present season, the AAP recommends use of either the inactivated trivalent or quadrivalent vaccine. Both contain a new influenza A H1N1 strain and influenza A and B strains from the previous season. The quadrivalent vaccine also has an additional B virus. The quadrivalent live attenuated vaccine should not be used. An adequate supply of this year's vaccine is anticipated.

Children aged 6 months to 8 years should receive 2 doses of vaccine if they have had <2 doses of any trivalent or quadrivalent vaccine before July 1, 2017. All others require only a single dose. Children with egg allergies can receive any influenza vaccine without additional precautions. Peak influenza activity is from January through March, but providers may continue to offer vaccines until June 30, the end of the flu season.

AAP Committee on Infectious Diseases: Recommendations for prevention and control of influenza in children, 2017–2018. *Pediatrics* 2017; doi 10.1541/peds.2017–2550. From the American Academy of Pediatrics. **The recommendations were created without external funding. The authors declared no competing interests.**

Antidiabetic Adherence

In a large observational study, patients with type 2 diabetes had higher rates of adherence and persistence with sodium-glucose cotransporter 2 (SGLT-2) inhibitors than with sulfonylureas.[1] However, adherence and persistence remained suboptimal in patients treated with either type of medication.

Methods: Claims data were analyzed from a database covering more than 70 million Americans with private insurance or Medicare supplemental plans. Patients were included in the analysis if they had a diagnosis of type 2 diabetes and a new outpatient pharmacy claim for a SGLT-2 inhibitor (e.g., canagliflozin, dapagliflozin, empagliflozin) or a sulfonylurea (e.g., glyburide, glipizide, glimepiride) during 2015. Medication adherence was measured using the proportion of days covered (PDC)—days with the medication on hand—during 6-months of follow-up. A PDC of ≥80% was the threshold for compliance. Persistence was defined as the number of days from the first claim until discontinuation of the medication or the end of follow-up. To control for baseline differences between the medication groups, the final study population comprised a sample of 25,314 patients (mean age, 54 years) propensity score matched* for the likelihood of being prescribed an SGLT-2 inhibitor.

Results: Among matched patients, about 75% were taking metformin, and >25% received a DPP-4 inhibitor (e.g., sitagliptin, saxagliptin, linagliptin). Medication adherence was significantly lower for sulfonylureas than SGLT-2 inhibitors (72% vs. 76%, p<0.0001). The proportion of patients with >80% adherence was 54% for sulfonylureas and 61% for SGLT-2 inhibitors (odds ratio,* 1.26; p<0.0001). Rates of discontinuation were 31% for sulfonylureas and 24% for SGLT-2 inhibitors (p<0.0001). SGLT-2 inhibitors were associated with a 25% lower hazard of discontinuation (p<0.0001).

Editorial: [2] Adverse effects and cost often play a role in medication nonadherence and/or discontinuation. Because of the claims-based design, reasons for nonadherence and discontinuation could not be assessed in the present study. While SGLT-2 inhibitors cost more than sulfonylureas by a multiple of 100 without evidence that they are more effective by a similar margin, medications that are not taken cannot benefit patients.

[1]Bell K, et al: Comparing medication adherence and persistence among patients with type 2 diabetes using sodium-glucose cotransporter 2 inhibitors or sulfonylureas. *American Health & Drug Benefits* 2017;10 (June):165–173. From AstraZeneca, Wilmington, DE; and Truven Health Analytics, Ann Arbor, MI. **Funded by AstraZeneca. All study authors disclosed financial relationships with commercial sources including AstraZeneca or Truven Health Analytics.**

[2]Caveney B: Real-world studies in diabetes needed to improve medication adherence and persistence [Editorial]. *American Health & Drug Benefits* 2017;10 (June):174. From Blue Cross & Blue Shield of North Carolina, Durham.

Common Drug Trade Names*: canagliflozin—*Invokana*; dapagliflozin—*Farxiga*; empagliflozin—*Jardiance*; glimepiride—*Amaryl*; glipizide—*Glucotrol*; glyburide—*Diabeta, Glynase*; linagliptin—*Tradjenta*; metformin—*Glucophage*; saxagliptin—*Onglyza*; sitagliptin—*Januvia

***See Reference Guide.**

Evolocumab and Cognitive Function

In a manufacturer-sponsored study, the cholesterol-lowering agent evolocumab (*Repatha*), a proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor, was not associated with reduced cognitive function.

Background: Concern has been raised that cognitive decline may be a consequence of cholesterol-lowering drugs or of low cholesterol levels. Studies of statins have not shown consistent evidence of adverse cognitive effects and the incidence with PCSK9 inhibitors has been shown to be <1%.

Methods: The primary aim of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial was to evaluate the efficacy and safety of evolocumab for the reduction of LDL cholesterol. At the time of enrollment in the FOURIER trial, patients were also invited to enroll in the study of cognitive effects, which was analyzed by a group independent of the sponsor. Participants were aged 40–85 years and had clinically evident atherosclerosis and an LDL cholesterol level of ≥70 mg/dL or a total non-HDL level of ≥100 mg/dL despite statin treatment. Treatments consisted of subcutaneous injections of evolocumab (140 mg biweekly or 420 mg monthly) or matching placebo. Cognitive function was measured using the computerized Cambridge Neuropsychological Test Automated Battery (CANTAB) at baseline, at 24 weeks, yearly, and at the end of the trial. The primary endpoint was the CANTAB score for the spatial working memory strategy index of executive function.

Results: The study population consisted of nearly 2000 patients who had a baseline CANTAB assessment and ≥1 follow-up assessment while receiving treatment. Patients had a mean age of 63 years and >75% had a prior MI; 71% were receiving high-intensity statin treatment and 29% were receiving a moderate-intensity regimen. The median duration of follow-up was 19 months.

Overall, patients had small declines from baseline in the primary executive function endpoint at 24 months, which did not differ between the evolocumab and placebo groups. The change in secondary endpoints—working memory, episodic memory, and processing speed—also did not differ between the groups. The mean changes in scores from baseline were similar within subgroups stratified for the lowest attained cholesterol levels and in most other subgroup analyses. However, a subgroup analysis of executive function favored placebo in patients with a baseline LDL cholesterol <85 mg/dL and favored evolocumab in those with higher baseline cholesterol. There was no difference between evolocumab and placebo groups on a self-rated measure of everyday cognitive function. Cognitive adverse events, consisting of self-reported memory or concentration problems, occurred in 1.9% of the evolocumab group and 1.3% of the placebo group.

Discussion: Evolocumab did not appear to adversely affect cognitive function in this study, but the follow-up duration was relatively short. A 5-year extension study of a subset of FOURIER participants is ongoing.

Giugliano R, et al: Cognitive function in a randomized trial of evolocumab. *NEJM* 2017:377 (August 17):633–643. From Brigham and Women's Hospital, Boston, MA; and other institutions including Amgen, Thousand Oaks, CA. **Funded by Amgen. All study authors disclosed financial relationships with financial sources, including or related to Amgen.**

Warfarin Safety with Herbal Medicines

Although some herbal supplements have antiplatelet and anticoagulant activity, according to a systematic review there is very little evidence that they interact with warfarin (*Coumadin*).[1]

Methods: A comprehensive literature search was undertaken to identify randomized controlled trials of pharmacokinetic or pharmacodynamic interactions between herbal medicines and warfarin. For the study, an herbal medicine was defined as a product or an extract from a single botanical source, including plants, plant extracts, and dietary supplements. A total of 9 studies, comprising 160 patients, met criteria for inclusion in the review. Of these, 3 were placebo-controlled studies and the rest were crossover studies, some with multiple groups receiving different herbal medicines. The studies evaluated 3 ginseng preparations, 2 garlic preparations, ginkgo biloba, echinacea, cranberry, St. John's wort, and ginger.

Results: St. John's wort and echinacea increased the clearance of warfarin in healthy subjects. Ginkgo biloba influenced warfarin kinetics in 1 study but not another. Ginseng, ginger, garlic, and cranberry did not affect the pharmacokinetics of warfarin overall, although garlic and cranberry had effects in subsets of patients based on cytochrome P450 genotypes. Cranberry increased the area under the international normalized ratio-time curve in healthy subjects (but not in a second study of patients with atrial fibrillation), and ginseng reduced the anticoagulant effect of warfarin.

All trials evaluated adverse events associated with coadministration. Few were reported and they were generally mild, and in many cases, not obviously related to coagulation mechanisms.

Discussion: Nearly 40% of patients with cardiovascular disease, including many who receive anticoagulants, have used complementary and alternative medicine, including herbal medicines.[2] While these results suggest that some herbal medications can be safely used with warfarin, low evidence quality, nonstandardization of herbal preparations, and methodological limitations of the included studies limit the conclusions that can be drawn from the data.

[1]Choi S, Oh D-S, Jerng U: A systematic review of the pharmacokinetic and pharmacodynamic interactions of herbal medicine with warfarin. *PLOS One* 2017; doi 10.1371/journal.pone.0182794. From the Korea Institute of Oriental Medicine, Daejeon, South Korea. **Funded by the Korea Institute of Oriental Medicine. The authors declared no competing interests.**

[2]Yeh G, et al: Use of complementary therapies in patients with cardiovascular disease. *American Journal of Cardiology* 2006; 98:673–80.

Evening Methylphenidate

An investigational once-daily methylphenidate formulation taken in the evening provided extended coverage from the early morning hours throughout the day in a phase-III trial.

Background: The new formulation—HLD200—consists of 2 microbead layers surrounding a methylphenidate core. The outer layer provides predictably delayed release about 8–10 hours after ingestion and the inner layer provides controlled extended release throughout the following day. The formulation was designed to address ADHD-related functional impairment in the early morning, before the AM stimulant dose takes effect.

Methods: Study participants were 163 children, aged 6–12 years, with ADHD who had difficulty performing a morning routine of ≥30 minutes between 6 AM and 9 AM. After a washout of prior medications, children were randomly assigned to receive HLD200 or placebo for 3 weeks. Study medication was taken between 6:30 PM and 9:30 PM at a starting dosage of 40 mg/day that was increased to 80 mg/day if tolerated. The primary outcome measure was the ADHD Rating Scale-IV (ADHD-RS-IV). In addition, functioning was measured using several standardized scales.

Results: After 3 weeks of treatment, HLD200 was associated with a larger improvement in ADHD-RS-IV score than placebo as well as greater early morning functional improvement.

Discussion: The short duration of the study and the inclusion of only school-aged children limit the generalizability of the results. However, if these limitations are addressed in future studies, HLD200 could fulfill an important unmet need in ADHD treatment: early morning efficacy that does not sacrifice later-day symptom control.

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

Pliszka S, et al: Efficacy and safety of HLD200, delayed-release and extended-release methylphenidate, in children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (August):474–482. From the University of Texas Health Science Center at San Antonio; and other institutions. **Funded by Ironshore Pharmaceuticals & Development, Inc. All 11 study authors disclosed financial relationships with commercial sources, all but 1 with Ironshore Pharmaceuticals and Development.**

***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.

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.

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Long-Term Efficacy of 9-Valent HPV Vaccine

The 9-valent human papillomavirus vaccine (*Gardasil 9*) retains its efficacy for up to 6 years, according to the final report from the international phase-III clinical trial comparing it to the quadrivalent HPV vaccine. The 9-valent vaccine has similar efficacy to the earlier vaccine in preventing high-grade cervical, vulvar, and vaginal disease caused by the 4 shared HPV types, plus additional protection against 5 more types.

Background: The 9-valent vaccine was developed to provide protection against the 4 most common HPV types (covered by the already available quadrivalent vaccine) and the next 5 most common types. A previous report from this trial indicated that the 9-valent vaccine effectively prevented disease caused by the 5 additional HPV types. The present study was a planned analysis of additional efficacy and safety follow-up from that trial, extending for up to 6 years post-vaccination.

Methods: Participants were healthy women, aged 16–26 years, enrolled in 18 countries. They received 3 randomly assigned intramuscular injections of either the 9-valent vaccine or the quadrivalent vaccine over 6 months. The primary outcomes of the current analysis were efficacy of the 9-valent vaccine in preventing the combined endpoint of high-grade cervical disease, vulvar disease, and vaginal disease caused by the 5 additional virus types; and noninferiority to the quadrivalent vaccine for the 4 shared types. High-grade disease was defined as cervical, vaginal, or vulvar intra-epithelial neoplasia grade 2 or 3, cervical adeno- carcinoma in situ, invasive cervical carcinoma, and vaginal or vulvar cancer. Invasive cancer was not a primary endpoint, in part because of its very long latency after HPV infection.

Results: The efficacy analysis included only women who received all 3 doses of the vaccine, >7100 in each group. The relative efficacy of the 9-valent vaccine for high-grade disease related to the 5 new strains was >97%, and the vaccine showed non-inferiority to the quadrivalent vaccine. The 9-valent vaccine was also associated with lower rates of secondary outcomes related to the 5 types, including persistent HPV infections, low-grade disease, cervical cytological abnormalities, cervical biopsy, cervical definitive therapy, and external genital surgical procedures. Women who received the 9-valent vaccine showed robust antibody responses to all 9 HPV types within 3 months of the first vaccination, and nearly all had seroconverted by month 7. Most participants remained seropositive for 5 years. There were no differences in clinically meaningful adverse events between the 2 vaccine groups: 4 women in the 9-valent vaccine group and 3 in the quadrivalent vaccine group experienced severe adverse events that were believed to be vaccine-related.

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

Huh W, et al: Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. *Lancet* 2017; doi 10.1016/S0140–6736(17)31821–4. From the University of Alabama at Birmingham; and other institutions including Merck & Co. Inc., Kenilworth, NJ. **Funded by Merck. Twenty-six of 28 study authors disclosed potentially relevant financial relationships with commercial sources, including Merck; the remaining authors declared no competing interests.**

***See Reference Guide.**

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PPIs and Depression in Elderly

In a community-based sample of elderly patients, use of proton pump inhibitors was associated with increased risk of depression.[1] The calculated population attributable risk* indicates that in this population, 14% of depression cases could be avoided by withdrawing PPIs.

Background: Research has suggested that PPIs are associated with neuropsychological adverse effects. A large cohort study recently found a significantly increased incidence of dementia in elderly patients receiving PPIs.[2] An incidental finding in that study was a higher prevalence of PPI use among patients with depression. Case reports also support the association. However, in the World Health Organization adverse drug reactions database, depression is rarely associated with PPI use.

Methods: The study population consisted of all persons aged ≥75 years living in a single town in Italy (n=344; mean age, 80 years; 55% women). No study subjects had active peptic ulcer or were receiving *H. pylori* eradication therapy, although they were not exclusion criteria. Depressive symptoms were assessed with the 30-item Geriatric Depression Scale (GDS), with a score of ≥11 indicating depression and scores of 21–30 indicating severe depression. The investigators also compiled data on medications, medical diagnoses, physical activity, cognitive performance, and functional ability.

Results: Although no patient had a diagnosis of DSM-IV major depressive disorder, depression was recorded in the medical records of 38% of the patients and the mean GDS score was 11. Using the GDS cutoff, 163 participants (47%) met criteria for depression. Of these patients, 44 (13%) were receiving treatment with a PPI, most commonly omeprazole (*Prilosec*), which was used by 29 people.

In the PPI-treated group, 73% had GDS scores above the cutoff for depression, compared with 48% of those not taking PPIs (p=0.002). The mean GDS score was 15 in patients taking PPIs and 10 in others (p<0.0001). In contrast, patients taking H2-receptor antagonists or other antacids did not have elevated average GDS scores or rates of depression. Measurements of physical activity and functional ability were also significantly decreased in patients taking PPIs, and cognitive function was somewhat worse, although not statistically significantly. Depression was associated with PPI use in a multivariate model that accounted for the influence of peptic ulcer disease and selective serotonin reuptake inhibitor use (odds ratio,* 2.38; p=0.045). PPI use was associated with both severe and milder depression. Increasing PPI dosages were associated with higher rates of depression.

Discussion: PPIs are often prescribed inappropriately, and in older patients they are generally prescribed on a long-term or continuous basis. They have not been associated with depression in younger patients taking them for shorter periods. Several mechanisms may link PPIs to depression: They may affect cognition, leading to depression as a prodromal symptom of dementia; they increase gastrin-releasing peptide, which may affect brain structures, leading to behavioral alterations found in anxiety, depression, and dementia; and hypergastrinemia may stimulate cholecystokinin B receptors in the CNS that regulate anxiety.

[1]Laudisio A, Incalzi R, Gemma A, Giovannini S, et al: Use of proton-pump inhibitors is associated with depression: a population-based study. *International Psychogeriatrics* 2017; doi 10.1017/S1041610217001715. From Campus Bio-Medico di Roma University, Rome, Italy; and other institutions. **Funded by the Italian Ministry of Health. The authors declared no competing interests.**

[2]Gomm W, et al: Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurology* 2016;73:410–416. See *Primary Care Drug Alerts* 2016;37 (June):21–22.

***See Reference Guide.**

Kayexalate Warning

The FDA is recommending that the potassium-lowering drug sodium polystyrene sulfonate (*Kayexalate*), used to treat hyperkalemia, not be taken at the same time as other oral medicines. The agent has been found to bind to many commonly prescribed medicines, which could decrease absorption and thus effectiveness of those medications. To reduce the likelihood of this interaction, dosing of sodium polystyrene sulfonate and other oral agents, both prescription and over-the-counter, should be separated by ≥3 hours. Time should be increased to ≥6 hours for patients with gastroparesis or other conditions resulting in delayed emptying of food from the stomach into the small intestine.

FDA MedWatch Alert: Kayexalate (sodium polystyrene sulfonate): drug safety communication–FDA recommends separating dosing. Available at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm574763.htm.

Rivaroxaban plus Aspirin

In patients with stable atherosclerotic vascular disease, the combination of rivaroxaban (*Xarelto*) with aspirin was associated with a lower incidence of cardiovascular events than aspirin alone. However, the benefit was partially offset by an increase in major bleeding events.

Methods: The COMPASS trial, conducted in 33 countries, enrolled patients with coronary artery disease (CAD), peripheral arterial disease, or both. The study subjects with CAD who were aged <65 years were also required to have additional risk factors. Patients were randomized to treatment with 2.5 mg rivaroxaban b.i.d. plus 100 mg/day aspirin; 5 mg rivaroxaban b.i.d. with an aspirin placebo; or 100 mg/day aspirin with a rivaroxaban placebo. The primary study outcome was a composite of cardiovascular death, stroke, and MI. The primary safety outcome was major bleeding, defined as fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, or bleeding that led to hospitalization or treatment at an acute care facility.

Results: More than 27,000 patients were enrolled and received treatment before the trial was terminated early (after a mean follow-up of 23 months) because of an observed difference in efficacy among the treatments. Combined rivaroxaban–aspirin was associated with a 24% reduction in risk of the primary outcome, compared with aspirin alone. Rates of various secondary composite cardiovascular outcomes were consistent with the main analysis. Mortality was lower with combined treatment than with aspirin alone (3.4% vs 4.1%; hazard ratio,* 0.82; p=0.01).

Major bleeding occurred more often with combined treatment than with aspirin alone (3.1% vs 1.9% p<0.001). Rivaroxaban alone, which had similar efficacy to aspirin monotherapy, was associated with a higher risk of major bleeding (2.8%). Differences in rates of major bleeding were driven mostly by GI bleeding, with no significant between-group differences in rates of fatal, intracranial, or other bleeding types. Patient age, gender, geographic location, body weight, history of cardiovascular risk factors, and other factors did not appear to affect outcomes.

Net clinical benefit was calculated as the combined risk of the primary cardiovascular outcome, fatal bleeding, and symptomatic bleeding into a critical organ. The rate of this outcome was 20% lower with combined treatment than with aspirin alone (4.7% vs 5.9%).

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

Eikelboom J, et al: Rivaroxaban with or without aspirin in stable cardiovascular disease. *NEJM* 2017; doi 10.1056/NEJMoa1709118. From McMaster University and Hamilton Health Sciences, Hamilton, Canada; and other institutions. **Funded by Bayer. Twenty-eight study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Methylphenidate in Mild Alzheimer's

In a placebo-controlled trial, methylphenidate (*Ritalin*) reduced apathy in male patients with mild Alzheimer's disease. Improvement occurred relatively early in treatment and was followed in time by improved cognition and function and reduced caregiver burden.

Background: Apathy is the most common behavioral problem in Alzheimer's disease and may have a greater impact on function than diminished cognition. It increases caregiver burden and service utilization.

Methods: Study participants were community-dwelling veterans, aged ≥60 years, recruited from the service records of a VA hospital. Patients were enrolled if they had a diagnosis of Alzheimer's disease by the study psychiatrist, had a caregiver, and scored ≥18 on the Mini-Mental State Examination (MMSE) and >40 on the Apathy Evaluation Scale–Clinician version (AES-C), a cutoff that is considered clinically significant in patients with the disease. Participants were randomly assigned to receive 12 weeks of treatment with either placebo or methylphenidate started at 5 mg b.i.d., and increased to 10 mg b.i.d. at 2 weeks. To avoid insomnia, the last dose was taken no later than 3 pm. The primary outcome measure was the AES-C, an 18-item scale that measures behavioral, cognitive, and emotional domains of apathy. Scores range from 18 to 72, and a change of 3.3 points is considered clinically meaningful.

Results: Of 60 patients enrolled, 1 withdrew from each group because of caregiver unavailability. Nearly all patients completed all study visits. Participants had a mean age of 77 years, all were men, and the mean baseline AES-C score was 50. The methylphenidate group had

significantly greater improvement in the AES-C score than the placebo group, beginning at week 4 and reaching a maximum decrease at the 12-week endpoint (10-point difference; p<0.001). The difference was driven by improvements in multiple apathy domains, with behavioral and cognitive scores improving significantly by week 8 and emotional scores by week 12. There was improvement in the other domains, novelty and persistence, but it did not reach statistical significance. Patients who received methylphenidate also showed a mean 2.6-point improvement in the MMSE by week 12 (p=0.001), along with significant improvement on other measures of cognition, instrumental activities of daily living, caregiver burden, depressive symptoms, and Clinical Global Impression Improvement and Severity measures.

Adverse events generally did not differ between the treatment groups. Compared with baseline, mean systolic blood pressure was significantly increased in methylphenidate-treated patients at 12 weeks; however, the between-group difference was not significant. One patient in the methylphenidate group had a serious adverse event possibly related to medication: seizures requiring hospitalization. Five patients receiving each treatment experienced dizziness and insomnia.

Discussion: The efficacy of methylphenidate in this study and in previous, smaller trials is consistent with the dopaminergic hypothesis of apathy. The ideal treatment duration may be longer than the 12 weeks provided in this study, as suggested by patients' continuing improvement over the study period.

Padala P, et al: Methylphenidate for apathy in community-dwelling older veterans with mild Alzheimer's disease: a double-blind, randomized, placebo-controlled trial. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.17030316. From the Central Arkansas Veterans Healthcare System, Little Rock; and other institutions. **Funded by the VA. One study author disclosed relevant financial relationships; the remaining 10 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.

Population-Attributable Risk: The portion of the incidence of a disease in the population (exposed and nonexposed) that is due to exposure. It is the incidence of a disease in the population that would be eliminated if exposure were eliminated.

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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PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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New Shingles Vaccine

The FDA has granted approval for a new vaccine, *Shingrix*, for the prevention of herpes zoster (shingles). The agent is a non-live, recombinant vaccine, administered intramuscularly in 2 doses and is approved for use in patients aged ≥50 years. Clinical trials showed >90% efficacy in prevention of shingles in >38,000 patients across all age groups. Preventive efficacy was sustained over 4 years of follow-up. By preventing cases of shingles, *Shingrix* also reduced the incidence of post-herpetic neuralgia, a common complication of shingles.

Shingrix approved in the US for prevention of shingles in adults aged 50 and over [press release]. London, U.K.; GlaxoSmithKline PLC: October 23, 2017. Available at https://www.gsk.com/en-gb/media/press-releases/shingrix-approved-in-the-us-for-prevention-of-shingles-in-adults-aged-50-and-over.

HRT and Long-Term Mortality

Menopausal hormone replacement therapy was not associated with overall mortality in an analysis of 18 years of follow-up data from the Women's Health Initiative.[1] Given the complex interplay of different types of HRT and various health risks and benefits, all-cause mortality provides a useful summary measure to help with decision-making, according to an accompanying editorial.[2] These study results should alleviate at least some of the concerns that keep women from receiving HRT for treatment for vasomotor symptoms, premature menopause, or early-onset osteoporosis.

Methods: The Women's Health Initiative enrolled >27,000 postmenopausal women, aged 50–79 years, in 1993–1998. Women with a uterus were randomized to receive daily conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) or placebo; those who had undergone hysterectomy received CEE alone or placebo. The primary Women's Health Initiative outcomes were incident coronary heart disease and invasive breast cancer. Both arms of the Women's Health Initiative were terminated before planned, the CEE/MPA trial after a median of 5.6 years and the CEE-alone trial after 7.2 years. The present report is based on follow-up of the Women's Health Initiative cohort ending in December 2014, using regular surveillance and the National Death Index.

Results: Since the beginning of the study, nearly 7500 participants have died, about 1100 during the intervention phase and 6400 during follow-up. All-cause mortality was nearly identical in the HRT and placebo groups: 27% and 28%, respectively. Mortality did not differ between the treatment groups during the intervention phase or during the post-intervention phase. Differences in overall mortality between hormone replacement and placebo groups were present in women aged 50–59 years, but the difference narrowed in older age groups.

Cardiovascular and cancer mortality also did not differ between the HRT and placebo groups. There were also no treatment-related differences in mortality specifically from colorectal cancer,

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all other cancers, or all non-cardiovascular, non-cancer causes. Risk for breast cancer mortality was higher in women who received combined CEE and MPA relative to the placebo group (hazard ratio,* 1.44), and lower in those who received CEE alone than in the placebo group (hazard ratio, 0.55).

Discussion: These findings support practice guidelines endorsing HRT for recently menopausal women, but not for prevention of chronic disease or mortality. However, according to the accompanying editorial, the risks and benefits of HRT in relation to patients' age and menopausal status and the optimal duration of therapy remain unclear.

[1]Manson J, et al: Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the Women's Health Initiative Randomized Trials. *JAMA* 2017;318 (September 12):927–938. From Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and other institutions. **Funded by National Heart, Lung, and Blood Institute; and other sources. Two of 18 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]McNeil M: Menopausal hormone therapy: understanding long-term risks and benefits [editorial]. *JAMA* 2017;318 (September 12):911–912. From the University of Pittsburgh, PA. **The author declared no competing interests.**

***See Reference Guide.**

Parental Diversion of ADHD Medications

Household diversion of stimulants was reported by 1 in 6 parents of children with ADHD who completed an anonymous survey. This preliminary study suggests that diversion is not limited to the better-recognized phenomenon of peer diversion among adolescents and young adults.

Methods: A sample of parents attending community-based educational presentations on ADHD were presented with the survey, which was developed for the study. Respondents were parents of children, adolescents, and young adults currently taking stimulant medications. The questionnaire assessed demographics, household stress levels, and medication storage and access, as well as the occurrence of diversion. In addition, to gauge media influence, respondents were asked if they had seen an episode of a specific television series that depicted parental diversion of stimulants.

Results: A total of 180 parents from 164 households completed the survey. Nearly 30% of parents reported storing their child's medication in plain sight, 42% kept it out of sight but available to anyone in the house, 24% kept it hidden but not locked, and only 3% kept it locked up.

A total of 28 parents (16%) reported household diversion of stimulant medications, most commonly taken by the responding parent or another adult, but occasionally given by an adult to another child in the household. Another 24 parents (13%) reported being tempted to take their child's stimulant, usually on isolated occasions under stressful circumstances.

About half of all parents reported that they either had a diagnosis of ADHD themselves or suspected that they had it. Those with diagnosed or suspected ADHD were more than twice as likely as others to self-administer their child's stimulants or to be tempted to do so (33% vs 17%; p=0.01). Of those who self-administered, 9 reported they were self-medicating their own ADHD and 4 were trying to see if they could get high. Less common reasons for taking their child's medication were the need to get work done, wanting to try the medication on themselves before giving it to the child, and concern about side effects.

Nearly 40% of adults had seen the TV series episode featuring medication diversion. These adults were more likely than others to self-administer stimulants or to be tempted, even though half agreed that the episode trivialized the danger of stimulants. Diversion was not associated with household stress levels or with the parent's gender, ethnicity, age, or educational level.

Discussion: Peer diversion of prescription stimulants among adolescents and young adults has received a considerable amount of study; however, household diversion, which has not previously been studied, also appears to be a significant issue. Clinicians should be aware that adults may be motivated to self-medicate for their own diagnosed or suspected ADHD. It should be noted that although the newer long-acting stimulants are marketed as being less prone to abuse than short-acting agents, at least half of the parents in this study who self-administered used a long-acting formulation.

Pham T, et al: Household diversion of prescription stimulants: medication misuse by parents of children with attention-deficit/hyperactivity disorder. J*ournal of Child and Adolescent Psychopharmacology* 2017;27 (October): 741–746. From Steven and Alexandra Cohen Children's Medical Center of New York, Lake Success. **Source of funding not stated. The authors declared no competing interests.**

Anacetrapib Development Halted

Merck has announced they will not file for FDA approval of their cholesteryl ester transfer protein (CETP) inhibitor anacetrapib.[1] The decision was announced despite preliminary findings that anacetrapib increased HDL cholesterol and lowered LDL cholesterol without increasing cardiovascular risks in patients with or at risk for coronary heart disease,[2] and an improved safety profile compared with an earlier CETP inhibitor torcetrapib, whose development was halted because of safety concerns. According to Merck, "…after comprehensive evaluation, we have concluded that the clinical profile for anacetrapib does not support regulatory filings."

[1]Merck Provides Update on Anacetrapib Development Program [press release]. Kenilworth, NJ; Merck: October 11, 2017. Available at http://investors.merck.com/ news/press-release-details/2017/Merck-Provides-Update-on-Anacetrapib-Development-Program/default.aspx.

[2]Cannon C, et al: Safety of anacetrapib in patients with or at high risk for coronary heart disease. *NEJM* 2010;363 (December 16):2406–2415. See *Primary Care Drug Alerts* 2011;32 (February):6–7.

Monthly Buprenorphine

The Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the FDA have recommended approval of an investigational once-monthly sustained-release buprenorphine injection (RBP-6000) for the treatment of moderate-to-severe opioid use disorder.

The new buprenorphine formulation makes use of the Atrigel® delivery system, which consists of a biodegradable polymeric solution and a water-miscible biocompatible solvent. After sub- cutaneous injection, the solvent diffuses out of the polymer matrix and the polymer precipitates, trapping buprenorphine inside and forming a solid depot at the injection site. The depot then releases buprenorphine over a 1-month period by diffusion as the polymer biodegrades. In clinical trials, RBP-6000 produced significantly greater abstinence rates than placebo, with a safety profile similar to that of oral transmucosal buprenorphine (*Subutex*). Injection-site reactions resulted in <1% of patients withdrawing from the trials.

While the recommendations of the advisory committees are not binding, they do play a major role in the decision process. The FDA expects to take action on the decision in late November.

FDA advisory committees recommend approval of Indivior's RBP-6000 for the treatment of opioid use disorder [press release]. Richmond, VA; Indivior PLC: October 31, 2017. Available at www.prnewswire.com/news-releases/fda-advisory-committees-recommend-approval-of-indiviors-rbp-6000-for-the-treatment-of-opioid-use-disorder-300546838.html.

Naltrexone for Opioid Dependence

In a randomized trial, injectable extended-release naltrexone was as effective as daily oral buprenorphine–naloxone in the short-term treatment of opioid dependence. Buprenorphine–naloxone is among the most commonly prescribed opioid medication treatments but requires daily or alternate-day dosing. An important potential advantage of extended-release naltrexone is once-monthly injection.

Methods: The trial recruited patients from 5 urban addiction clinics in Norway. Participants met DSM-IV criteria for opioid dependence, but were not dependent on other drugs or alcohol and did not have other serious psychiatric illness. All participants received treatment as outpatients after discharge from detoxification units, inpatient treatment, or prison. Patients were randomly assigned to receive naltrexone injections (380 mg every 4 weeks) or flexible-dose, daily oral buprenorphine–naloxone, given in a controlled environment. Treatment was provided for 12 weeks. The primary study outcomes were retention in the study, the number of weekly urine drug tests free of opioids, and the patient-reported number of days of use of heroin and other illicit opioids. Missing drug screens were considered to be positive for opioids.

Results: Of 232 patients assessed for the study, 51 refused to participate. After exclusions for other reasons, 159 (mean age, 36 years; 28% women) were randomized. Patients had an average of >6 years of heavy heroin use. Similar numbers of patients completed 12 weeks of treatment: 56 in the naltrexone group and 49 in the buprenorphine–naloxone group.

The treatments were similar with regard to the mean proportion of opioid-negative urine tests: 90% for naltrexone, 80% for buprenorphine–naloxone. Naltrexone was noninferior with regard to the mean number of days of heroin use

(mean difference, 3.2 days) and days of use of other opioids (mean difference, 2.7 days). However, patients who received naltrexone used significantly less heroin at all 3 time points and significantly less other illicit opioids at weeks 4 and 8. At all time points, patients receiving naltrexone reported less craving and thoughts about heroin. They also had a higher level of satisfaction with treatment and were more likely to recommend it to others than those in the buprenorphine–naloxone group.

Adverse events related to opioid withdrawal—e.g., nausea, chills, and diarrhea—were more common in the naltrexone group (39% vs 14%). Insufficient detoxification appeared to be a factor, and the incidence of these adverse effects declined when the detoxification strategy for the study was strengthened.

Discussion: These results apply to illicit opioids but are likely clinically relevant for people addicted to prescribed opioids as well. The relatively high level of patient satisfaction with naltrexone may be related to the feeling of being protected against relapse and the freedom from having to attend supervised medication intake. Study participants were highly motivated to achieve opioid abstinence, and it is unknown whether extended-release naltrexone would be as effective in a less motivated population.

Tanum L, et al: Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.3206. From the University of Oslo, Norway; and other institutions. **Funded by the Research Council of Norway; and other sources. The authors declared no competing interests.**

Common Drug Trade Names*: buprenorphine–naloxone—*Suboxone*; naltrexone, injectable extended release—*Vivitrol

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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.

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PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Asthma Medication Warning Removed

Based on the findings of 4 FDA-required safety trials, the boxed warning about asthma-related death has been removed from the labels of drugs that contain both an inhaled corticosteroid and long-acting beta-agonist. These reviewed trials found that compared with inhaled corticosteroids alone, when used in combination, the drugs do not significantly increase the risk of asthma-related hospitalizations, intubation, or asthma-related deaths. The studies also found that combined treatment reduced asthma exacerbations compared with inhaled corticosteriods alone.

FDA MedWatch Alerts: Long-Acting Beta agonists (LABAs) and Inhaled Corticosteroids (ICS): Drug Safety Communication - Boxed Warning About Asthma-Related Death Removed. Available at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm590001.htm.

Generic ER Methylphenidate Failure

Approved generic formulations of extended-release (ER) methylphenidate in Canada were associated with a 10-fold higher rate of reported therapeutic failure, compared with branded OROS methylphenidate (*Concerta*). Inequivalence of generic extended-release methylphenidate is also under investigation by the U.S. FDA, which has recommended withdrawal of previously approved generics. The present study examined adverse events reported to Health Canada, primarily, but also analyzed events reported to the FDA.

Methods: Adverse-event reports of therapeutic failure were identified in Health Canada's online reporting system for the 1-year period beginning 8 months following the market approval of branded OROS methylphenidate and generic extended-release methylphenidate. The 8-month lag was intended to reduce the influence of inflated early reports for a new drug. Exposure was quantified as the total number of tablets dispensed, assuming once-daily dosing. Narratives of individual cases were reviewed to characterize the features of therapeutic failure. The authors also conducted a similar analysis of U.S. FDA adverse-events reports involving the authorized generic of OROS methylphenidate (the branded product that is distributed as a generic and that is identical to Canadian branded OROS methylphenidate), comparing it to a generic that was the subject of the FDA investigation.

Results: In both the Canadian and U.S. data, reports of therapeutic failure were about 10 times more frequent with generic than OROS methylphenidate. In the Canadian data, the rates of therapeutic failure per 100,000 patient-years of exposure were 412 with generic ER methylphenidate and 38 with branded OROS methylphenidate (rate ratio,* 10.99). Corresponding numbers from the U.S. data were 69 and 7 per 100,000 patient-years of exposure, respectively (rate ratio, 9.51).

Of the 230 Canadian reports that were individually reviewed, 26% were assessed as probably related and 74% as possibly related to the generic medication, based on recognized causality criteria. No cases were determined to be unrelated. Nearly all patients reported being switched to the generic

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from branded OROS methylphenidate. The generic was reported as not being effective throughout the day in half of patients, mainly with loss of efficacy in the afternoon. Some 13.5% of reports concerned symptoms of excessive drug exposure, occurring primarily in the morning. Adverse effects on social functioning were reported in 22% of cases. Findings in the U.S. data were similar; however, 29% of reports involved loss of efficacy and 40% involved excessive exposure.

Discussion: In Canada, clinical deterioration after a medication switch is a reportable adverse effect. In both countries, approval of generics is based on the assumption that pharmacokinetic bioequivalence predicts therapeutic equivalence. Adverse-event reports in the U.S. have led the FDA to revise its bioequivalence standards and to withdraw its designation of 2 extended-release generics as bioequivalent to OROS methylphenidate. The observed adverse effects of generic ER methylphenidate are consistent with pharmacokinetic data indicating an earlier peak and decline of the generic product.

Park-Wyllie L, et al: Differences in adverse event reporting rates of therapeutic failure between two once-daily extended-release methylphenidate medications in Canada: analysis of spontaneous adverse event reporting databases. *Clinical Therapeutics* 2017;39 (October):2006–2023. **From Janssen Inc., Canada; and other institutions. Funded by Janssen Inc. Canada. All study authors disclosed financial relationships with commercial sources, including Janssen, manufacturer of Concerta and the FDA-authorized generic marketed by Actavis.**

***See Reference Guide.**

Hormonal Contraceptives and Suicide Risk

Risk of a suicide attempt was increased 2-fold in young women using hormonal contraceptives in a Danish nationwide cohort. The risk increase was particularly large in adolescents.

Methods: The study cohort consisted of women living in Denmark who turned age 15 years between 1996 and 2013 and who had no prior history of hormonal contraceptive use, suicide attempts, antidepressant use, or psychiatric diagnoses. Contraceptive use was defined as current or recent (within the past 6 months), and former use was defined as discontinuation ≥6 months in the past. Study outcomes were a first suicide attempt and completed suicide.

Results: The study population comprised nearly 500,000 women aged 15–33 years. The average follow-up was >8 years, and the mean age during follow-up was 21 years. About half of all women (54%) were current or recent users of hormonal contraceptives.

Compared with never-users, current/recent users of hormonal contraception had a nearly 2-fold elevation in risk for a first suicide attempt and a 3-fold increase in suicide. (See table). Risk was highest in adolescents and increased rapidly after the initiation of hormonal contraceptives. Risk remained at least doubled until 1 year after initiation, and subsequently subsided to levels that were still 30% higher than in non-users after >7 years of use. Former users of hormonal contraceptives were also found to have increased risk of a first suicide attempt or of completed suicide. Risks were elevated for all types of hormonal contraceptives. Patch, vaginal ring, and progestin-only contraceptives were associated with higher risk than oral combined products.

Adjusted risk of a first suicide attempt and completed suicide†

Outcome	Hazard Ratio*
Suicide attempt	
All current/recent	1.97
15–19 years	2.06
20–24 years	1.61
25–33 years	1.64
Former users	3.40
Suicide	
Current/recent users	3.08
Former users	4.82

†Adjusted for age, calendar year, education, polycystic ovary syndrome, and endometriosis

Discussion: Most previous studies have failed to show an association between hormonal contraceptive use and suicide risk, perhaps because they included women several years after they started using the agents, resulting in selection bias favoring women who can tolerate hormonal contraception. In the present study, the decrease in suicide risk after 1 year of contraceptive use was probably the result of discontinuation by women sensitive to the adverse mood effects of these drugs.

Skovlund C, et al: Association of hormonal contraception with suicide attempts and suicides. *American Journal of Psychiatry* 2017; doi 10.1176/appi.ajp.2017.17060616. From the University of Copenhagen, Denmark; and Peking University, China. **Funded by the Lundbeck Foundation; and Rigshospitalet, University of Copenhagen. Three of 5 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

Potency-Based Dosing of PPIs

According to an analysis of clinical trials, available proton pump inhibitors are functionally equivalent and dosing can be guided by relative potency. Reasonable options for gastric acid suppression may include low-cost generics, b.i.d. dosing, on-demand therapy, and use of the least potent effective regimen to avoid adverse effects.

Background: PPI potency can be measured by pH4time, the amount of time during which the intragastric pH is 4 over a 24-hour period. The measure has been shown to be a valid surrogate marker for symptom relief and clinical efficacy.[1]

Methods: Data was analyzed from 56 randomized clinical trials of oral PPIs in which intragastric pH was measured during steady-state dosing, after ≥5 days. Trials were limited to western countries where the rapid metabolizer phenotype is prevalent. Relative potency of PPIs was based on a previous study[2] that modeled their effects on intragastric pH and was expressed as omeprazole equivalents. (See table.) The present analysis estimated the relationship of omeprazole equivalents (OE) to pH4time for esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole and for different dosing regimens.

Potency of PPIs based on omeprazole equivalents

Drug at lowest available dosage	Omeprazole equivalent
Pantoprazole 20 mg	4.5 mg
Lansoprazole 15 mg	13.5 mg
Omeprazole 20 mg	20 mg
Esomeprazole 20 mg	32 mg
Rabeprazole 20 mg	36 mg

Results: For once-daily administration, even the lowest PPI dose, 2.5 mg OE, had a marked effect on pH4 time. The relationship was linear for OEs ranging from 9 mg, with a pH4time of about 40%, to 64 mg, with a pH4time of about 65%. The relationship tapered with doses >70 mg OE, suggesting the amount of PPI in the bloodstream limits the effective dose. For b.i.d. dosing, the lowest dose, 9 mg OE, resulted in a mean pH4time comparable to the most potent dose tested in once-daily dosing. The highest b.i.d. OE doses resulted in a peak ph4time of about 85%. Thrice-daily dosing did not provide a further increase in pH4time. Costs per OE for the 5 PPIs were also compared. Each drug had a generic formulation that cost less than 10 cents per OE, markedly lower than the proprietary formulations.

Discussion: This research confirms recent consensus-based recommendations that PPIs given in equivalent dosages do not differ much in efficacy. Increasing the dosing frequency to b.i.d. may be a more effective strategy than escalating once-daily dosing. In patients requiring long-term therapy for erosive esophagitis, dosing may be reduced to once-daily after 8 weeks of successful treatment. Pantoprazole may be best avoided unless low-potency therapy is important—for example, in reducing risk of *C. difficile.*

[1]Graham D, Tansel A: Interchangeable use of proton pump inhibitors based on relative potency. *Clinical Gastroenterology and Hepatology* 2017; doi 10.1016/j.cgh.2017.09.033. From Michael E. DeBakey VA Medical Center; and Baylor College of Medicine, Houston, TX. **Funded by the Department of Veterans Affairs; and the US Public Health Service. One study author disclosed a financial relationship with a commercial source; the remaining author declared no competing interests.**

[2]Kirchheiner J, et al: Relative potency of proton-pump inhibitors-comparison of effects on intragastric pH. *European Journal of Clinical Pharmacology* 2009;65:19–31.

Common Drug Trade Names*: esomeprazole—*Nexium*; lansoprazole—*Prevacid*; omeprazole—*Zegerid*; pantoprazole—*Protonix*; rabeprazole—*Aciphex

Prenatal Acetaminophen and ADHD Risk

According to the results of a population-based study, long-term maternal use of acetaminophen during pregnancy is associated with a >2-fold increase in risk of ADHD in offspring. The increased risk appears to be independent of maternal indications for acetaminophen use and familial ADHD risk.

Methods: The study, conducted by the Norwegian Institute of Public Health, began with an invitation to all pregnant women in the country to complete a mailed questionnaire at about 18 weeks of gestation. About 40% of invited women agreed to participate. The cohort consisted of nearly 115,000 children born in 1999 and 2009, about 95,000 mothers, and about 75,000 fathers. Both mothers and fathers completed questionnaires about their acetaminophen use during the 6 months before the pregnancy, indications for use, ADHD symptoms, and other factors. Mothers completed additional questionnaires at the 30th gestational

week and again 6, 18, and 36 months after delivery. The study outcome was an ICD-10 diagnosis of hyperkinetic disorder, which requires the presence of both inattentive and hyperactive symptoms, in the offspring between 2008 and 2014.

Results: Nearly half of the women (47%) reported acetaminophen use during pregnancy, and about 2200 children received a diagnosis of hyperkinetic disorder. Preconception acetaminophen use by fathers was associated with a small increase in ADHD risk, but preconception maternal use was not. However, compared with children with no prenatal acetaminophen exposure, those whose mothers reported acetaminophen use during pregnancy had increased risk of developing ADHD (based on unadjusted hazard ratios*) of 17–46%, depending on the number of trimesters exposed. These risks were not diminished after adjusting for pre-pregnancy use by either parent and were reduced slightly after adjustment for parental ADHD symptoms and other potential confounders including indication for use. Risk increased with increasing exposure. Hazard ratios for exposure during 1, 2, or all 3 trimesters ranged from 1.07 to 1.27, and the greatest increase was observed with ≥29 days of prenatal use (hazard ratio, 2.20).

Discussion: A possible explanation for the association between ADHD and paternal acetaminophen use is endocrine disruption in the testis, leading to germ line epigenetic effects. ADHD is highly familial; however, the present observations suggest that the association of acetaminophen with ADHD in the offspring occurs regardless of parental ADHD symptoms. In addition, fever and infection, common indications for acetaminophen, may adversely affect neurodevelopment, but these results suggest the indications for maternal use are not a major factor in the association. Finally, the lack of an association with pre-pregnancy maternal use indicates that there is a specific gestational effect, which is consistent with but not proof of causality.

Ystrom E, et al: Prenatal exposure to acetaminophen and risk of ADHD. *Pediatrics* 2017; doi 10.1542/peds.2016–3840. From the Norwegian Institute of Public Health, Oslo; and other institutions. **Funded by the European Research Council; the NIH; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

Semaglutide for Diabetes

The FDA has approved the long-acting glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide (*Ozempic*) as an adjunct to diet and exercise for the treatment of type 2 diabetes in adults. The agent will be available for once weekly administration via a dedicated prefilled pen device. Semaglutide is the third approved weekly-dosed GLP-1 receptor agonist, but clinical trial data suggest it may have advantages over some of its competitors. Studies found semaglutide reduced hemoglobin A1c by nearly 2%, significantly more than did active comparators, including extended-release exenatide (*Bydureon*), and was associated with a 10–14 lb weight loss. The most common adverse effect, mild-to-moderate nausea, diminished over time.

Tucker M: FDA Approves Semaglutide for Type 2 Diabetes Medscape Medical News 2017; available at www.medscape.com.

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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.

Rate Ratio: A comparison of the rates of a disease/event in 2 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.