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PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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PPI Therapy and Gastric Cancer

Long-term use of proton pump inhibitors was associated with a >2-fold increase in risk of gastric cancer in patients with prior *H. pylori* eradication. The risk was increased with higher frequency and longer duration of PPI use.

Background: *H. pylori* eradication reduces risk of gastric cancer by at least one-third, but there are few data on other modifiable risk factors. PPIs are associated with an increase in risk, but it has not been known whether this risk could be eliminated by clearance of *H. pylori*.

Methods: Data were analyzed for all patients in Hong Kong who received clarithromycin-based triple therapy, the first-line treatment for *H. pylori* infection in 2003–2012, the study period. Patients who received a diagnosis of gastric cancer within 1 year after triple therapy were excluded from the analysis, as were those with failed *H. pylori* eradication. The primary outcome was the development of gastric adenocarcinoma, and the primary exposure of interest was prescription of PPIs after receiving successful *H. pylori* eradication therapy. The study included 2 comparison groups of patients with successful triple therapy: those who received no PPIs and those who received histamine-2 receptor antagonists (H2RAs).

Results: The study cohort comprised >63,000 patients who received successful *H. pylori* eradication therapy. The mean age was 55 years, 47% of study patients were men, and the median follow-up time was 7.6 years. Nearly 3300 patients (5% of the cohort) were PPI users, with a median duration of use of almost 3 years; nearly 22,000 patients (35%) were H2RA users. Gastric cancer developed in 153 patients (0.24%) during follow-up. Patients who used a PPI ≥1 time per week had a >2-fold higher incidence of gastric cancer than those with less frequent use (hazard ratio,* 2.44 after propensity score adjustment;* p=0.002). The propensity score-adjusted absolute risk increase with PPI use was 4.29 excess gastric cancer cases per 10,000 person-years. A gradient in risk was observed with frequency of PPI use (less than once a week, weekly, and daily) and with duration of use (≥1 year, ≥2 years, or ≥3 years). Risk of gastric cancer was not associated with use of H2RAs.

Discussion: PPIs may increase gastric cancer risk by acid suppression, which could worsen atrophic gastritis, and by stimulating gastrin, a growth factor. Long-term PPIs should be prescribed cautiously after successful clearance of *H. pylori*.

Cheung K, et al: Long-term proton pump inhibitors and risk of gastric cancer development after treatment for *Helicobacter pylori*: a population-based study. *Gut* 2017; doi 10.1136/gutjnl-2017–314605. From the University of Hong Kong; and other institutions. **Source of funding not stated. One study author disclosed financial relationships with commercial sources; the remaining 5 authors declared no competing interests.**

***See Reference Guide.**

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Prenatal Safety of Methylphenidate

According to the results of a study conducted by the International Pregnancy Safety Study Consortium, methylphenidate exposure during pregnancy is associated with a small increase in risk of congenital cardiac malformations, while amphetamine exposure is not.[1]

Methods: The study was conducted in 2 populations in tandem. The primary analysis included pregnant women enrolled in Medicaid during 2000–2013. Results of this analysis were validated in a cohort of all women enrolled in the national health registries of 5 Scandinavian countries during a similar time span. A pregnancy was considered exposed if a woman filled a prescription for a stimulant—methylphenidate or amphetamine/dextroamphetamine—during the first 90 days of pregnancy, the period of embryogenesis. Pregnancy was considered unexposed if no ADHD medication prescription was filled in the 3 months before conception to the end of the first trimester. Pregnancies were excluded from the analysis if there was a fetal chromosomal abnormality or exposure to a known teratogen. Outcomes were analyzed separately for all malformations and for cardiovascular malformations. The analyses were adjusted for a broad range of known or possible risk factors, and sensitivity analyses were carried out using a propensity score* based on 200 potential confounding factors. The primary U.S. methylphenidate analysis was repeated in the Nordic cohort, but the amphetamine analysis was not because there were too few exposed pregnancies.

Results: Of >1.8 million U.S. pregnancies ending in a live birth, only about 2000 (0.11%) were exposed to methylphenidate and about 5500 (0.31%) to amphetamine. In the U.S. cohort, the fully adjusted model found no association for either category of malformation with amphetamine exposure. In contrast, for methylphenidate-exposed pregnancies, the fully adjusted relative risks* were 1.11 for any malformation and 1.28 for cardiac malformations. Propensity score adjustment had a negligible effect on these results. When specific cardiac malformations were examined, methylphenidate was associated with increased occurrence of conotruncal defects (relative risk, 3.44), but this finding was based on a small number of cases. The observations were generally confirmed in the Nordic cohort. In pooled data from the 2 cohorts, the relative risks for any malformation and a cardiac malformation with methylphenidate were 1.07 and 1.28, respectively.

Discussion: Methylphenidate was associated with a 28% increased risk of cardiac malformations; this increase corresponds to 3 additional infants born with congenital cardiac malformations for every 1000 women who receive methylphenidate during the first trimester of pregnancy. ADHD medication use is increasing in women of childbearing age, in whom a substantial portion of pregnancies are unplanned, as well as in pregnant women.[2] Although the absolute risk with methylphenidate is small, it should be considered for women who are or could become pregnant.

[1]Huybrechts K, et al: Association between methylphenidate and amphetamine use in pregnancy and risk of congenital malformations: a cohort study from the International Pregnancy Safety Study Consortium. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.3644. From Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and other institutions. **Funded by the NIMH; and other sources. The authors declared no competing interests.**

[2]Cooper W: Shedding light on the risks of methylphenidate and amphetamine in pregnancy [editorial]. *JAMA Psychiatry* 2017; doi 10.1001/jamapsychiatry.2017.3882. From Vanderbilt University School of Medicine, Nashville, TN. T**he author declared no competing interests.**

Common Drug Trade Names: amphetamine/dextroamphetamine—*Adderall, Dexedrine*; methylphenidate—*Concerta, Ritalin*

***See Reference Guide.**

Semaglutide Approval

The once-weekly injectable glucagon-like peptide (GLP-1) receptor agonist semaglutide (*Ozempic*) has received FDA approval as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The drug will be available in pre-filled pens at dosages of 0.5 mg and 1 mg.

In clinical trials, semaglutide produced clinically meaningful and statistically significant reductions in HbA_{1c} compared with placebo, sitagliptin, and exenatide extended-release, as well as reductions in body weight. Common adverse effects of semaglutide include nausea, vomiting, diarrhea, abdominal pain, and constipation. Serious adverse effects could include medullary thyroid carcinoma (MTC), pancreatitis, hypoglycemia,

and kidney failure. The agent should not be used in patients who have a personal or family history of MTC or those who have multiple endocrine neoplasia syndrome type 2. Semaglutide is not recommended as first-line treatment for diabetes—it is not a substitute for insulin—and it is not known whether it can be used by patients with a history of pancreatitis.

Novo Nordisk receives FDA approval of Ozempic® (semaglutide) injection for the treatment of adults with type 2 diabetes [press release]. Bagsvaerd, Denmark; Novo Nordisk: December 5, 2017. Available at http://press.novonordisk-us.com.

Common Drug Trade Names*: exenatide, extended-release—*Bydureon*; semaglutide—*Ozempic*; sitagliptin—*Januvia

Type 1 Diabetes Standards of Care

The 2017 annual update of the American Diabetes Association's Standards of Medical Care for type 1 diabetes includes recommendations about monitoring glycemia, HbA_{1c} targets, non-insulin and investigational medications, and treatment of hypoglycemia.

Monitoring Recommendations. Patients receiving intensive insulin regimens—i.e., multiple daily injections or continuous subcutaneous insulin infusion—should self-monitor blood glucose before meals and snacks; at bedtime; occasionally after meals when they suspect low blood glucose; after treating low glucose until they are normoglycemic; and before exercise and critical tasks such as driving. This could be as often as ≥6–10 times daily.

Continuous glucose monitoring, combined with intensive insulin regimens, can further lower HbA_{1c} levels in selected adults (aged ≥25 years) and may particularly benefit those with hypoglycemia unawareness or frequent hypoglycemic episodes. Because of variable adherence, continuous glucose monitoring requires an assessment of individual readiness and ongoing education and support.

HbA_{1c} should be tested semi-annually in patients who are meeting treatment goals and have stable glycemic control and quarterly in those whose regimens have changed and others. Point-of-care A_{1c} testing allows more timely treatment changes.

Treatment. Avoiding hypoglycemia should always take precedence over achieving A_{1c} targets. A reasonable HbA_{1c} target for most is <7%, and a more stringent goal can be considered in selected patients, such as those with recent-onset diabetes or no cardiovascular disease, as long as this can be achieved without hypoglycemia or other adverse effects. Less stringent goals, such as <8%, may be considered in patients with limited life expectancy, extensive complications/comorbidity, or a history of severe hypoglycemia.

Most patients with type 1 diabetes should receive both prandial and basal insulin; rapid-acting insulin analogues are preferred to reduce hypoglycemia risk. However, patient education about matching prandial insulin dosing to carbohydrate intake, premeal glucose levels, and anticipated exercise should be considered.

Rapid-acting inhaled insulin, taken before meals, was shown to be noninferior to aspart insulin with respect to HbA_{1c} lowering, with less risk of hypoglycemia; but the availability of inhaled insulin cartridges in a limited number of doses limits patients' ability to fine-tune dosing.

Many other pharmacologic agents are being used or tested in type 1 diabetes: pramlintide, an injectable amylin analogue that delays gastric emptying and enhances satiety; metformin, which reduced insulin requirements and led to modest weight loss and lipid lowering in a clinical trial; liraglutide, which improved HbA_{1c} and led to weight loss, but at a cost of increased hypoglycemia risk; and sodium-glucose cotransporter-2 inhibitors that block glucose reabsorption in the kidney.

Glucagon should be prescribed for all patients at risk of clinically significant hypoglycemia and should be available to persons in close contact with the patient. Family members, school personnel, correctional institution staff, and/or coworkers should be instructed how to use glucagon kits.

Chamberlain J, et al: Treatment of type 1 diabetes: synopsis of the 2017 American Diabetes Association standards of medical care in diabetes. *Annals of Internal Medicine* 2017; doi 10.7326/M17–1259. From St. Mark's Hospital, Salt Lake City, UT; and other institutions. **Funded by the American Diabetes Association. Five of 7 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names*: glucagon—*GlucaGen*; liraglutide—*Victoza, Saxenda*; metformin—*Glucophage*; pramlintide—*Symlin

Genotype-Guided Warfarin Dosing

In a randomized trial of patients undergoing elective hip or knee arthroplasty, genotype-guided warfarin dosing was associated with fewer adverse outcomes than clinically guided warfarin dosing.[1] However, the risk reduction was driven largely by a lower incidence of international normalized ratio (INR) values ≥4, while rates of symptomatic adverse events did not differ significantly between treatments.

Methods: The Genetics Informatics Trial of Warfarin to Prevent Deep Vein Thrombosis trial was conducted at 6 U.S. medical centers in 1650 patients, aged ≥65 years, undergoing elective hip or knee arthroplasty. All patients were genotyped for polymorphisms in genes that influence warfarin sensitivity (VKORC1), S-warfarin metabolism (CYP2C9), or vitamin K metabolism (CYP4F2). Patients were then randomly assigned to genotype- or clinically guided warfarin dosing during the first 11 days of therapy. Dosing was guided by a web-based application that incor-porated clinical data for all patients and, in addition, data on gene polymorphisms for the genotype-guided group. The primary study outcome was a composite of major bleeding within 30 days, INR ≥4 within 30 days, death within 30 days, or venous thromboembolism within 60 days.

Results: In the genotype-guided group, 11% of patients experienced ≥1 composite endpoint, compared with 15% of the clinically guided group (p=0.02). None of the other individual outcomes within the composite differed significantly in incidence between the groups. No study patient died. For INR values ≥4, the difference in risk between the groups significantly favored genotype-guided dosing (p=0.04). Genotype dosing also significantly improved patients' percentage of time with INR in the therapeutic range: 55% versus 51% for clinically guided dosing (p=0.004). Genotyping especially benefited a pre-specified high-risk group.

Discussion: Previous studies of genotype-guided warfarin dosing, conducted mainly in patients with atrial fibrillation, have had mixed results. The present study was larger, used genotype-guided dosing for a longer period, and was based on more genes, allowing analysis of clinical outcomes rather than the surrogate outcome of percentage of time in the therapeutic range. However, the vast majority of patients (91%) were white, which limits the generalizability of the results because the gene variants are relatively uncommon in persons of African ancestry. The study results have no clear clinical implications, and although genotype-guided dosing might have some clinical utility, it is likely simpler and less expensive to implement wider use of clinical dosing algorithms.[2]

[1]Gage B, et al: Effect of genotype-guided warfarin dosing on clinical events and anticoagulation control among patients undergoing hip or knee arthroplasty: the GIFT randomized clinical trial. *JAMA* 2017;318 (September 16):1115–1124. From the University in St. Louis, MO; and other institutions. **Funded by National Heart, Lung, and Blood Institute; and other sources. Two of 26 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Emery J: Pharmacogenomic testing and warfarin: what evidence has GIFT Provided? [editorial]. *JAMA* 2017:318 (September 16):1110–1112. From the University of Melbourne, Australia. **The author declared no relevant financial relationships with commercial sources.**

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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.

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.

PRIMARY CARE DRUG ALERTS

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Plecanatide: New Indication

The FDA has approved plecanatide (*Trulance*) for treatment of irritable bowel syndrome with constipation (IBS-C) in adults. The agent was previously indicated only for chronic idiopathic constipation.

In clinical trials, patients who took plecanatide experienced significant reductions in abdominal pain, as well as improvements in stool frequency, stool consistency, and straining with bowel movements. In these trials, rates of response (both a ≥30% reduction in worst abdominal pain and an increase of ≥1 complete spontaneous bowel movements from baseline for ≥6 weeks) with plecanatide ranged from 22% to 30%. Diarrhea was the most common adverse effect of plecanatide treatment, affecting about 4% of treated patients, and was severe in 1%. Plecanatide is contraindicated in patients aged <6 years and should be avoided in patients aged <18 years.

Plecanatide (*Trulance*) Gets FDA Nod for IBS With Constipation in Adults. Medscape: Jan 26, 2018. Available at https://www.medscape.com/viewarticle/891839.

Erenumab for Episodic Migraine

In a phase III placebo-controlled trial, erenumab reduced migraine frequency in patients with episodic migraine.

Background: Episodic migraine, defined as <15 migraine days per month, affects about 90% of migraine sufferers. Currently used preventive medications were developed for other indications and are not targeted to the specific pathways involved in migraine. Erenumab is a monoclonal antibody antagonist to the calcitonin gene-related peptide receptor, a pathway involved in nociceptive mechanisms believed to be important in migraine.

Methods: Study participants (n=955) were adults with a ≥12-month history of episodic migraine, with 4–14 migraine days per month. Patients concomitantly using stable doses of most other migraine-prevention medication were included. However, those who had received a botulinum toxin injection in the previous 4 months or who had received ergotamine derivatives, steroids, or triptans in the previous 2 months were excluded. After a 4-week observation phase, patients were randomly assigned to receive monthly subcutaneous injections of 70 mg or 140 mg erenumab or placebo in a double-blind fashion for 6 months. Headaches were self-reported in an electronic diary, and the primary outcome was change in the mean number of migraine days per month from baseline to the last 3 months of treatment. Secondary endpoints included a ≥50% reduction in migraine frequency and reduction in the use of acute migraine medications.

Results: A total of 858 patients (90%) completed the 6 months of double-blind treatment. At baseline, patients had an average of 8.3 migraine days per month and about 3% were using other migraine-preventive medications concomitantly. Nearly 40% had discontinued previous migraine preventive medication because of intolerance or lack of efficacy.

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Both doses of erenumab were associated with significantly larger mean reductions in migraine days than placebo: 3.2 and 3.7 days, respectively, compared with 1.8 days with placebo ($p<0.001$ for both comparisons). About half of patients in the erenumab groups had a ≥50% reduction in monthly migraine days, compared with 27% of the placebo group ($p<0.001$). Use of acute migraine medications was also reduced to a greater degree. Patients in the erenumab groups also reported reduced interference of migraine with their daily lives, relative to the placebo group.

The frequency of most adverse events did not differ between erenumab and placebo, with the exception of injection-site pain, which affected 11 erenumab-treated patients and 1 placebo-treated patient. Serious medication-related adverse effects were uncommon. There were no between-group differences in hepatic-function, creatinine levels, total neutrophil counts, vital signs, or electrocardiographic findings.

Discussion: These results, while preliminary, support the short-term preventive effects of erenumab on episodic migraine. Following the acute double-blind phase, patients in the study were eligible to participate in an open-label extension study; these results will be reported separately.

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

Goadsby P, et al: A controlled trial of erenumab for episodic migraine. *NEJM* 2017;377 (November 30):2123–2132. From King's College Hospital, London, U.K.; and other institutions. **Funded by Amgen and Novartis. Nine of 10 study authors disclosed financial relationships with commercial sources including Amgen and/or Novartis; the remaining author declared no competing interests.**

***See Reference Guide.**

Loperamide Packaging Limits

The over-the-counter antidiarrheal opioid receptor agonist loperamide (*Imodium*) is being used increasingly to self-medicate for opioid withdrawal and, less frequently, to achieve opioid psychoactive effects.[1] Using higher than recommended doses of loperamide can result in serious cardiac adverse events, including QT interval prolongation, Torsades de pointes or other ventricular arrhythmias, syncope, and cardiac arrest. Despite warnings issued in 2016, the FDA continues to receive reports of serious cardiac effects and deaths with much higher than the recommended doses of loperamide, primarily in patients misusing the product. In an effort to support safe use of loperamide, the FDA has requested the manufacturers use blister packs or other single-dose packaging and to limit the number of doses in each package.[2]

[1]Stanciu C, Gnanasegaram S: Loperamide, the "poor man's methadone": brief review. *Journal of Psychoactive Drugs* 2016; doi 10.1080/02791072.2016.1260188. See *Primary Care Drug Alerts* 2017;38 (January):3–4.

[2] FDA Drug Safety Communication: Imodium (loperamide) for Over-the-Counter Use: FDA Limits Packaging To Encourage Safe Use. Available at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm594403.htm.

Statins and Diabetes

According to results of a secondary analysis of a clinical trial of diabetes-prevention interventions, statin therapy is associated with a 30% increase in type 2 diabetes incidence in high-risk individuals. The evidence suggests glucose status should be monitored and healthy behaviors should be encouraged in patients at high risk for diabetes who are taking statins.

Methods: Data were analyzed from the Diabetes Prevention Program (DPP) and the subsequent DPP Outcomes Study (DPPOS). Participants were >3200 overweight adults with impaired glucose tolerance who did not meet criteria for diabetes based on fasting plasma glucose levels. Patients were randomly assigned to intensive lifestyle intervention, metformin (*Glucophage*), or placebo for about 3 years, followed by additional lifestyle programs or open-label metformin for an additional 7 years. Lipid-lowering medications were prescribed by each patient's own physician, outside of the study protocol, and use was ascertained every 6 months based on self-report. The primary study outcome was diabetes onset, determined by an annual oral glucose tolerance test or a semiannual fasting plasma glucose tolerance test with confirmation by a second test.

Results: Statin use in study participants increased from about 4% at baseline to 35% after 10 years, with similar proportions in the 3 treatment groups. Patients taking statins were older, more likely to be male, and had modestly higher baseline levels of fasting plasma glucose and HbA1c and a lower insulinogenic index. The hazard ratio* for diabetes onset with statin use in the pooled cohort was 1.36. Risk was attenuated only slightly to 1.27 with adjustment for multiple confounding factors including baseline diabetes risk and indication for statin use. Statin dosage

was not measured, but diabetes risk did not differ in patients taking high- versus low-potency statins; nor was risk associated with change in LDL-cholesterol levels.

Discussion: This analysis suggests that the indications for statin therapy or a higher level of baseline diabetes risk factors are not a major influence on statin-associated diabetes risk. The mechanisms linking statins with diabetes onset are not clear.

Crandall J, et al: Statin use and risk of developing diabetes: results from the Diabetes Prevention Program. *BMJ Open Diabetes Research & Care* 2017; doi 10.1136/bmjdrc-2017–000438. From Albert Einstein College of Medicine, Bronx, NY; and other institutions. **Funded by the National Institute of Diabetes and Digestive and Kidney Diseases; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

Statins and Erectile Dysfunction

Results of a meta-analysis that included nearly 70,000 men with cardiovascular disease or risk factors indicate that statin therapy is not associated with increased onset of erectile dysfunction.

Background: A potential link between statin use and erectile dysfunction was suspected because statins are known to reduce testosterone levels. The association was supported by case reports, post-marketing studies, and case-control studies but was not validated in 2 recent propensity score-matched cohort studies.

Methods: A literature search identified randomized controlled trials and observational studies of statins that reported new onset of erectile dysfunction in men with established cardiovascular disease or cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, and elevated C-reactive protein levels. A total of 6 studies—3 randomized trials and 3 observational studies, with a total of nearly 70,000 patients—were included in the meta-analysis. The average follow-up was 3.5 years, and about one third of patients were statin users. All but 1 of the studies had a low risk of methodologic bias, and there was no evidence of publication bias.

Results: Compared with non-use, statin use was not associated with new-onset erectile dysfunction, which affected 5% and 4% of the groups, respectively (relative risk,* 0.96). No effects were observed in subgroup analyses of randomized trials versus observational studies, large versus small studies, or the 4 studies in which erectile dysfunction was the primary outcome. The analysis found that the effect of statins did not differ according to patient age or presence of diabetes. Analyses based on the type of statin (i.e., hydrophilic or lipophilic) were not conducted due to limited data.

Discussion: Although statins lower testosterone levels, they do not appear to induce erectile dysfunction and may actually have effects that protect against it. The drugs may counteract LDL-cholesterol-related oxidative injury and vascular inflammation, improving endothelial function in the penile vascular tissue and improving penile blood flow.

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

Elgendy A, et al: Statin use in men and new onset of erectile dysfunction: a systematic review and meta-analysis. *American Journal of Medicine* 2017; doi 10.1016/j.amjmed.2017.10.043. From the University of Florida, Gainesville; and other institutions. **This study was conducted without funding. The authors declared no competing interests.**

***See Reference Guide.**

Blood Test for Concussion

The FDA has authorized marketing of the Brain Trauma Indicator, the first blood test to evaluate mild traumatic brain injury or concussion in adults. Following head injury, patients are typically evaluated using a neurological scale and CT scan. However, most of these patients are not found to have intracranial lesions. The Brain Trauma Indicator measures proteins released from the brain into blood after a head injury. Results can be available within 3–4 hours. Levels of these proteins can help predict which patients may have intracranial lesions and require CT scans, thus potentially preventing unnecessary neuroimaging and associated radiation exposure. In clinical trials, The Brain Trauma Indicator predicted the presence or absence of intracranial lesions following head injury in 97.5% and 99.6% percent of patients, respectively.

FDA News Release: FDA authorizes marketing of first blood test to aid in the evaluation of concussion in adults. New quick testing option to help reduce need for CT scans, radiation exposure for patients. Available at www.fda.gov/newsevents/newsroom/pressannouncements/ucm596531.htm.

Mixed-Release Amphetamine

The newly-approved triple-bead mixed amphetamine salts SHP465 (*Mydayis*) was effective and well tolerated in a clinical trial in children and adolescents. The new formulation contains 3 types

of drug-releasing beads, providing immediate and delayed release at pH values of 5.5 and 7.

Methods: Study participants, recruited from 36 U.S. sites, were aged 6–17 years and had a primary diagnosis of ADHD, with a baseline ADHD Rating Scale-IV (ADHD-RS-IV) score of ≥28. After a washout of previous medications, patients were randomly assigned to receive double-blind treatment with 12.5 mg SHP465 or placebo, taken once daily at 7AM. At the end of the first study week, the dose was increased to 25 mg based on response and tolerability. The primary efficacy outcome, assessed after 4 weeks, was change from baseline in the ADHD-RS-IV total score. The 4-week score on the Clinical Global Impression–Improvement* scale was the key secondary endpoint.

Results: Of 264 enrolled patients, about 40% were aged ≤12 years, and 234 completed the study. The most frequent reasons for withdrawal were adverse events (11 patients receiving active treatment and 3 receiving placebo) and lack of efficacy (1 with SHP465, 4 with placebo). The optimal daily dose of SHP465 was 25 mg in 72% of patients and 12.5 mg in 24%.

At baseline, the mean total ADHD-RS-IV scores were 39 and 40 in the SHP465 and placebo groups, respectively. At the 4-week assessment, scores were reduced by 21 points with SHP465, compared with 11 points with placebo (effect size,* 0.80; p<0.001). Scores on both the hyperactivity/impulsivity and inattentiveness subscales decreased by a significantly larger extent with SHP465 than placebo (p<0.001 for both). The mean CGI-I score at week 4 was 3 for placebo and 2.2 for SHP465 (effect size, 0.65; p<0.001).

The most frequently reported adverse events with SHP465 were decreased appetite and insomnia. Of the adverse events that led to study discontinuation, 9 were related to the study drug. All were of mild or moderate severity and resolved with treatment discontinuation.

Discussion: Previously published studies have shown that SHP465 is safe and efficacious in adults. This is the first published phase III study in children and adolescents; the agent is approved for use in patients aged ≥13 years. Although efficacy cannot be compared directly, the effects of SHP465 appear similar to other long-acting stimulants. The adverse-effect profile is also consistent with other long-acting amphetamines.

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

Brams M, et al: SHP465 mixed amphetamine salts in the treatment of attention-deficit/hyperactivity disorder in children and adolescents: results of a randomized, double-blind placebo-controlled study. *Journal of Child and Adolescent Psychopharmacology* 2018;28 (January):19–28. From Baylor College of Medicine, Houston, TX; and other institutions including Shire, Lexington, MA. **Funded by Shire Development, LLC. All study authors disclosed financial relationships with commercial sources including Shire.**

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Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

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

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

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

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For Physicians and Nurses

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Clarithromycin Safety in Heart Disease

A large-scale clinical trial found an unexpected increase in heart problems and deaths among patients with coronary heart disease who had received a 2-week course of clarithromycin (*Biaxin*). The increase in risk was not apparent until patients had been followed for ≥1 year. Although there is no clear explanation for the increase, the FDA is urging caution and suggests considering an alternate agent when prescribing antibiotics for patients with heart disease. Warnings about the increased risk have been added to the labeling for clarithromycin, and the FDA continues to monitor safety reports for the drug.

Clarithromycin (Biaxin): Drug Safety Communication–Potential increased risk of heart problems or death in patients with heart disease. Available at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm597862.htm.

Contraceptives and Breast Cancer Risk

Use of modern formulations of hormonal contraceptives was associated with a 20% increase in risk of breast cancer in a nationwide cohort of Danish women.[1] The absolute excess in risk is small and counterbalanced by the effect of hormonal contraceptives in reducing risk of other types of cancer.[2]

Methods: This analysis, part of the ongoing Danish Sex Hormone Register study, included all women who were aged 15–49 years on January 1, 1995, as well as those who turned age 15 years before the end of 2012. Women with a cancer diagnosis were excluded. Information on the use of hormonal contraception, breast cancer onset, and confounding factors was obtained from linked registries.

Results: The cohort consisted of about 1.8 million women, with a mean follow-up of nearly 11 years. During follow-up, there were 9101 incident cases of invasive breast cancer. Women who were current or recent users of hormonal contraceptives (within the past 6 months) had a 20% increase in breast cancer risk (relative risk,* 1.20). Risk was increased to a similar degree in women who used combined or progestin-only contraceptives and, within each of these categories, in users of oral and non-oral formulations. There were no robust associations of increased risk with any individual formulation, relative to the overall effect of all contraceptives. Risk was associated with duration of use and was statistically significant for 5–10 years of use (relative risk, 1.33) and for >10 years of use (relative risk, 1.52). The absolute difference in cancer incidence between women who had never used hormonal contraceptives and current or recent users was small at 13 cases per 100,000 person-years. Approximately 1 extra breast cancer case was diagnosed for every 7700 women using hormonal contraception for 1 year.

Discussion: The 20% excess breast cancer risk demonstrated in this study is similar to rates reported in studies from the 1980s, with older, high-dose formulations. The present observations should be viewed in the context of the low incidence of breast cancer in young women. Most of the cases that occurred in this cohort were in

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women who used hormonal contraception in their 40s, and the excess risk in women younger than 35 years was only 2 per 100,000.

[1]Morch L, et al: Contemporary hormonal contraception and the risk of breast cancer. *NEJM* 2017;377 (December 7):2228–2239. From the University of Copenhagen, Denmark; and the University of Aberdeen, U.K. **Funded by the Novo Nordisk Foundation. Two of 6 study authors disclosed financial relationships with commercial sources including Novo Nordisk; the remaining authors declared no competing interests.**

[2]Hunter D: Oral contraceptives and the small increased risk of breast cancer (editorial). NEJM 2017;377 (December 7):2276–2277. From the University of Oxford, U.K. **The author declared no competing interests.**

***See Reference Guide.**

Teriparatide vs Risedronate for Osteoporosis

In a randomized trial, postmenopausal women with severe osteoporosis who received the bone-forming agent teriparatide experienced fewer osteoporotic fractures over 2 years than those who received the antiresorptive agent risedronate.

Background: Approved treatments for post-menopausal osteoporosis include antiresorptive and bone-forming drugs. Although several studies have compared the effects of the 2 drug classes on surrogate markers of bone quality and strength, there have been no previous, adequately powered head-to-head studies that compared the effects of antiresorptives and bone-forming drugs using fractures as the primary outcome.

Methods: Study participants were postmenopausal women, aged >45 years, with a bone mineral density T score of -1.50 standard deviations or less at the femoral neck, total hip, or lumbar spine, and radiographic evidence of at least 1 severe or 2 moderate vertebral fragility fractures. For study entry, patients were required to have baseline serum calcium, parathyroid hormone, and free thyroxine concentrations in the normal range, as well as 25-hydroxy-vitamin D concentrations >23 nmol/L. Previous treatment with most osteoporosis medications was permitted if these agents were discontinued at study entry. Study subjects were randomly assigned to receive either 20 µg/day injectable subcutaneous teriparatide plus an oral weekly placebo, or 35 mg/week oral risedronate with an injectable daily placebo. Study participants also received calcium and vitamin D supplements. The primary efficacy outcome was the percentage of patients with ≥1 new vertebral fracture assessed with spinal radiographs at 12 and 24 months. Clinical vertebral fractures were defined as an episode of suggestive signs or symptoms, such as acute onset of back pain, confirmed by radiography.

Results: Of 1360 women enrolled who received randomized treatment, 75% completed the trial. Patients had a mean age of 72 years and a mean of nearly 3 fractures before study entry; 36% had a clinical vertebral fracture in the year before enrollment, and 72% had received a previous osteoporosis medication.

The 24-month incidence of new vertebral fractures in the teriparatide group was less than half that in the risedronate group (5% vs 12%; p<0.0001; effect size,* 0.44). Teriparatide was also associated with reduced incidence of pooled new and worsened vertebral fractures (effect size, 0.46) and of clinical vertebral and non-vertebral fragility fractures (effect size, 0.48). The number needed to treat* (NNT) with teriparatide to prevent 1 fracture was 15, and the NNT to prevent 1 clinical fracture was 20. Teriparatide was associated with numerically fewer non-vertebral fragility fractures than risedronate, but the difference was not statistically significant.

Patients in both groups reported comparable improvement from baseline in back pain and health-related quality of life. Overall adverse-event rates were similar in the 2 treatment groups. Rates of dizziness and limb pain, known adverse effects of teriparatide, were higher in the teriparatide group. There were no instances of osteonecrosis of the jaw or atypical femur fractures.

Discussion: These results support those of previous research using surrogate markers for bone health and suggest that teriparatide should be considered over risedronate for optimal management of patients with severe osteoporosis.

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

Kendler D, et al: Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet* 2018;391 (January 20):230–240. From the University of British Columbia, Canada; and other institutions. **Funded by Lilly. Eleven of 16 study authors disclosed financial relationships with commercial sources, including Lilly, manufacturer of Forteo; the remaining authors declared no competing interests.**

Common Drug Trade Names*: risedronate—*Actonel*; teriparatide—*Forteo

***See Reference Guide.**

Fatty Acids: Cardiovascular Effects

The American Heart Association recommendations suggest that use of omega-3 fatty acids for prevention of coronary heart disease (CHD) is probably justified for patients with prior CHD and those with heart failure and reduced ejection fractions. However, the results of a meta-analysis of clinical trials involving nearly 80,000 patients indicate that supplementation with omega-3 fatty acids has no effect on cardiovascular outcomes.

Methods: A comprehensive literature search identified randomized controlled trials of marine-derived omega-3 fatty acid supplements, with either a placebo or an open-label control. Included trials had a sample size of ≥500 and provided ≥1 year of treatment. Studies were excluded if the intervention was dietary advice to eat fish. The main study outcomes included nonfatal MI, cardiovascular death, revascularization, major vascular events, and all-cause mortality. Multiple prespecified subgroup analyses were carried out to identify any groups that might benefit from supplementation.

Results: The analysis included 8 placebo-controlled trials and 2 open-label trials. Sample sizes ranged from 563 to >18,000 (total, 77,917), and the mean treatment duration ranged from 1 to 6.2 years. Mean eicosapentaenoic acid dosages ranged from 226 to 1800 mg/day, and mean docosahexaenoic acid dosages ranged from 0 to 1700 mg/day. Study subjects had a mean age of 64 years, and about 61% were men. About two-thirds of subjects had a history of CHD.

About 12,000 major vascular events occurred during the studies. Omega-3 supplementation was not associated with the rate of these events (relative risk,* 0.96), all-cause mortality (relative risk 0.96), or any other study outcome. Omega-3 fatty acids had no significant association with major vascular events in subgroup analyses stratified by gender, history of CHD, history of diabetes, use of statin therapy, or baseline levels of total cholesterol, HDL cholesterol, LDL cholesterol, or triglycerides.

Discussion: Previous large clinical trials have generally failed to show a protective association of omega-3 fatty acids with cardiovascular outcomes, but it was not clear whether the effect was consistent across outcomes, in different patient groups, or for primary and secondary prevention. Reasons for the discrepant results of prior trials may include different patient selection criteria, effects of other preventive interventions, and failure to account for the effect of increasing use of statins to control lipids. While the present results do not support a protective effect of fatty acids, 2 large trials of much higher, triglyceride-reducing doses of omega-3 fatty acids are underway and could provide additional evidence.

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

Aung T, et al: Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77,917 individuals. *JAMA Cardiology* 2018; doi 10.1001/jamacardio.2017.5205. From the University of Oxford, U.K.; and other institutions. **Funded by the British Heart Foundation; and the Medical Research Council. Six of 16 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

Fraudulent Flu Products

This year's severe flu season has impacted millions of patients across the country, resulting in a large number of flu-related hospitalizations. The FDA has issued a reminder/warning that there are no legally marketed over-the-counter (OTC) drugs to prevent or cure the flu and that any OTC products that claim to do so are fraudulent. According to the agency, the following are claims that may indicate an OTC product is fraudulent and should be avoided:

- Reduces severity and length of the flu
- Boosts immunity naturally without a flu shot
- Safe and effective alternative to the flu vaccine
- Prevents catching the flu
- Effective treatment for the flu
- Faster recovery from the flu
- Supports your body's natural immune defenses to fight off the flu.

FDA News Release: FDA warns of fraudulent and unapproved flu products. Available at www.fda.gov/newsevents/newsroom/pressannouncements/ucm599223.htm.

Safety of Serotonergic Coprescription

Incidence of serotonin syndrome was low in patients who received concomitantly prescribed triptan antimigraine drugs and serotonergic antidepressants, according to an analysis of 14 years of electronic medical records from a large registry.

Background: In 2006, the FDA issued a warning regarding the risk of serotonin syndrome with concomitant use of triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs). However, the warning was based on a small number of cases, and population-based studies were not conducted to confirm the association. In addition, based on their receptor affinity, the biological plausibility of triptans as a cause of serotonin syndrome is questionable.

Methods: The present analysis was based on the Partners Research Patient Data Registry, which includes information on >6.5 million patients receiving care in the Boston area. Patients were identified who received prescriptions for a triptan and an SSRI or SNRI in 2001–2014. Within this population, investigators searched for all cases of potential serotonin syndrome and examined the records of these patients.

Results: The number of patients who received prescriptions for triptans increased steadily during the study period. In spite of the warning, the proportion of patients who concomitantly received an SSRI or SNRI remained stable between 21% and 29%.

More than 19,000 patients received prescriptions for both a triptan and an SSRI or SNRI during the study period, of whom 229 (0.01%) experienced extrapyramidal symptoms. Serotonin syndrome was clinically suspected in 17 of these patients. Of these, 7 cases met criteria for serotonin syndrome based on ≥1 set of standardized criteria. Detailed records review indicated that triptans had been used in close temporal association with serotonin syndrome-like symptoms in only 2 cases, but in both cases symptoms had onset before triptans were started. Using a strict, conservative case definition, the incidence of serotonin syndrome in this population was 0.6 per 10,000 person-years. Assuming, less conservatively, that serotonin syndrome occurred in all 17 suspected cases, the estimated incidence was 2.3 per 10,000 person-years. No cases of serotonin syndrome, either suspected or confirmed, were life-threatening.

Discussion: These observations suggest there is reason to be skeptical that triptans increase the risk of serotonin syndrome beyond that associated with SSRIs and SNRIs alone. They also provide evidence that patients with affective disorders and migraine do not necessarily need to forgo treatment of 1 disorder to manage the other.

Orlova Y, et al: Association of coprescription of triptan antimigraine drugs and selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitor antidepressants with serotonin syndrome. *JAMA Neurology* 2018; doi 10.1001/jamaneurol.2017.5144.
From Brigham and Women's Hospital, Boston, MA; and other institutions. Funded by Harvard Catalyst; and other sources. The authors declared no competing interests.

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Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

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

Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

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

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Aneurysm Risk with Fluoroquinolones

Fluoroquinolone antibiotics were associated with a 66% increase in risk of aortic aneurysm or dissection in a large cohort study. The risk increase is probably the result of degradation of collagen and related processes, as outlined in a boxed warning in the labeling for the drugs.

Background: Fluoroquinolones were initially observed to increase risk of Achilles tendon rupture and tendinopathy. The agents induce degradation of collagen by stimulating the activity of matrix metalloproteinases, reducing production of new collagen and inducing oxidative stress. Observational studies have suggested a >2-fold increase in aneurysm risk with fluoroquinolones.

Methods: The study was based on nationwide data from Swedish healthcare, demographic, and death-certificate registries. Potential subjects were adults who received a prescription for a fluoroquinolone or amoxicillin in 2006–2013. Amoxicillin, the comparator, is prescribed for similar indications as fluoroquinolones and has no known association with aneurysms. Each fluoroquinolone prescription was propensity score matched* for 47 covariates with an amoxicillin prescription, resulting in 360,088 matched pairs of exposures. Rates of the primary study outcome—a first diagnosis of aortic aneurysm or dissection requiring hospitalization or resulting in death occurring in the 60 days following antibiotic initiation—were compared across the groups.

Results: During the 60-day risk period, there were 64 cases of aortic aneurysm or dissection in patients exposed to fluoroquinolones and 40 cases among those exposed to amoxicillin (1.2 and 0.7 cases per 1000 person-years, respectively). The hazard ratio* for aortic aneurysm with fluoroquinolones was 1.66, which corresponded to an absolute increase of 82 cases per 1 million treatment episodes in the 60-day risk period.

In secondary analyses, risk was increased with fluoroquinolones for the outcome of aortic aneurysm but not for aortic dissection. Fluoroquinolones did not increase risk of death. When the 60-day risk period was divided into 10-day spans, the first 10 days were the peak risk period, with 26 aneurysms in the fluoroquinolone group and 9 in the amoxicillin group. Risk of aneurysm or dissection was not increased with fluoroquinolones between 60 and 120 days after exposure.

Discussion: The present study, which used an active control and propensity score matching to address the limitations of previous observational studies, resulted in a less pronounced but still significant risk estimate. The risk increase is most pronounced in the first 10 days, when treatment is active, which suggests the mechanism is acute and wanes with treatment discontinuation.

Pasternak B, et al: Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. *BMJ* 2018; 10.1136/bmj.k678. From the Karolinska Institutet, Stockholm, Sweden; and other institutions.
This study was conducted without external funding. The authors declared no competing interests.

***See Reference Guide.**

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Cardiac Safety of Smoking Cessation Agents

In a large trial in a general population of smokers, smoking cessation medications were not associated with cardiovascular risk.

Background: Early clinical trials of bupropion and varenicline did not show excess risk of cardiovascular events in treated patients. However, in 2011 the FDA mandated that smoking-cessation medications carry warnings of possible cardiovascular events in smokers with established cardiovascular disease. Findings of subsequent studies were mixed, and the FDA mandated the extension of a large clinical trial to monitor cardiovascular safety.

Methods: Participants in the original multinational study were adults, aged 18–75 years, who smoked ≥10 cigarettes per day and wanted to quit. Those with recent clinically significant cardiovascular or cerebrovascular disease were excluded. Randomized treatment, provided for 24 weeks in a triple-dummy fashion, consisted of 1 mg varenicline b.i.d., 150 mg bupropion b.i.d., a nicotine-replacement patch as an active control, or placebo. Patients were invited to participate in the extension study regardless of whether they stopped study medication prematurely, as long as they remained in follow-up throughout the 24-week trial. During the nontreatment extension, patients were evaluated in the clinic every 4 weeks up to week 52. The primary outcome was time to a major adverse cardiovascular event (i.e., cardiovascular death, nonfatal MI, or nonfatal stroke). The incidence of these events was compared during treatment, during the 30 days after completion, and at 1 year.

Results: More than 8000 patients received randomized medication or placebo in the original 24-week study. Their average age was 46 years, 44% were men, and about half had a neuropsychiatric disorder. Between 77% and 79% of each treatment group completed the 24-week trial, and 56% of the original cohort enrolled in the extension trial. Of this group, 90% completed the additional half year of follow-up. Patients were exposed to medication (or placebo) for an average of about 74 days.

Major adverse cardiovascular events were infrequent, occurring in <0.5% of all groups. Overall there were 14 nonfatal MIs, 8 nonfatal strokes, and 5 cardiovascular deaths. The groups also did not differ in time to major adverse cardiovascular event or a composite outcome consisting of a major adverse cardiovascular event plus new-onset or worsening peripheral vascular disease requiring treatment, coronary revascularization, or hospitalization for unstable angina. Results of the analysis did not differ for each of the 3 observation periods or in patients in low, medium, or high baseline cardiovascular risk categories.

Discussion: Participants in the present study were in generally good health and representative of the population of smokers in general medical practice. No evidence was found in these patients that smoking-cessation agents increase the risk of serious cardiovascular events during or after treatment. In addition, the number of adverse cardiac events that did occur was small and the incidence of serious events was low, suggesting that any absolute increase in risk is low and not clinically meaningful.

Benowitz N, et al: Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers: a randomized clinical trial. *JAMA Internal Medicine* 2018; doi 10.1001/jamainternmed.2018.0397. From the University of California, San Francisco; and other institutions. **Funded by Pfizer; and GlaxoSmithKline. All 9 study authors disclosed financial relationships with commercial sources including Pfizer and/or GlaxoSmithKline.**

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

Fostamatinib for Thrombocytopenia

The first-in class spleen tyrosine kinase inhibitor fostamatinib has received FDA approval for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP) that has not been sufficiently responsive to previous treatment including steroids, platelet production boosters, or splenectomy.[1] Fostamatinib, which targets the underlying autoimmune cause of ITP by impeding platelet destruction, is expected to be available in late May 2018.

Common adverse reactions to fostamatinib in clinical trials included diarrhea, nausea, dizziness, rash, and neutropenia. The agent can induce hypertension, and patients with preexisting hypertensive disorders may be more susceptible to BP increases. In patients with hypertension, BP should be monitored biweekly until stable, and then monthly. Elevations in liver enzymes (primarily alanine aminotransferase, aspartate aminotransferase) were also reported; liver function should be evaluated monthly during treatment. Because of the risk for neutropenia

with treatment, absolute neutrophil counts should also be monitored monthly. Fostamatinib should not be used by pregnant or breastfeeding women. Interactions are possible with strong CYP3A4 inhibitors (e.g., clarithromycin) or inducers (e.g., carbamazepine), CYP3A4 substrate drugs (e.g., simvastatin),[2] breast cancer resistance protein substrate drugs (e.g., rosuvastatin), and P-glycoprotein substrate drugs (e.g., digoxin).

[1]Rigel announces FDA approval of tavalisse™ (fostamatinib disodium hexahydrate) for chronic immune thrombocytopenia (ITP) in adult patients [press release]. South San Francisco, CA; Rigel Pharmaceuticals: April 17, 2018. Available at http://ir.rigel.com/phoenix.zhtml?c=120936&p=irol-newsArticle&ID=2343080.

[2]Drug development and drug interactions: table of substrates, inhibitors and inducers. Available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1.

Common Drug Trade Names*: clarithromycin—*Biaxin*; carbamazepine—*Carbatrol, Epitol, Tegretol*; digoxin—*Lanoxin*; fostamatinib—*Tavalisse*; rosuvastatin—*Crestor*; simvastatin—*Zocor

Trimethoprim Safety in Older Patients

Compared with other antibiotics, trimethoprim was associated with an increase in acute kidney injury and hyperkalemia in older patients receiving treatment for urinary tract infection (UTI), according to a large population-based study. In contrast to previous reports, trimethoprim was not associated with increased risk of sudden death overall or in patients also taking renin-angiotensin system antagonists.

Methods: Electronic medical records from the U.K.'s Clinical Practice Research Datalink were used to identify all patients aged ≥65 years who received a prescription for 1 of 5 commonly used antibiotics for a UTI between mid-1997 and late-2015. Episodes treated with co-trimoxasole were excluded because it is typically used to treat more severe infections. Study outcomes were acute kidney injury, hyperkalemia, and death within 14 days of antibiotic initiation. Rates of these outcomes were compared among patients who received trimethoprim, amoxicillin, cephalexin, ciprofloxacin, and nitrofurantoin, all considered first-line treatment for uncomplicated UTIs during the study years. The analyses were adjusted for an extensive list of covariates. Because evidence suggests that combined use of trimethoprim with renin-angiotensin system antagonists (e.g., ACE inhibitors and ARBs) may increase risk for severe and potentially life-threatening hyperkalemia, a separate analysis restricted to these patients was also conducted.

Results: Nearly 179,000 patients received antibiotics for a total of 422,514 UTI episodes. Trimethoprim was prescribed in 59% of infections, nitrofurantoin and cephalexin each in 15%, and the other antibiotics each in 5%. Within 14 days of antibiotic initiation, there were 1345 episodes of acute kidney injury, 648 episodes of hyperkalemia, and 2214 deaths. Patients who took each of the antibiotics had broadly similar clinical and demographic characteristics.

Trimethoprim was associated with the highest odds of kidney injury compared with amoxicillin, the reference drug (adjusted odds ratio,* 1.72) and of hyperkalemia (odds ratio, 2.27). Ciprofloxacin was also associated with increased risk of acute kidney injury (odds ratio, 1.48), but not hyperkalemia. Cephalexin and nitrofurantoin were not associated with either outcome, and no antibiotic conferred increased risk of death. When the analysis was restricted to patients taking renin-angiotensin system antagonists, risk comparisons were essentially unchanged.

Crellin E, et al: Trimethoprim use for urinary tract infection and risk of adverse outcomes in older patients: cohort study. *BMJ* 2018; doi 10.1136/bmj.k341. From the London School of Hygiene and Tropical Medicine. **Funded by the Wellcome Trust. The authors declared no competing interests.**

Common Drug Trade Names*: amoxicillin—*Moxatag*; cephalexin—*Keflex*; ciprofloxacin—*Cipro*; nitrofurantoin—*Macrodantin*; trimethoprim—*Primsol*; trimethoprim–sulfamethoxazole (co-trimoxazole)—*Bactrim

***See Reference Guide.**

Antidepressants: Comparative Efficacy

According to the results of a systematic review and network meta-analysis including 21 different antidepressants, several agents are significantly more effective than others. The analysis also identified differences in patient acceptability among the antidepressants .

Methods: The present analysis was based on randomized controlled trials comparing antidepressants with placebo or other antidepressants as oral monotherapy in adults with major depressive disorder. The primary efficacy outcome was response, defined as a ≥50% improvement in a standardized, observer-rated depression scale score. Acceptability was measured using the rate of withdrawal for any reason.

Results: A total of 522 controlled trials were identified with >116,000 patients enrolled. All medications were more effective than placebo at producing a response. (See table.) Relative to placebo, amitriptyline had the highest odds ratio* of response at 2.13. Odds ratios for other antidepressants compared with placebo ranged from 1.37 to 1.89, with wide confidence intervals. In head-to-head studies, several antidepressants were shown to be superior to others, with odds ratios ranging from 1.19 to 1.96: amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine. The least effective drugs in head-to-head comparisons were fluoxetine, fluvoxamine, and trazodone. Overall, antidepressants were also more effective than placebo at inducing remission (effect size,* 0.30; p<0.0001).

Antidepressant Response Relative to Placebo

Agent	Odds Ratio	Agent	Odds Ratio
Amitriptyline	2.13	Vortioxetine	1.66
Mirtazapine	1.89	Vilazodone	1.60
Duloxetine	1.85	Levomilnacipran	1.59
Venlafaxine	1.78	Bupropion	1.58
Paroxetine	1.75	Fluoxetine	1.52
Milnacipran	1.74	Citalopram	1.52
Fluvoxamine	1.69	Trazodone	1.51
Escitalopram	1.68	Clomipramine	1.49
Nefazodone	1.67	Desvenlafaxine	1.49
Sertraline	1.67		

Citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were significantly better tolerated than other drugs in comparative studies, with odds ratios for dropout ranging from 0.43 to 0.77. Amitriptyline, clomipramine, duloxetine, fluvoxamine, trazodone, and venlafaxine were associated with the highest dropout rates.

Discussion: The summary effect sizes for most antidepressants were relatively modest. However, several agents emerged as combining a relatively high response rate and a low dropout rate: escitalopram, mirtazapine, paroxetine, and sertraline.

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

Cipriani A, et al: Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018; doi 10.1016/S0140-6736(17)32802-7. From the University of Oxford, U.K.; and other institutions. **Funded by the National Institute for Health Research Oxford Health Biomedical Research Centre; and the Japan Society for the Promotion of Science. Six of 18 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Drug Trade Names: **amitriptyline—*Elavil*; bupropion—*Wellbutrin*; citalopram—*Celexa*; clomipramine—*Anafranil*; desvenlafaxine—*Pristiq*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; levomilnacipran—*Fetzima*; milnacipran—*Savella*; mirtazapine—*Remeron*; nefazodone—*Serzone*; paroxetine—*Paxil*; sertraline—*Zoloft*; trazodone—*Oleptro*; venlafaxine—*Effexor*; vilazodone—*Viibryd*; vortioxetine—*Brintellix***

***See Reference Guide.**

Reference Guide

Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

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

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

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

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

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Erenumab for Migraine Prevention

The fully human monoclonal antibody erenumab (*Aimovig*) has received FDA approval for the prevention of migraine in adults. Erenumab, a once-monthly self-injectable, is the first in class calcitonin-gene-related peptide (CGRP) antagonist to receive approval. Clinical trials have included >3000 patients with chronic or episodic migraines. The most recent results indicate that erenumab can reduce the average number of monthly migraine days by 50% in nearly one-third of patients. Commonly reported adverse effects included injection site reactions and constipation. The agent will be available in 70- and 140-mg single-use prefilled autoinjectors.

In addition to erenumab, there are 3 other agents in the anti-CGRP antibody class; fremanezumab and galcanezumab are currently under FDA review, and the approval process for eptinezumab is expected to begin by year end.

FDA Approves First-in-Class Drug Erenumab (Aimovig) for Migraine Prevention. Medscape Medical News: available at https://www.medscape.com/viewarticle/896851.

DPP-4 Inhibitors and IBD

In a population-based cohort study, patients taking dipeptidyl peptidase-4 inhibitors for type 2 diabetes had an increased risk of inflammatory bowel disease (IBD). Although the absolute risk increase is low, prescribing DPP-4 inhibitors in patients with a family history of the disease or known autoimmune conditions should be done cautiously.

Background: The use of DPP-4 inhibitors as second- or third-line antidiabetic treatment has been increasing, in part because of their neutral effects on body weight and cardiovascular outcomes. The DPP-4 receptor is expressed on a variety of cells including those involved in the immune response, possibly leading to unintended effects. DPP-4 inhibition results in reduced disease activity in animal models of inflammatory bowel disease, but patients with the disease have decreased levels of the DPP-4 enzyme.

Methods: The analysis used data from the Clinical Practice Research Datalink, a British database of >700 primary care practices. Cohort members were all adult patients with type 2 diabetes who received a new prescription for a non-insulin diabetes medication between 2007 (the year the first DPP-4 inhibitor was introduced) and 2016. Patients were excluded if they had a diagnosis of IBD or a related condition at baseline or if they received a prescription for insulin before their first non-insulin drug. A comparison group consisted of patients newly prescribed any other antidiabetic drug. Incidence of IBD was compared between the groups.

Results: The cohort consisted of >141,000 adults, including 7231 who received a DPP-4 inhibitor. Follow-up averaged nearly 4 years, during which 208 patients received a new diagnosis of IBD. The incidence of inflammatory bowel disease in exposed and unexposed groups were 53.4 and 34.5 per 100,000 per year, respectively (hazard ratio,* 1.75). The number needed to harm* was 2291 patients over 2 years to result in

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1 additional case. Incidence reached a peak after 3–4 years of DPP-4 inhibitor use and declined afterward. DPP-4 inhibitors were associated with increased incidence of ulcerative colitis (hazard ratio, 2.23) but not Crohn's disease.

Abrahami D, et al: Dipeptidyl peptidase-4 inhibitors and incidence of inflammatory bowel disease among patients with type 2 diabetes: population based cohort study. *BMJ* 2018; doi 10.1136/bmj.k872. From Jewish General Hospital, Montreal, Canada; and other institutions. **Funded by the Canadian Institutes of Health Research. The authors declared no competing interests.**

***See Reference Guide.**

Legal Marijuana and Adolescent Health

Survey data suggest that Colorado's legalization of medical marijuana in 2009, followed by recreational use in 2014, was not accompanied by increased use of the drug by adolescents. However, the number of marijuana-related emergency and urgent-care visits to a Colorado pediatric hospital increased nearly 5-fold in subsequent years.

Methods: To assess the effect of legalization on one facet of adolescent health, the investigators examined data from admissions to the emergency and urgent-care facilities of a tertiary-care children's hospital system in the Denver metropolitan area. Data were collected from visits between 2005 and 2015 by patients aged 13–20 years with a discharge diagnosis of marijuana/cannabis use or with a positive toxicology screen for tetrahydrocannabinol (THC). Urine drug screens were mandatory for patients admitted for behavioral health disorders.

Results: A total of 4202 marijuana-related visits occurred in patients with a mean age of 16 years (54% male) during the study years. The annual total increased steadily over the years, from 161 in 2005 to 777 in 2015. The number of behavioral health evaluations, which were provided for 67% of patients, also showed a steady increase from 84 in 2005 to 500 in 2015. The majority of patients received a diagnosis of cannabis use/abuse/misuse (62%) or substance abuse (33%). Comorbid psychiatric diagnoses were also common and included depression (39%), mood disorder (22%), conduct disorder (13%), anxiety/ panic disorder (13%), ADHD (12%), bipolar disorder (6%), schizophrenia (5%), and "other" (31%).

Rates of marijuana-related visits, relative to all emergency/urgent care visits, were compared for 2009 and 2015, the first full years of medical and recreational marijuana legalization, respectively. The frequency increased from 1.8 per 1000 visits in 2009 to 4.9 per 1000 in 2015. Marijuana-related behavioral health consultations increased from 1.2 per 1000 visits in 2009 to 3.2 per 1000 visits in 2015.

Discussion: Although there has been an increase in the frequency of urine drug screens overall, this does not fully account for the increase in cannabis-related visits. These data should prompt concern now that more than half of states have legalized at least some type of marijuana use, in part because adolescents' risk perception of marijuana may have decreased, even if data do not consistently show an increase in actual use.

Wang G, et al: Impact of marijuana legalization in Colorado on adolescent emergency and urgent care visits. *Journal of Adolescent Health* 2018; doi 10.1016/j.jadohealth.2017.12.010. From the University of Colorado Anschutz Medical Campus; and Children's Hospital Colorado, Aurora, CO. **This research was conducted without specific funding. One of 5 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Mazindol for Adult ADHD

In a phase-II placebo-controlled trial, controlled-release mazindol was effective in adults with ADHD, with an effect size comparable to stimulants. Mazindol is a serotonin, noradrenaline, and dopamine reuptake inhibitor (SNDRI) previously introduced for treatment of obesity but withdrawn from the market because of low sales. This is the first clinical trial of a controlled-release formulation, following promising results of an open-label study of immediate-release mazindol in children with ADHD.

Methods: Study participants were 84 adults with a diagnosis of ADHD meeting minimum severity criteria when unmedicated. Patients received mazindol or placebo for 6 weeks, with mazindol dosed flexibly within a range of 1–3 mg/day. The primary efficacy measure was change from baseline in the ADHD Rating Scale for DSM-5 (ADHD-RS-DSM5). Efficacy was also assessed with the Clinical Global Impression–Improvement (CGI-I) scale and with the Target Impairment Scale, which measures changes in 3 functional goals selected by the patient.

Results: Mazindol was associated with a significantly larger improvement in ADHD-RS-DSM5 score after 6 weeks of treatment (19 vs 6 points;

p<0.001; effect size,* 1.09). Effects of mazindol differed statistically from placebo after the first week of treatment, and differences grew larger over the subsequent weeks. Significantly more patients were classified as "excellent responders" (≥50% improvement on the ADHD-RS-DSM5) in the mazindol group beginning at 2 weeks. By 6 weeks, 55% of the mazindol group and 16% of the placebo group were classified as excellent responders (p=0.002). CGI-I ratings of much or very much improved were observed in 62.5% of the mazindol group and 21% of the placebo group (p<0.001). Improvement in target areas was also significantly greater with mazindol.

The most common adverse effects of mazindol, relative to placebo, were dry mouth, nausea, fatigue, increased heart rate, decreased appetite, and constipation. Patients receiving mazindol lost an average of nearly 4 lbs during the 6-week study. However, previous experience indicates the effects of mazindol on weight are short-lived.

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

Wigal T, et al: A double-blind, placebo-controlled, phase II study to determine the efficacy, safety, tolerability and pharmacokinetics of a controlled release (CR) formulation of mazindol in adults with DSM-5 attention-deficit/hyperactivity disorder (ADHD). *CNS Drugs* 2018;32 (March):289–301. From AVIDA Inc., Newport Beach, CA; and other institutions. **Funded by NLS-1 Pharma AG. All study authors disclosed relevant financial relationships with NLS-1 Pharma AG and other sources.**

Common Drug Trade Names*: mazindol—*Mazanor, Sanorex

***See Reference Guide.**

Lamotrigine Immune System Reaction

The FDA has issued a warning that the anticonvulsant lamotrigine (*Lamictal*) can cause hemophagocytic lymphohistiocytosis (HLH), a rare but serious immune system reaction that can trigger severe inflammation throughout the body. HLH causes an uncontrolled immune response that can lead to serious problems liver, kidney, lung, and blood cell issues. Patients with HLH typically present with persistent fever, rash, or other nonspecific symptoms. The diagnosis of HLH is based upon the patient exhibiting ≥5 of the following 8 symptoms: fever and rash; enlarged spleen; cytopenia; elevated triglyceride levels or low fibrinogen levels; high serum ferritin levels; hemophagocytosis identified through bone marrow, spleen, or lymph node biopsy; decreased or absent natural killer cell activity; or elevated blood levels of CD25 indicating prolonged immune cell activation. Lamotrigine should be discontinued if HLH is suspected.

Lamictal (lamotrigine): Drug Safety Communication - Serious Immune System Reaction. Available at https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm605628.htm.

Lofexidine for Opioid Withdrawal

Physical dependence is an expected physiological response to opioid use. In patients using the medications appropriately, opioid withdrawal is typically accomplished using a slow taper. In patients with opioid use disorder, the abused medication is typically replaced with an alternate opioid medicine, which is then gradually reduced and then followed by transition to maintenance therapy to an agent such as methadone, buprenorphine, or naltrexone.

The FDA recently approved lofexidine hydrochloride, the first nonopioid medication for the alleviation of opioid withdrawal symptoms in adults in order to expedite abrupt discontinuation. Lofexidine is a selective alpha 2-adrenergic receptor agonist that reduces the release of norepinephrine, the effects of which are thought to have a role in many of the symptoms of opioid withdrawal. The newly approved drug is not a treatment for opioid use disorder; however, it can lessen the severity of withdrawal symptoms including anxiety, agitation, sleep difficulty, muscle ache, runny nose, sweating, nausea, vomiting, diarrhea, and drug craving. In clinical trials, the most common adverse effects associated with lofexidine were hypotension, bradycardia, somnolence, sedation, and dizziness. Because lofexidine can affect cardiac conduction, patients may experience a marked blood pressure increase when the agent is stopped. Safety and efficacy have not been established in children or adolescents, and the approval covers only a 14-day course of treatment in adult patients.

FDA News Release: FDA approves the first non-opioid treatment for management of opioid withdrawal symptoms in adults. Available at https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm607884.htm.

Common Drug Trade Names*: buprenorphine—*Buprenex*; lofexidine—*Lucemyra*; methadone—*Methadose*; naltrexone—*ReVia

Reference Guide

Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

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

Number Needed to Harm: A measure of how many patients need to be exposed to a risk-factor to cause harm in 1 patient that would not otherwise have been harmed. Lower NNH indicates more attributable risk.

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.

"Change is the law of life and those who look only to the past or present are certain to miss the future."—John F. Kennedy

Starting with the August issue, the delivery of *Primary Care Drug Alerts* will be 100% electronic; we are leaving the printing to you. The content of the newsletter will be unchanged; only the method of delivery will change. Why?

- The majority of our readers prefer to read their issues of *Primary Care Drug Alerts* online—either through the email they receive before the paper version is even mailed or directly from our website. The electronic version is a PDF document and reads very clearly on any computer or device. And there's always the option to print it yourself.
- The U.S. Postal Service has become increasingly slow and unreliable. Our customer service representatives spend a disproportionate amount of time replacing issues that were lost in the mail.
- The price of printing, paper, and mailing have become prohibitively expensive over the years—too much for a small publisher to absorb without increasing prices significantly.

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PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XXXIX / June 2018 / Number 6 www.alertpubs.com

Tofacitinib for Ulcerative Colitis

The first oral medication for chronic use in ulcerative colitis has received FDA approval. Previously approved agents were required to be administered via IV infusion or subcutaneous injection. Tofacitinib (*Xeljanz*) is now licensed to treat moderately-to-severely active disease in adults. Clinical efficacy and safety of the agent were demonstrated in clinical trials showing that short-term (8 weeks) treatment with oral tofacitinib could induce sustained, corticosteroid-free remission of ulcerative colitis in nearly half of patients. Common adverse effects of tofacitinib in clinical trials included: diarrhea; increased cholesterol levels; headache; herpes zoster; increased creatine phosphokinase levels; nasopharyngitis; rash; and upper respiratory tract infection. Although less common, serious adverse effects, including malignancy and opportunistic infections, did occur. Tofacitinib carries a boxed warning about the potential for serious infections and malignancy. Use of tofacitinib in combination with biological therapies for ulcerative colitis or with potent immunosuppressants is not recommended.

FDA News Release: FDA approves new treatment for moderately to severely active ulcerative colitis. Available at www.fda.gov/newsevents/newsroom/pressannouncements/ucm609225.htm.

Antibiotics and Kidney Stone Risk

Oral antibiotic therapy was associated with increased risk of kidney stones in a large population-based study. This finding may help explain the increase in incidence of nephrolithiasis that has occurred over the past 30 years.

Methods: The study was based on electronic records of patients receiving care in general practices in the U.K. in 1994–2015. For each patient with a diagnosis of nephrolithiasis, 10 age- and gender-matched controls were selected from the same practice. The primary exposure was an outpatient oral antibiotic prescription 3–12 months before the index date. The 3-month lag was included to reflect the biology of kidney-stone formation following alterations in the urinary microbiome and to exclude antibiotics that might have been prescribed for kidney-stone symptoms. Data were analyzed for each of the 12 major classes of antibiotics and also for *H. pylori* treatment, which reduces intestinal colonization by *Oxalobacter* species.

Results: The study included nearly 26,000 patients with nephrolithiasis and 260,000 controls (mean age, 51 years) observed for a median of >5 years. The most common reasons for outpatient antibiotic prescriptions were chest infection, cough, upper respiratory infection, tonsillitis, and urinary tract infection.

Risk of nephrolithiasis was significantly increased in the 3–12 months after exposure to 5 different classes of antibiotics: sulfas (odds ratio* [OR], 2.33); cephalosporins (OR, 1.88); fluoroquinolones (OR, 1.67); nitrofurantoin/methenamine (OR, 1.70); and broad-spectrum penicillins (OR, 1.27). Risk was also increased following antibiotic treatment of *H. pylori* (OR, 1.79), although this increase was not statistically significant in all of the statistical models applied. Antibiotic-associated risk was highest in patients exposed at younger age;

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the exact pattern of age-related risk varied with each antibiotic class. Risk was greatest for antibiotic exposure within 3–6 months of the diagnosis date, but risk was also statistically significantly higher for 3–5 years after exposure for the 5 antibiotic classes except broad-spectrum penicillins.

Discussion: Antibiotics are suspected to increase risk of kidney stones by altering the intestinal and urinary-tract microbiome. Previous studies have shown that patients with kidney stones had reduced diversity of bacteria in the gut microbiome. It is likely that multiple gut organisms, acting as a community, mediate the association of antibiotics and nephrolithiasis.

Exposure to some oral antibiotics might explain the increase in the prevalence of nephrolithiasis, which has been most pronounced in children, adolescents, and young adults. Given that antibiotic use is highest in children, these findings provide another reason to reduce the prevalence of inappropriate prescribing.

Tasian G, et al: Oral antibiotic exposure and kidney stone disease. *Journal of the American Society of Nephrology* 2018; doi 10.1681/ASN.2017111213. From the Children's Hospital of Philadelphia, PA; and other institutions. **Funded by the NIH. The authors declared no competing interests.**

Common Drug Trade Names*: methenamine—*Hiprex*; nitrofurantoin—*Furadantin

***See Reference Guide.**

Flu Shot Recommendation

After reviewing efficacy data, the American Academy of Pediatrics (AAP) has announced they will recommend that families choose the inactivated influenza vaccine (flu shot) over the nasal spray vaccine when they vaccinate their children for the 2018–2019 flu season. The injectable formulation has been shown to be consistently more effective than the nasal spray over the past few flu seasons. Although the AAP will not release their formal policy statement until September, they have announced the decision early so that physicians can order an adequate supply of the injection. The nasal spray remains an option for children who could otherwise not be vaccinated.

AAP News Release: American Academy of Pediatrics advises parents to choose the flu shot for 2018-2019 flu season. Available at https://www.aap.org/en-us/about-the-aap/aap-press-room/Pages/AAP-Advises-Parents-to-Choose-the-Flu-Shot-For-2018-2019-Flu-Season.aspx.

ACE Inhibitors or ARBS in Diabetes

A meta-analysis found convincing evidence that angiotensin-converting enzyme inhibitors, but not angiotensin II receptor blockers (ARBs), prevented mortality and other adverse cardiovascular outcomes in patients with hypertension and type 2 diabetes.

Methods: The analysis included randomized controlled trials, published since 2000, conducted in patients with both hypertension and type 2 diabetes. The endpoints of the included studies were all-cause mortality, cardiovascular mortality or events, MI, stroke, or heart failure. Additional study requirements were a sample size of >500, patient age >55 years, and >1 year of follow-up. For the meta-analysis, the primary outcomes were all-cause mortality and cardiovascular mortality.

Results: A total of 13 studies were included in the analysis; 5 trials compared ACE inhibitors with placebo, 6 compared ARBs with placebo, and 2 compared ARBs with an active control drug. Study participants had a mean age of about 65 years and were followed for a mean of about 4 years.

ACE-inhibitor therapy was associated with significant reductions in all-cause and cardiovascular mortality, while ARBs were not. (See table.) ACE inhibitors were also associated with significant reductions in all of the secondary study outcomes—MI, stroke, heart failure, and all cardiovascular events—with odds ratios* ranging from 0.65 to 0.88. Risk reductions with ARBs for all of these events were not statistically significant.

Effect of antihypertensive treatment on mortality outcomes in patients with type 2 diabetes

	All-cause mortality		Cardiovascular mortality	
	Odds Ratio*	Significance	Odds Ratio	Significance
ACE Inhibitors (n=24,976)	0.87	p=0.0008	0.81	p=0.03
ARBs (n=22,032)	1.06	p=ns	1.02	p=ns

Discussion: These results differ somewhat from previous meta-analyses, which showed a beneficial effect of ARBs for several outcomes. The difference is likely the result of requiring a larger

sample size and limiting the present patient population to those aged >55 years with both hypertension and type 2 diabetes.

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

Xiaodan I, et al: Comparison of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular outcomes in hypertensive patients with type 2 diabetes mellitus: a PRISMA-compliant systematic review and meta-analysis. *Medicine* 2018; doi 10.1097/MD.0000000000010256. From Shenyang Pharmaceutical University, China; and other institutions. **Source of funding not stated. The authors did not include disclosure of potential competing interests.**

***See Reference Guide.**

Antidepressants in Pediatric Anxiety

In children and adolescents with anxiety disorders, antidepressant-related improvements occur quickly and selective serotonin reuptake inhibitors (SSRIs) are associated with earlier and larger improvement than serotonin–norepinephrine reuptake inhibitors (SNRIs), according to the results of a meta-analysis.

Background: SSRIs and SNRIs have both been recommended as first-line treatment of pediatric anxiety disorders. However, duloxetine is the only FDA-approved antidepressant for this indication, and it is unknown whether SSRIs are superior to SNRIs. The present meta-analysis was conducted to evaluate the trajectory of response to antidepressants in pediatric anxiety disorders and to compare the effects of drug class and dose.

Methods: Studies were included if they were prospective, randomized, parallel-group, placebo-controlled trials that evaluated the efficacy of SSRIs or SNRIs in social, generalized, and/or separation anxiety disorder in patients aged ≤18 years. For inclusion, studies were required to use a standardized rating scale to measure anxiety symptoms. The primary outcome of the analysis was change from baseline in a standardized measure of anxiety for the active medication in comparison with placebo. Dose comparisons were based on fluoxetine equivalents of the labeled therapeutic range of each drug. Atomoxetine was included in the analysis because of its potent norepinephrine reuptake blockade and serotonin transporter inhibition.

Results: The comprehensive literature search identified 9 studies conducted in 1805 patients, evaluating 7 different drugs: 4 SSRIs (i.e., fluoxetine, fluvoxamine, paroxetine, and sertraline) and 3 SNRIs (i.e., atomoxetine, duloxetine, and venlafaxine). The median study duration was 10 weeks. The Pediatric Anxiety Rating Scale was the outcome measure in all but 2 studies.

Overall, statistically significant differences between drug and placebo appeared at week 2 ($p=0.005$) and reached a clinically significant effect size* of 0.44 by week 6 ($p=0.001$). Both SSRIs and SNRIs were associated with statistically significant improvement, relative to placebo, at treatment week 2 and remained statistically superior to placebo up to week 12. SSRIs were superior to SNRIs beginning at week 2 ($p=0.026$) and continuing to week 12 ($p<0.03$ for all 2-week intervals). The results were essentially unchanged in a sensitivity analysis that excluded data from the atomoxetine trial. Industry-funded and government-funded studies had generally similar results. Low doses of SSRIs (<1.5 fluoxetine equivalents per day) were no less effective than higher doses overall, but high doses were associated with an earlier response.

Discussion: These results suggest that SSRIs may be more effective than SNRIs against pediatric anxiety. It is possible that SSRIs could be superior because the serotonin system matures earlier than the noradrenergic system and may be a more available treatment target. In addition, SNRIs have class-specific tolerability concerns, including suicidality with venlafaxine. The study findings regarding dosage raise questions regarding the long-held belief that antidepressants should be titrated.

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

Strawn J, et al: The impact of antidepressant dose and class on treatment response in pediatric anxiety disorders: a meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry* 2018;57 (April): 235–244. From the University of Cincinnati College of Medicine; and other institutions, OH. **Funded by the NIMH. Two of 4 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names: **atomoxetine—*Strattera*; duloxetine—*Cymbalta*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor***

***See Reference Guide.**

Generic Suboxone

The first generic versions of sublingual buprenorphine/naloxone have received FDA approval. This approval advances the FDA commitment to combating the opioid crisis by increasing access to the safe and effective medications needed for pharmacotherapy-assisted treatment of opioid dependence. Two generic versions will now be available; however, as with the branded version, prescribing is limited to physicians with Addiction Treatment Act (DATA)-certification.

FDA News Release: FDA approves first generic versions of Suboxone sublingual film, which may increase access to treatment for opioid dependence. Available at www.fda.gov/newsevents/newsroom/pressannouncements/ucm610807.htm.

Reference Guide

Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

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

Volume XXXIX / July 2018 / Number 7 www.alertpubs.com

Fluoroquinolone Warnings Strengthened

Most fluoroquinolone antibiotic labels carry warnings about potential blood sugar disturbances and psychiatric adverse effects. However, these warnings vary by individual drug within the class. The FDA is now requiring that the labels for all fluoroquinolones include a warning that hypoglycemia, which can lead to coma, is possible and occurs more frequently in elderly patients and those taking oral hypoglycemic medications or insulin for diabetes. In addition, the psychiatric adverse effects that will now be added or updated across all agents in the class include: disturbances in attention; disorientation; agitation; nervousness; memory impairment; and delirium. Prescribers are reminded that when other options are available, fluoroquinolones should not be used for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, or uncomplicated urinary tract infection as the risks of these agents outweigh the benefits.

FDA MedWatch Alert: Fluoroquinolone antibiotics: FDA requires labeling changes due to low blood sugar levels and mental health side effects. Available at https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm612979.htm.

Second-Line Diabetes Drugs and Mortality

According to results of a meta-analysis of clinical trials, sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists are associated with reduced mortality outcomes compared with placebo. The third class of second-line glucose-lowering medications, dipeptidyl peptidase 4 (DPP-4) inhibitors, was not superior to placebo with regard to mortality outcomes.

Background: According to current international guidelines, escalation to any of the 3 drug classes is recommended in patients who do not achieve glycemic control with metformin (*Glucophage*). However, no randomized trials have directly compared the mortality effects of these 3 classes.

Methods: The network meta-analysis included randomized controlled trials of drugs from any of the 3 classes in patients with type 2 diabetes. Medications could be compared with placebo, no treatment, or each other. The primary outcome of the analysis was all-cause mortality. Secondary outcomes included cardiovascular mortality and several cardiovascular endpoints.

Results: The network meta-analysis included 236 publications with a total of >176,000 participants. The analysis of all-cause mortality was based on 97 studies with >134,000 participants. Nine trials, which comprised nearly half of study participants, were cardiovascular outcome trials in patients with or at risk for cardiovascular disease.

Compared with placebo or no treatment, all-cause mortality was significantly reduced with SGLT-2 inhibitors (hazard ratio [HR],* 0.80) and GLP-1 agonists (HR, 0.88), but not with DPP-4 inhibitors. There was no difference between SGLT2-inhibitors and GLP-1 agonists in overall mortality, but both were superior to DPP-4 inhibitors (HRs, 0.78 and 0.86, respectively).

Results for cardiovascular mortality were similar to those for overall mortality, with HRs of 0.79 and

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0.85 for SGLT-2 inhibitors and GLP-1 agonists, respectively, compared with control treatments. With regard to individual cardiovascular outcomes, only SGLT-2 inhibitors were superior to control treatments for heart failure events (HR, 0.62) and MIs (HR, 0.86). GLP-1 agonists were superior to DPP-4 agonists (HR, 0.82) but not control treatments for heart failure. No treatment was superior to control at reducing strokes or unstable angina.

In an analysis of the likelihood of superiority to other treatments, SGLT-2 inhibitors were ranked best for all-cause and cardiovascular mortality, GLP-1 agonists second best, and DPP-4 inhibitors worst. SGLT-2 inhibitors also were most likely to rank best for heart failure and MI outcomes, and GLP-1 agonists ranked best for stroke outcomes.

Both DPP-4 inhibitors and SGLT-2 inhibitors were associated with a higher rate of hypoglycemia than controls. SGLT-2 inhibitors were associated with a lower risk of serious adverse events than control treatments, and GLP-1 agonists had the highest rate of withdrawal for adverse events.

Discussion: The present analysis suggests SGLT-2 inhibitors may be preferable to incretin-based therapies, based on both lower mortality and a more favorable adverse-event profile. However, it is noteworthy that efficacy and safety was evaluated by drug class, rather than by individual agent. While this increases statistical power to detect treatment effects, within-class treatments may not be interchangeable.

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

Zheng S, et al: Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2018;319 (April 17):1580–1591. From Imperial College Healthcare NHS Foundation Trust, London, U.K.; and other institutions. **Funded by the British Heart Foundation; and other sources. One of 7 authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Depression as Medication Adverse Effect

Use of medications that have depression as a potential adverse effect is common and increasing, according to a longitudinal series of surveys of American adults. Use of ≥3 of these medications was associated with simultaneous depression.

Methods: The authors analyzed 5 waves of data from the U.S. National Health and Nutrition Examination Survey, an in-person audit of a representative sample of community-dwelling adults, which is conducted in 2-year cycles. The final sample included >26,000 persons interviewed between 2005–2006 and 2013–2014. Participants showed interviewers containers for all prescription medications taken in the past 30 days. Information about the relationship of drugs to depression and suicidal thoughts or behavior was obtained from Micromedex, an online database that lists FDA-labeled adverse events. Depression was assessed using the Patient Health Questionnaire 9 (PHQ-9).

Results: Use of any medication with depression as a listed potential adverse effect increased from an estimated 35% of the population in 2005–2006 to 38% in 2013–2014. Concurrent use of ≥3 of these medications increased from 7% to 9.5%, and use of medications with suicidal symptoms as a potential adverse effect increased from 17% to 23.5%. Overall, antidepressants with depression as a labeled adverse effect were the most widely used medication class, and use increased significantly between the study waves, from 11% to 15% of surveyed patients (p=0.001). Use of gastrointestinal agents (in particular proton pump inhibitors and histamine H_2 antagonists), anxiolytics and sedative/hypnotics, and anticonvulsants also increased significantly (p≤0.01 for all). Use of depression-related anti-hypertensives, analgesics and muscle relaxants, hormonal contraceptives, and hormone replacement therapy was frequent but did not increase over the 10 study years.

The estimated prevalence of depression increased from 4.7% in patients taking no medications with depression as a labeled adverse effect to 6.9% in those taking 1 medication (p=0.002), 9.5% for those taking 2 (p<0.001), and 15.3% for those taking ≥3 medications (p<0.001). A similar trend was seen for patients taking increasing numbers of medications with suicidal symptoms as potential adverse effects. Most of the combinations associated with depression involved the beta-blockers atenolol or metoprolol, the narcotic hydrocodone, or the anticonvulsant gabapentin. Use of multiple medications without depression as an adverse effect was not associated with depression risk, compared with no medication use. The associations persisted in analyses that excluded users of psychotropic drugs, suggesting

the association was not dependent upon the underlying psychiatric diagnosis.

Discussion: The study population reported using >200 different drugs with depression or suicidal symptoms as a labeled adverse effect. Some of these drugs, including proton pump inhibitors and emergency contraceptives, are also available over the counter, and product labeling does not always include full information about adverse effects. Furthermore, commonly used screening instruments for depression do not include evaluation of prescribed medications that have depression as a potential adverse effect.

Qato D, Ozenberger K, Olfson M: Prevalence of prescription medications with depression as a potential adverse effect among adults in the United States. *JAMA* 2018:319 (June 12):2289–2298. doi 10.1001/jama.2018.6741. From the University of Illinois College of Pharmacy, Chicago; and other institutions. **Funded by the Robert Wood Johnson Foundation; and other sources. Two of 3 study authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

Common Drug Trade Names*: atenolol—*Tenormin*; gabapentin—*Neurontin*; hydrocodone—*Hysingla*, *Zohydro*; metoprolol—*Lopressor

Anticholinergics and Dementia Risk

Exposure to anticholinergic antidepressant, antiparkinsonian, and urological drugs was associated with an increase in the incidence of dementia in a population-based study. Increased risk for several other anticholinergic categories could not be ruled out.

Methods: The study was based on data from the U.K.'s Clinical Practice Research Datalink, which contains primary-care records for >11 million patients. Case patients were aged ≥65 years and had received a diagnosis of dementia between 2006 and 2015. Each was matched with up to 7 control patients based on gender, age, and other factors. An anticholinergic drug exposure period was defined as a prescription lasting ≥1 year and ending ≥4 years before the date of dementia diagnosis. Anticholinergic drugs were classified according to the 3-point Anticholinergic Cognitive Burden (ACB) scale, based on serum anticholinergic activity, blood-brain penetration, and known associations with delirium. Drugs with serum anticholinergic activity or affinity for muscarinic receptors, but without known clinically relevant negative cognitive effects, are assigned an ACB score of 1 (possibly anticholinergic). Drugs with established and clinically relevant anticholinergic effects are assigned a score of 2, and drugs that meet those criteria and also have reported associations with delirium are assigned a score of 3. Drugs were further classified according to indication, and exposures were quantified by the defined daily dose, based on average maintenance doses. The analysis was adjusted for covariates suspected to be linked to dementia incidence and many other factors.

Results: The study population consisted of nearly 41,000 patients with dementia and >280,000 controls. Patients had a median age of 83 years at the index date (diagnosis of dementia). The median drug exposure period was >7 years.

During the anticholinergic drug exposure period, 35% of cases and 30% of controls were given a prescription for a drug with an ACB score of 3. The most frequently prescribed ACB-3 drugs were amitriptyline (29%), dosulepin or dothiepin (16%), paroxetine (8%), oxybutynin (7%), and tolterodine (7%). Use of drugs with an ACB score of 2 was rare, and use of drugs with an ACB score of 1 was near-universal. After adjustment, each ACB category was associated with a significant increase in risk for dementia. (See table.) A dose-response relationship was evident for drugs with an ACB

Odds ratios* for dementia by ACB score

ACB score	Incidence of dementia		Adjusted odds ratio†
	% of cases	% of controls	
0	10.5%	12.8%	1.00 (reference)
1	89.4%	87.1%	1.11
2	3.5%	2.8%	1.10
3	35.5%	30.4%	1.16
ACB-3 drug class			
Anti-depressant	21.6%	17.9%	1.13
Anti-parkinsonian	0.7%	0.3%	1.45
Urologic	8.0%	5.9%	1.23

†Odds ratios are adjusted for covariates present at start of the drug exposure period

score of 2 or 3. When drugs were analyzed by indication, significant risk of dementia was associated with ACB-3 anticholinergics prescribed as antidepressants, antiparkinsonian agents, and urologic treatments. Associations were also positive for ACB-2 antiparkinsonian drugs and for ACB-1 antidepressants. Anticholinergic antidepressants were consistently associated with dementia across the board, and these associations persisted after controlling for the presence and severity of depression. Gastrointestinal drugs had a negative association with dementia.

Exposure times were also classified in 3 different periods: 4–10, 10–15, and 15–20 years before the index date. Associations for drug classes with an ACB score of 3 were consistent across all of these timespans, with no decrease when used 15–20 years in the past. In contrast, associations of dementia with drugs with an ACB-1 or 2 rating were more apparent closer to the index date.

Discussion: The study included a 4-year diagnostic lag designed to reduce the chances that the anticholinergic drugs were prescribed for early or prodromal symptoms of dementia. The present findings suggest that the relationship of anticholinergic drugs to dementia is specific to the drugs, not the underlying conditions that they treat; however, a link to underlying disorders other than dementia cannot be ruled out. The observed class-specific effects may be related to differential ability of drugs to cross the blood-brain barrier.

Richardson K, Fox C, Maidment I, Steel N, et al: Anticholinergic drugs and risk of dementia: case-control study. *BMJ* 2018; doi 10.1136/bmj.k1315. From the University of East Anglia, Norwich, U.K.; and other institutions. **Funded by the Alzheimer's Society. Four of 16 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: amitriptyline (not available in the U.S.)—*Elavil*; dosulepin/dothiepin (not available in the U.S.)—*Prothiaden*; oxybutynin—*Ditropan*; paroxetine—*Paxil*; tolterodine—*Detrol

***See Reference Guide.**

Reference Guide

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

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

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

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Starting with the next issue, the delivery of *Primary Care Drug Alerts* will be 100% electronic. The content of the newsletter will be unchanged; only the method of delivery will change.

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PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Important Reminder . . . Delivery of *Primary Care Drug Alerts* is now 100% electronic.

EpiPen Availability

The start of the school year typically results in increased demand for epinephrine auto-injectors (*EpiPens*). However, in certain areas of the U.S., availability is limited due to regional supply disruptions and manufacturing issues. To mitigate potential shortages, the FDA has extended the expiration dates by an additional 4 months for specific lots of 0.3-mg products that have expired or are close to expiring.[1] In addition, the first generic *EpiPen* has received FDA approval for emergency treatment of allergic reactions, including anaphylaxis. The generic version will be available in 0.15 and 0.3 mg strengths.[2]

[1]FDA in Brief: FDA takes additional action to mitigate shortages of EpiPen by extending expiration date for specific lots of medication. Available at https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm617724.htm.

[2]FDA News Release: FDA approves first generic version of EpiPen. Available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm617173.htm.

Essure Contraceptive Market Withdrawal

Following reports of serious adverse events associated with its use and FDA action including boxed warnings and restricted prescribing, Bayer Pharmaceuticals has announced that its permanent birth control device *Essure* will be removed from the U.S. market effective December 31, 2018. The device consists of coils that are inserted into the fallopian tubes, creating a blockage that prevents the passage of an egg from the ovary. The *Essure* device has been associated with persistent pain, uterine and/or fallopian tube perforation, and coil migration into the pelvis or abdomen.

FDA News Release: Statement from FDA Commissioner Scott Gottlieb, M.D., on manufacturer announcement to halt Essure sales in the U.S.; agency's continued commitment to postmarket review of Essure and keeping women informed. Available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm614123.htm.

Lasmiditan for Migraine

A new class of antimigraine drugs, the ditans, target the 5-HT_{1F} serotonin receptor, which is not involved in vasoconstriction, giving them the potential to avoid the primary safety issue associated with triptans.

Triptans lack many of the adverse effects of ergot alkaloids—the first-developed specific antimigraine agents—but their use is limited by their potential to cause cerebral and peripheral vasoconstriction and they are contraindicated in migraine patients with cardiovascular or cerebrovascular disease, uncontrolled hypertension, or particular forms of hemiplegic migraine. 5-HT_{1F} receptors are widely expressed in the central nervous system, including the main regions involved in migraine pathophysiology, and in central and peripheral sensory trigeminal neurons. 5-HT_{1F} receptors are also expressed in cerebral blood vessels, although at low concentrations and without vasoconstrictor properties, and their expression is very low in coronary arteries and absent in the heart.

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Of several 5-HT_{1F} receptor agonists in development, only lasmiditan is currently in clinical trials. In preclinical studies, lasmiditan had very low cross-reactivity with other 5-HT receptor subtypes, had no affinity for other monoamine receptor subtypes that regulate vascular tone, and was shown to cross the blood-brain barrier, where it may dampen the activation of neurons in the trigeminal nucleus caudalis, currently thought to be the main region involved in migraine. Lasmiditan was evaluated in 2 phase II placebo-controlled trials: 1 evaluating a range of intravenous doses (2.5–45 mg) in 130 patients treated in hospital during a migraine attack, and the other evaluating oral lasmiditan (50, 100, 200, or 400 mg) in 534 patients who self-administered the drug at home. All lasmiditan doses significantly improved headache at 2 hours, compared with placebo.

Lasmiditan has also been evaluated in 3 phase III clinical trials. In the first to be completed, >2000 patients with disabling migraine were randomly assigned to oral lasmiditan (100 or 200 mg) or placebo. Both doses were superior to placebo at relieving headache within 2 hours of treatment. The second trial also enrolled >2000 patients and differed only by also including a 50-mg dose. Two hours after treatment, the proportion of patients free of migraine pain was 29% for 50 mg lasmiditan (p=0.003), 31% for 100 mg (p<0.001), and 39% for 200 mg (p<0.001), compared with 21% for placebo. A third study is currently enrolling patients.

Combining observations from all of the trials, lasmiditan is reportedly well tolerated, with no serious adverse events and no important changes in vital signs, ECG, or hematologic or clinical chemistry parameters. The most common adverse effects are dizziness and paresthesia, followed by drowsiness and somnolence. Lasmiditan did not cause QT prolongation or triptan-like chest symptoms in healthy study subjects. Also, the headache relief obtained at 2 hours after receiving 20 mg intravenous or 400 mg oral lasmiditan is comparable to that reported with subcutaneous or oral sumatriptan (*Imitrex*).

Vila-Pueyo M: Targeted 5-HT1F therapies for migraine. *Neurotherapeutics* 2018;15 (April):291–303. doi 10.1007/s13311-018-0615-6. From King's College London, U.K. **Source of funding not stated. The author declared no competing interests.**

Plazomicin for UTI

The new intravenous antibiotic plazomicin (*Zemdri*) has received FDA approval for the treatment of complicated urinary tract infections, including pyelonephritis caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Enterobacter cloacae*, in patients who have limited or no alternative treatment options. Approval was also sought for treatment of bloodstream infections; however, due to lack of supporting evidence, approval for that indication was denied.

FDA Approves Plazomicin (Zemdri) for Urinary Tract Infections. Medscape: June 26, 2018. Available at https://www.medscape.com/viewarticle/898542.

Escitalopram and Cardiac Outcomes

In a placebo-controlled trial, patients who received treatment with escitalopram (*Lexapro*) for depression following acute coronary syndrome (ACS) had a reduced incidence of cardiovascular events in the subsequent 8 years.[1]

Methods: This study was a planned secondary analysis of an escitalopram efficacy trial in patients with ACS. Potential patients were hospitalized for ACS at a central hospital in South Korea, treated by study cardiologists, and screened for depression within 2 weeks of admission. After further diagnostic evaluation by a study psychiatrist, patients who met criteria for minor or major depressive disorder were offered random assignment to escitalopram or placebo for 24 weeks of double-blind treatment. Previously published primary study results indicated that escitalopram was significantly superior to placebo for the principal outcome of depression remission.[2] The focus of the present analysis is major adverse cardiac events (MACE), a composite of cardiovascular death, all-cause mortality, myocardial infarction (MI), and percutaneous coronary intervention.

Results: More than 4800 patients with ACS were screened for depression, 1152 underwent depression screening, 446 received a diagnosis of depression, and 300 were included in the randomized trial. Participants were followed for a mean of 8 years (range, 5–11 years). During follow-up, MACE occurred in 41% of the escitalopram group, compared with 54% of the placebo group (hazard ratio [HR],* 0.69; p=0.03). This difference was entirely accounted for by MIs (HR, 0.54; p=0.04). The treatment groups did not differ in rates of all-

cause mortality, cardiac death, or percutaneous procedures. After adjustment for age, gender, and cardiac factors (e.g., hypertension, smoking, history of ACS, left ventricular ejection fraction), regardless of treatment group, patients in whom depression remitted had significantly lower hazards of MACE (HR, 0.52; p=0.001), all-cause mortality (HR, 0.46; p=0.01), and percutaneous procedures (HR, 0.48; p=0.05) compared with those without remission.

Discussion: These observations conflict with 2 previous, large trials of antidepressant treatment in patients with ACS, which found antidepressant treatment did not improve depression or long-term cardiac outcomes.[3,4] Escitalopram may modify the course of ACS through reduction of depressive symptoms or via positive effects on levels of brain-derived neurotrophic factor and proinflammatory cytokines and normalization of autonomic and platelet dysfunction.

[1]Kim J-M, et al: Effect of escitalopram vs placebo treatment for depression on long-term cardiac outcomes in patients with acute coronary syndrome: a randomized clinical trial. *JAMA* 2018:320 (July 24–31):350–357. From Chonnam National University Medical School, Republic of Korea; and other institutions. **Funded by the National Research Foundation of Korea; and other sources. One of 15 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Kim J, et al: Escitalopram treatment for depressive disorder following acute coronary syndrome: a 24-week double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry* 2015;76:62–68.

[3]vanMelle J, et al: MIND-IT Investigators: effects of antidepressant treatment following myocardial infarction. *British Journal of Psychiatry* 2007;190:460–466.

[4]Glassman H, et al: Psychiatric characteristics associated with long-term mortality among 361 patients having an acute coronary syndrome and major depression: seven-year follow-up of SADHART participants. A*rchives of General Psychiatry* 2009;66:1022–1029.

***See Reference Guide.**

Statin-Associated Gynecomastia

According to the results of a population-based study, statin use is associated with increased risk of gynecomastia. Although it is labeled as a rare adverse effect for only a few statins, the current study suggests it is not uncommon.

Background: Statins may cause gynecomastia by reducing the availability of cholesterol for androgen synthesis, resulting in reduced testosterone levels. Previous evidence of the link between statins and gynecomastia consists only of case reports and case series, and no previous information about the magnitude of risk exists.

Methods: The study population comprised a random sample of >9 million men included in a large U.S. health claims database between 2006 and 2016. Each man with a new diagnosis of gynecomastia was matched for age and follow-up time with 10 controls who did not experience gynecomastia. Statin use before the diagnosis (or a corresponding index date in controls) was stratified as current, recent, or past. As a quality measure, risk was also analyzed for finasteride, a drug known to cause gynecomastia.

Results: The cohort included 6147 men with gynecomastia and 61,470 controls. Risk of gynecomastia was increased with statin use during the past year, compared with non-use; and it was increased for all 3 exposure windows. (See table.) As expected, risk was also increased with finasteride.

Risk of gynecomastia in statin users and users of finasteride (active control)

	Adjusted rate ratio*
Any statin use	1.23
Current (past 1–30 days)	1.19
Recent (31–60 days)	1.38
Past (61–365 days)	1.20
Any finasteride use	3.71

Discussion: While resolution of gynecomastia could not be evaluated in the present study, the previously published case reports suggest it resolved with discontinuation of the offending statin and did not recur when an alternative statin was prescribed. These reports suggest risk of gynecomastia may be higher with the more potent statins such as atorvastatin or rosuvastatin.

Skeldon S, et al: Statin medications and the risk of gynecomastia. *Clinical Endocrinology* 2018; doi 10.1111/cen.13794. From the University of Toronto, Canada; and other institutions. **Funded by the British Columbia Provincial Health Services Authority. The authors declared no competing interests.**

Common Drug Trade Names*: atorvastatin—*Lipitor*; finasteride—*Propecia, Proscar*; rosuvastatin—*Crestor

***See Reference Guide.**

Evening-Dosed Methylphenidate Approval

A new extended-release methylphenidate formulation (*Jornay PM*), designed to be administered in the evening in order to control early morning ADHD symptoms, has received FDA approval for use in patients aged ≥6 years. The proprietary delivery system of *Jornay PM* delays initial methylphenidate release for up to 10 hours, followed by a controlled release throughout the day. Administration timing can be adjusted between 6:30 and 9:30 PM to optimize early-morning and later-day symptom control. In clinical trials, adverse effects of *Jornay PM* were generally those expected with methylphenidate including appetite suppression, weight loss, insomnia, dizziness, and increased blood pressure. Additional adverse reactions specific to *Jornay PM* included headache, psychomotor hyperactivity, and mood swings. Commercial availability of *Jornay PM* is expected in the early half of 2019.

Ironshore Pharmaceuticals announces FDA approval of Jornay PM™ (methylphenidate) extended-release capsules CII for the treatment of ADHD [press release]. George Town, Cayman Islands; Ironshore Pharmaceuticals: August 9, 2018. Available at http://www.ironshorepharma.com/pdf/Ironshore-Announces-FDA-Approval-JORNAY-PM.pdf.

Timolol Eyedrops for Migraine

According to the results of a small pilot study, timolol eyedrops (*Timoptic*) may be an effective treatment for acute migraine.

Background: Several oral beta blockers are FDA approved for migraine prevention, but gradual absorption and first-pass metabolism limit their usefulness in acute migraine attacks. In contrast, maximal plasma concentrations are achieved within 15 minutes with timolol eyedrops, making them a potentially attractive option for acute migraine attacks.

Methods: Study subjects were 10 adults who met International Headache Society criteria for migraine with or without aura who were recruited from neurology and ophthalmology clinics. Participants were randomized to receive 0.5% timolol eyedrops or an artificial-tears placebo and instructed to administer 1 drop in each eye at migraine onset and again at 30 minutes. After 2 months, patients were crossed over to the alternate treatment. Migraine severity and patients' perception of the effectiveness of medication were rated on 4-point scales. At study end, patients were asked whether they would like to continue using timolol in place of or in addition to their previous abortive medications.

Results: During the study period, 198 migraine episodes were treated with timolol or placebo. Although migraine occurrence and severity did not differ between the treatment periods, patients rated the overall effectiveness of timolol at 2.4 on the 4-point scale, compared with 1.4 for placebo. At study exit interviews, 25% of patients indicated that they would like to use the timolol drops in place of their previous abortive medication and 55% reported they would like to use the drops in addition to other medications. No timolol-related adverse effects were reported during the study.

Discussion: Because of the very small sample size, lack of blinding, and an imperfect placebo (artificial tears can cause a burning sensation), no strong conclusions can be drawn from these study results. They do, however, suggest that additional study may be warranted.

Cossack M, et al: Timolol eyedrops in the treatment of acute migraine attacks: a randomized crossover study. *JAMA Neurology* 2018;75 (August 1):1024–1025. From the University of Missouri–Kansas City School of Medicine. **Source of funding not stated. The authors declared no competing interests.**

Reference Guide

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

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.

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XXXIX / September 2018 / Number 9 www.alertpubs.com

Important Reminder . . . Delivery of *Primary Care Drug Alerts* is now 100% electronic.

SGLT2 Inhibitors and Necrotizing Fasciitis

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

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

Safety of Switching to Sulfonylureas

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

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

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

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

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

***See Reference Guide.**

Antibody Treatment for Episodic Migraine

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

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

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

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

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

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

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

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

***See Reference Guide.**

Aspirin Benefits and Body Weight

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

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

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

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

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

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

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

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

***See Reference Guide.**

Bleeding Risk with Antidepressants

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

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

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

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

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

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

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

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

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

***See Reference Guide.**

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

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

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

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

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Baloxavir Approved for Influenza Treatment

A new antiviral treatment, baloxavir marboxil (*Xofluza*), has received expedited FDA approval through the Priority Approval Process for the treatment of acute uncomplicated influenza in patients aged ≥12 years who have been symptomatic for ≤48 hours. Safety and efficacy of the agent were demonstrated in 2 controlled trials, comprising >1800 patients, in which patients who received baloxavir experienced a shorter time to alleviation of symptoms than those who received placebo. In 1 trial, time to symptom alleviation did not differ between baloxavir and an alternate antiviral. Although there are now several antivirals approved to treat emergent influenza, none are considered a substitute for prophylactic vaccination.

FDA News Release: FDA approves new drug to treat influenza. Available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624226.htm.

Psychiatric Effects of Oseltamivir

Prophylactic use of oseltamivir (*Tamiflu*) is associated with a small but statistically significant increase in psychiatric adverse events, according to an analysis of adverse-event data from clinical study reports.[1]

Background: Following the reports of 2 suicides in adolescents who received treatment with oseltamivir, as well as >100 reports of neuropsychiatric adverse effects with the drug, the FDA issued an alert in 2006 warning that patients should be carefully monitored for abnormal behavior during treatment.[2] Analyses of neuropsychiatric adverse effects conducted since then, including several Cochrane Reviews based on published trials, have been inconclusive. Clinical study reports—produced by manufacturers seeking regulatory approval of drugs and containing individual patient-level data on adverse events with a high level of detail, including duration and severity—have recently been made available to researchers by the European Medicines Agency and by some manufacturers. To further clarify the risk of neuropsychiatric effects with prophylactic oseltamivir use, the present study evaluated adverse events in clinical study reports.

Methods: The present analysis was based on clinical study reports from 4 placebo-controlled trials of oseltamivir. The analysis was limited to prophylactic trials to avoid counting any psychiatric symptoms related to existing influenza. Data on clinical adverse events classified under the psychiatric system organ class, representing a change from baseline that occurred after study treatment began, were collected from the reports irrespective of whether study investigators believed it was related to oseltamivir treatment. The primary outcome of the analysis was the proportion of days patients suffered from psychiatric adverse events. This method allowed grouping of multiple adverse events, regardless of their

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nature—e.g., days suffering from depression and from anxiety by a single patient could be combined. In a secondary analysis, adverse events were weighted based on severity.

Results: The main analysis was based on combined data from 1 trial conducted in adults (n=1559) and 2 trials in elderly nursing-home residents (n=920), all of whom received oseltamivir or placebo for 6 weeks. An additional short-term trial was conducted in adults and adolescents (n=955) who received treatment for 7 days. Psychiatric adverse events were not reported in the journal publications from any of the trials.

A total of 35 psychiatric adverse events (10 of depression) occurred with oseltamivir and 15 with placebo. Excluding the 7-day trial, which reported very few events, the proportion of days patients suffered from a psychiatric adverse event was significantly greater with oseltamivir than placebo (odds ratio,* 4.12). There was little difference between oseltamivir and placebo for less severe adverse events, but severe events occurred on more days with oseltamivir (odds ratio, 34.5). However, the absolute difference between oseltamivir and placebo was small: For every 290 days of treatment, there was 1 additional day of suffering from a psychiatric adverse event of any level of severity.

Discussion: The increasing chance of more severe adverse events with oseltamivir suggests a causal relationship. Although the relative effect of oseltamivir is very high for severe events, the absolute increase is small in the context of all patients included in the trials.

[1]Jones M, Tett S, Del Mar C: Psychiatric adverse events in oseltamivir prophylaxis trials: novel comparative analysis using data obtained from clinical study reports. *Pharmacoepidemiology and Drug Safety* 2018; doi 10.1002/pds.4651. From the University of Queensland, Brisbane; and Bond University, Gold Coast, Australia. **This research was conducted without specific funding. All 3 authors disclosed potentially relevant financial relationships.**

[2]Maxwell S: Tamiflu and neuropsychiatric disturbance in adolescents: the case is not proved but caution is advisable. *British Medical Journal* 2007;334 (June 16): 1232–1233.

***See Reference Guide.**

Expanded Gardasil Use

The human papillomavirus (HPV) 9-valent vaccine, recombinant (*Gardasil 9*) indication has been expanded to include women and men aged 27–45 years. Effectiveness of *Gardasil 9* was evaluated in >3000 women in that age range who were followed for an average of 3.5 years. The vaccine was 88% effective at preventing the combined endpoint of persistent infection, genital warts, vulvar and vaginal precancerous lesions, cervical precancerous lesions, and cervical cancer related to HPV types covered by the vaccine. Effectiveness of the vaccine in men is inferred from this data in women, along with efficacy data in younger males.

FDA News Release: FDA approves expanded use of Gardasil 9 to include individuals 27 through 45 years old. Available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm622715.htm.

Galcanezumab for Migraine Prevention

In a phase III trial, the calcitonin gene-related peptide (CGRP) antagonist galcanezumab reduced the frequency of episodic migraines.[1] The agent also reduced migraine-related disability and improved patient functioning.

Methods: The multicenter trial enrolled patients with a ≥1-year history of migraine with onset before age 50 years, who had experienced ≥2 migraine attacks with 4–14 migraine days during the month before the baseline observation period. Patents who had failed to respond to ≥3 classes of migraine preventive treatments were excluded from the study. Patients who had received botulinum toxin were required to have discontinued treatment ≥4 months before screening, and all other migraine preventive treatments were subject to a washout before the baseline observational month. Patients were randomly assigned to receive galcanezumab by subcutaneous injection (either 120 mg per month with a 240-mg loading dose or 240 mg per month) or placebo injections. The primary efficacy outcome was overall mean change from baseline in monthly headache days during 6 months of double-blind treatment.

Results: A total of 858 patients were randomized and received ≥1 injection. At baseline, patients had a mean of 9.1 monthly headache days, 5.7 monthly migraine attacks, and 60.6 monthly headache hours. The study dropout rate was 18%, but <5% of the patients withdrew because of adverse events, with similar proportions in the medication and placebo groups.

During treatment, both doses of galcanezumab were associated with about 2 fewer migraine days per month than placebo (p=0.02). About 60% of patients who received galcanezumab achieved a

≥50% response, compared with 39% of the placebo group (p=0.02). Rates of 75% and 100% response were nearly 40% and about 15%, respectively, with galcanezumab, compared with 6–19% with placebo (p=0.02). The migraine reductions with galcanezumab translated to approximately 8 weeks of additional migraine-free days per year, on average. The onset of action was within the first month of treatment.

Galcanezumab was also associated with superior outcomes measured using the Migraine-Specific Quality of Life Questionnaire, the Patient Global Impression of Severity, and the Migraine Disability Assessment. The active agent was associated with about 30 fewer migraine hours per month on average. There was no significant difference between the 2 galcanezumab dosage groups for any outcome.

Injection site pain was the most frequently reported adverse effect in all groups, including placebo. Rates of injection site erythema, pruritus, and reaction were higher in patients receiving the active agent, but these reactions were usually mild or moderate in severity.

Discussion: The recent FDA approval of galcanezumab was based in part on the results of this study.[2] Galcanezumab joins 2 other recently approved anti-CGRP agents, erenumab and fremanezumab, as options for migraine prevention.

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

[1]Stauffer V, et al: Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. *JAMA Neurology* 2018; doi 10.1001/jamaneurol.2018.1212. From Eli Lilly and Company, Indianapolis, IN; and other institutions. **Funded by Eli Lilly and Company. All study authors disclosed financial relationships with commercial sources including Eli Lilly and Company.**

[2]Brauser D: FDA Greenlights Galcanezumab (*Emgality*) for Migraine Prevention. Available at https://www.medscape.com.

Common Drug Trade Names*: erenumab—*Aimovig*; fremanezumab—*Ajovy*; galcanezumab—*Emgality

***See Reference Guide.**

Lisdexamfetamine: Raynaud's Phenomenon

A 16-year-old boy presented with a 3-year history of ADHD that had been temporarily controlled with immediate-release methylphenidate and then an extended-release preparation. Neither agent produced significant adverse effects. When symptom control waned with the extended-release preparation, the patient was switched to 30 mg/day lisdexamfetamine. Symptom control improved, but after 1 week, the patient began to experience symptoms of secondary Raynaud's phenomenon (i.e., pallor and cyanosis of his fingers followed by redness and tingling). Episodes occurred 1–2 times per day, lasted 5–10 minutes each, and were distressing to the patient. He underwent screening for collagen vascular diseases, but no physical cause was uncovered. Because secondary Raynaud's phenomenon has been described with other stimulants, the lisdexamfetamine was stopped and replaced with atomoxetine. The Raynaud's episodes resolved gradually over the subsequent 2 weeks.

According to the Naranjo probability scale,* the association between lisdexamfetamine and Raynaud's phenomenon was probable. This appears to be the first reported case of Raynaud's associated with lisdexamfetamine. Although the reaction is uncommon, clinicians should be aware of the potential as it could adversely affect medication compliance.

Gnanavel S: Lisdexamfetamine and secondary Raynaud's phenomenon [letter]. *Primary Care Companion for CNS Disorders* 2018;20(5):17l02240. From Child and Adolescent Mental Health Services, Northumberland; and Tyne and Wear NHS Foundation Trust, Morpeth, U.K. **The author declared no competing interests.**

Common Drug Trade Names*: atomoxetine—*Strattera*; lisdexamfetamine—*Vyvanse*; methylphenidate, extended-release—*Concerta*; methylphenidate, immediate-release—*Ritalin

***See Reference Guide.**

Perimenopausal Depression Guidelines

Although perimenopause has been recognized as a window of vulnerability for the development of both depressive symptoms and major depressive episodes, clinical recommendations are lacking. The North American Menopause Society and the National Network of Depression Centers Women and Mood Disorders Task Group convened an expert panel to review the literature on depressive symptoms and disorders in midlife women and to develop guidelines addressing epidemiology, clinical presentation, antidepressant treatment, hormone therapy, and other therapies for affected women.

According to the panel, midlife depression in women commonly presents with the classic depressive symptoms, combined with menopausal complaints such as vasomotor symptoms,

sleep and sexual disturbances, weight and energy changes, and concentration problems. Often the situation is further complicated by bereavement and other losses and stressors such as career shifts or caring for an aging parent. Contrary to previous beliefs, grown children leaving the home (the "empty nest") is believed to have positive rather than negative effects on mood.

Antidepressants, cognitive behavioral therapy, and other proven psychotherapies should remain first-line treatment options for depression during menopause. Women with a history of successfully treated depression should receive the previously effective agent. Desvenlafaxine, the only agent that has been investigated specifically in perimenopausal women, has shown efficacy in short-term trials. Small open-label studies have shown SSRIs (e.g., citalopram, escitalopram, fluoxetine, sertraline, vortioxetine), SNRIs (e.g., desvenlafaxine, duloxetine, venlafaxine), and mirtazapine improved mood in perimenopausal women and also had positive effects on vasomotor symptoms, sleep, and other menopausal symptoms. Bupropion is often prescribed because it produces less weight gain, sexual dysfunction, and sleepiness than other agents.

Some evidence suggests concomitant estrogen can improve response to antidepressant drugs, but it is not FDA approved to treat depression. Hormonal contraceptives may improve mood in women approaching menopause. This and other evidence suggests there may a window of opportunity with estrogen that does not extend into the postmenopausal period. The available evidence is insufficient to recommend herbal or other alternative remedies for perimenopausal depression.

Maki P, et al: Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *Menopause: The Journal of the North American Menopause Society* 2018; doi 10.1097/GME.0000000000001174. From the University of Illinois at Chicago; and other institutions. **These guidelines were created without funding. Five of 11 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: bupropion—*Wellbutrin*; citalopram—*Celexa*; desvenlafaxine—*Pristiq*; duloxetine—*Cymbalta*; escitalopram—*Lexapro*; fluoxetine—*Prozac*; mirtazapine—*Remeron*; sertraline—*Zoloft*; venlafaxine—*Effexor*; vortioxetine—*Trintellix

Lower-Dose EpiPen Alternative

A new lower-dose version of the prefilled epinephrine syringe (*Symjepi*) has received FDA approval for use in children weighing between 33 and 65 lbs. The new dosage strength, 0.15 mg, joins the 0.3-mg dose approved in 2017 for children weighing <66 lbs. Both strengths are indicated for the emergency treatment of allergic reactions including anaphylaxis.

FDA OKs pediatric version of alternative to EpiPen (*Symjepi*). Medscape: September 28, 2018. Available at www.medscape.com.

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Naranjo Probability Scale: A 10-point scale used to determine the likelihood that an adverse reaction is caused by an implicated medication. Based on scores, associations are considered doubtful, possible, probable, or highly probable.

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).

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PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Important Reminder . . . Delivery of *Primary Care Drug Alerts* is now 100% electronic.

Safety of Long-Acting β2-Agonists

In a combined analysis of FDA-mandated manufacturer-sponsored trials, long-acting β2-agonists (LABAs) were not found to increase risk of serious asthma-related events. This analysis supports the FDA's decision to remove the boxed warning from combination therapies with a LABA plus an inhaled glucocorticoid for asthma treatment.

Background: Safety concerns initially arose from a large postmarketing trial in which LABA use was associated with increased risk of death. Subsequent meta-analyses had mixed findings, and the FDA required the 4 companies that market LABAs to perform prospective, randomized safety studies.

Methods: An independent joint oversight committee analyzed combined data from the 4 trials. Each trial had a target enrollment of nearly 12,000 adolescent and adult patients with persistent asthma. Participants received treatment for 26 weeks with randomly assigned combination therapy (a LABA plus an inhaled glucocorticoid) or the glucocorticoid alone. The primary study outcome was a composite of asthma-related intubation or death. The secondary safety outcome, serious asthma-related events, was a composite consisting of asthma-related hospitalization, intubation, or death

Results: The final sample consisted of about 18,000 patients in each group. During the study period, 4 patients experienced a primary study outcome: 3 asthma-related intubations (1 in the combination group) and 2 asthma-related deaths (both in the combination group). Because there were so few events, between-group comparisons could not be done. Rates of the secondary safety outcome did not differ between the groups: 119 in the combination group and 108 in the comparison group (relative risk,* 1.09). The rate of asthma exacerbation was 9.8% in the combination therapy group and 11.7% in the comparison group, suggesting superior efficacy of combined therapy (relative risk, 0.83; p<0.001).

Discussion: The present results can be widely generalized, not only because of the representative study population, but also because of the use of several different drugs, formulations, and glucocorticoid doses. The observations support current treatment guidelines, which recommend the use of LABAs with glucocorticoids but not as monotherapy.

Busse W, et al: Combined analysis of asthma safety trials of long-acting 2-agonists. *NEJM* 2018;378 (June 28):2497–2505. doi 10.1056/NEJMoa1716868. From the University of Wisconsin School of Medicine and Public Health, Madison; and other institutions. **Funded by ICON Clinical Research; and other sources. Four of 7 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

GLP-1 Analogues for Weight Loss

Semaglutide was an effective weight loss agent across a range of doses in a phase II clinical trial in nondiabetic patients with obesity.[1] The active control medication—liraglutide, another GLP-1

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analogue—also resulted in weight loss. According to an accompanying editorial,[2] prophylactic use of GLP-1 receptor agonists in overweight adults may improve health by reducing weight and preventing diabetes onset.

Methods: The multicenter study (8 countries, 71 sites) enrolled nondiabetic adults with a body mass index (BMI) of ≥30 who had undergone ≥1 unsuccessful nonsurgical weight-loss attempt and were free of depression. To enroll enough men, enrollment of women was capped at 70%. Participants were randomly assigned to receive double-blind treatment with: 1 of 5 dosages of subcutaneous semaglutide (0.05–0.4 mg/day); 3 mg/day subcutaneous liraglutide; or placebo. Semaglutide was started at 0.05 mg/day and increased every 4 weeks to reach the target dose in each of the 5 patient groups. Two additional fast-escalation groups had dosage increases every 2 weeks to 0.3 and 0.4 mg/day. All participants received counseling about nutrition and physical activity. The primary study endpoint was the percent change from baseline in body weight after 52 weeks of treatment.

Results: A total of 957 patients (65% women) participated in the study, with about 100 in each of the drug and dosage groups. Patients had a mean baseline BMI of 39. A total of 180 patients (19%) discontinued treatment before the end of the study year, primarily because of adverse events.

Patients in the dosage groups that received semaglutide on the 4-week titration schedule lost between 6.0% and 14% of their initial weight on average; weight loss was dose dependent. The rapid-escalation groups lost 11% (0.3 mg/day) and 16% (0.4 mg/day) of their initial weight on average. Patients receiving liraglutide lost 8% of their initial weight, and the placebo group lost 2%. All active treatment groups lost significantly more weight than placebo at 1 year. Patients receiving semaglutide had larger categorical weight losses than placebo: 5–35% of the semaglutide groups lost ≥20% of their initial weight, compared with 6% of the liraglutide group and 2% of the placebo group. Semaglutide was also associated with improvement in glucose metabolism and most anthropometric outcomes, as well as some lipid parameters. All active treatments were associated with reductions in systolic and diastolic blood pressure. Adverse effects of semaglutide and liraglutide were generally mild and transient, consisting largely of gastrointestinal effects. Serious adverse events were uncommon and not dose related.

Discussion: Liraglutide has been approved for weight reduction in the U.S. at the 3.0-mg dosage used in this study, higher than the dosage used to treat type 2 diabetes. Semaglutide induces at least comparable weight loss, which the investigators attribute to its appetite-suppressant effects. At the higher doses, weight loss continued throughout the year of treatment, in contrast with other FDA-approved weight loss medications whose effects plateau. No firm conclusion could be drawn about the efficacy and tolerability of rapid dose titration.

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

[1]O'Neil P, et al: Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet* 2018;392 (August 25):637–649. From the Medical University of South Carolina, Charleston; and other institutions. **Funded by Novo Nordisk A/S. All study authors disclosed relevant financial relationships with commercial sources, including Novo Nordisk.**

[2]Kluger A, McCullough P: Liraglutide and GLP-1 analogues as weight-loss agents [editorial]. *Lancet* 2018;392 (August 25):615–616. From Baylor Heart and Vascular Institute, Dallas, TX; and other institutions. **The authors declared no competing interests.**

Common Drug Trade Names*: liraglutide—*Saxenda*; semaglutide—*Ozempic

***See Reference Guide.**

New Indication for Dupilumab

The monoclonal antibody dupilumab (*Dupixent*), previously indicated for the treatment of moderate-to-severe atopic dermatitis, has now received FDA approval as an add-on to maintenance therapy for patients aged ≥12 years with moderate-to severe eosinophilic or oral corticosteroid-dependent asthma. Dupilumab, an interleukin (IL)-4 and 13 inhibitor, reduces inflammatory biomarkers that underlie asthma. The agent will be available in prefilled syringes for subcutaneous injection every other week. Injections can be administered in clinic or by patients at home. In clinical trials, the most common adverse effects of dupilumab included injection site reactions, sore throat, and increased eosinophil levels.

FDA Approves Dupilumab for Moderate-to-Severe Asthma. Medscape Oct 22, 2018. Available at www.medscape.com/viewarticle/903761.

Antihypertensive Recalls

The FDA has announced voluntary recalls of several agents containing the angiotensin receptor blockers (ARBs) irbesartan, losartan, and valsartan due to contamination with trace amounts of *N*-Nitrosodiethylamine (NDEA) and possibly *N*-Nitrosodimethylamine (NDMA). The contaminating substances naturally occur in some foods, drinking water, air pollution, and industrial processes and have been classified as a probable human carcinogen. Included in the recall are losartan–hydrochlorothiazide, irbesartan, and agents containing valsartan alone and in combination with amlodipine and hydrochlorothiazide. Information on specifically affected lots is available on the FDA website, and the agency is continuing to test all ARBs for the presence of the contaminants. Patients affected by the recall should not stop their antihypertensive, as abruptly stopping treatment without a replacement agent poses a health risk.

FDA Drug Safety Communication: FDA updates on angiotensin II receptor blocker (ARB) recalls. Available at www.fda.gov/Drugs/DrugSafety/ucm613916.htm.

Common Drug Trade Names*: irbesartan—*Avapro*; losartan–hydrochlorothiazide—*Hyzaar*; valsartan—*Diovan*; valsartan–amlodipine—*Exforge*; valsartan–hydrochlorothiazide—*Diovan HCT

Beta-Blocker Safety in Pregnancy

In a large cohort study, use of beta-blockers during pregnancy was not associated with increased risk of congenital malformations.

Background: Beta-blockers are a first-line therapy for hypertension in pregnancy and are also widely used by nonpregnant hypertensive women of reproductive age. These drugs cross the placenta, and results of some studies in animal models suggest a potential teratogenic effect. A meta-analysis identified increased risk of some malformations, but it included many studies that had numerous flaws, including failure to account for the mother's underlying hypertension.

Methods: Study data were collected from nationwide health registries for women living in the 5 Scandinavian countries who gave birth between 1996 and 2010, and from a U.S. Medicaid database of women who gave birth between 2000 and 2010. The study comparison was restricted to women who had hypertension and who gave birth to a live singleton infant. The analysis also excluded pregnancies with a chromosomal abnormality and those exposed to known teratogens and to other categories of antihypertensive drug, some of which are suspected of teratogenicity. Birth outcomes in >18,000 patients were compared between those who filled a prescription for a beta-blocker during the first trimester and those who received no antihypertensive medication.

Results: Beta-blockers were prescribed for 19% of the Nordic cohort and for 11% of the U.S. cohort. After adjustment for multiple risk factors, beta-blocker use was not associated with an overall increased risk of congenital malformation in either cohort or when the 2 cohorts were pooled (incidence, 5.4% and 4.3% in exposed and unexposed groups, respectively; adjusted relative risk,* 1.07). Analysis of specific malformations with a suspected association (i.e., cardiac malformations, cleft lip/palate, central nervous system malformations) found beta-blocker use was also not associated with higher risk. A separate analysis estimating the potential effects of excluding pregnancies that did not result in a live birth indicated that under the most extreme hypothetical conditions, the relative risk estimate would shift from 1.07 to 1.26 for all malformations.

Discussion: Cardiac malformations are the most commonly occurring of the studied outcomes. The present results were able to rule out large increases in overall malformations as well as cardiac malformations specifically. However, the incidence of the other malformation types (0.1–0.7%) was too low to allow for definitive conclusions, but any increase is likely to be modest.

Bateman B, et al: β-blocker use in pregnancy and the risk for congenital malformations: an international cohort study. *Annals of Internal Medicine* 2018; doi 10.7326/M18-0338. From Brigham and Women's Hospital and Harvard Medical School, Boston, MA; and other institutions. **Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development; and other sources. Four of 15 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Personal Pharmacogenetic Testing Approved

The 23andMe Personal Genome Service Pharmacogenetic Reports test has gained FDA approval for direct-to-consumer sale.[1] The test provides information about genetic variants that may be related to patients' ability to metabolize certain medications. The FDA cautions that these test results do not determine which medications are appropriate for a patient, provide medical

advice, or diagnose any health conditions. Rather, the results should be used to help inform discussions with the patient's healthcare provider.

In a separate news release, the FDA cautions that some genetic tests claim to predict how a person will respond to specific medications.[2] However, these claims have not been reviewed by the FDA and may not be backed by sufficient scientific or clinical evidence. They warn that changing treatment based on the results of these tests could lead to inappropriate decisions and potentially serious health consequences. The agency acknowledges that there are a limited number of cases for which at least some evidence supports a correlation between a genetic variant and drug levels. However, in these cases, the evidence is described in the labeling for approved genetic tests and medications.

[1]FDA News Release: FDA allows marketing of first direct-to-consumer tests that provide genetic risk infor-mation for certain conditions. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnoun cements/ucm551185.htm.

[2]FDA Drug Safety Communication: The FDA warns against the use of many genetic tests with unapproved claims to predict patient response to specific medications. Available at: www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm624725.htm.

Amitriptyline for Chronic Back Pain

In a randomized controlled trial in patients with chronic low back pain, a low dose of the tricyclic antidepressant amitriptyline was associated with reduced disability at 3 months, but not with other significant positive outcomes. Based on these results, the authors conclude that low-dose amitriptyline merits large-scale trials and consideration as an alternative in patients whose only other option is an opioid.

Methods: The trial recruited 146 adults, aged ≤75 years, with chronic nonspecific low back pain lacking a specific cause and present for >3 months. Patients were randomly assigned to receive 25 mg/day amitriptyline or 1 mg/day benztropine, a comparator with similar adverse effect profile but no known effect on low back pain. Outcomes were assessed at 3 and 6 months. The primary efficacy measure was pain intensity at 6 months, measured with a visual analog scale. Disability, the secondary outcome, was measured with the Roland Morris Disability Questionnaire.

Results: At study entry, the mean pain score was 41.6 out of 100. Average pain intensity decreased from baseline to 6 months by 13 points in the amitriptyline group and by 5 points in the control group (p=0.05). After accounting for missing data, the difference was no longer significant. Amitriptyline was associated with significantly reduced disability at 3 months, but not at 6 months. The treatment groups did not differ significantly at 3 or 6 months for any other outcomes—i.e., absence from work, interference with work, global improvement, depression, general health, or fear of movement.

Discussion: Antidepressants are commonly used to treat low back pain, but treatment guidelines are inconsistent. There have been few high-quality studies of low-dose antidepressants. Despite a lack of evidence, low-dose amitriptyline is often used to treat chronic pain, in the absence of depression. The present observations suggest a statistically significant pain reduction might be observed in a trial with a larger sample size.

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

Urquhart D, et al: Efficacy of low-dose amitriptyline for chronic low back pain: a randomized clinical trial. *JAMA Internal Medicine* 2018; doi 10.1001/jamainternmed.2018.4222. From Monash University, Melbourne, Australia; and other institutions. **Funded by the National Health and Medical Research Council, Australia. The authors declared no competing interests.**

Common Drug Trade Names*: amitriptyline—*Elavil*; benztropine—*Cogentin

***See Reference Guide.**

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Relative Risk: The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) group.

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

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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Fluoroquinolones and Aortic Dissection

Following a safety review, the FDA is requiring a new warning about risk for aortic dissection be added to the prescribing information and patient medication guide for all fluoroquinolone antibiotics. The review found both oral and injectable fluoroquinolone use can increase the occurrence of aortic dissections and ruptures of aortic aneurysms, which can lead to serious bleeding or death. Patients at increased risk include those with or at risk for an aortic aneurysm, those with hypertension, high blood pressure, or genetic disorders that involve blood vessel changes (e.g., Marfan syndrome and Ehlers-Danlos syndrome), and the elderly. Fluoroquinolones should not be prescribed for these patients unless there are no other treatment options available.

FDA Drug Safety Communication: FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. Available at www.fda.gov/Drugs/DrugSafety/ucm628753.htm.

Infants' Ibuprofen Recall

Tris Pharma has issued a recall for several lots of 50 mg per 1.25 mL infant's concentrated ibuprofen suspension. The affected lots, sold as Equate, CVS Health, and Family Wellness brands, may have higher than labeled ibuprofen concentrations. Adverse effects of increased ibuprofen doses can include nausea, vomiting, epigastric pain, and diarrhea. Tinnitus, headache, and gastrointestinal bleeding are also possible. Although permanent NSAID-associated renal injury is unlikely, infants—who may be more susceptible to a higher potency level of drug—may be more vulnerable.

FDA Drug Safety Communication: Tris Pharma issues voluntary nationwide recall of infants' ibuprofen concentrated oral suspension, USP (NSAID) 50 mg per 1.25 mL, due to potential higher concentrations of ibuprofen. Available at www.fda.gov/Safety/Recalls/ucm627780.htm.

Gabapentin Abuse

A 51-year-old man with a history of substance-induced mood disorder, as well as opioid, cocaine, and alcohol use disorders, presented to the emergency department following an intentional gabapentin overdose with suicidal intent. His regular medication regimen included sertraline, divalproex, trazodone, and gabapentin. Review of his medication use suggested a pattern of gabapentin abuse characterized by overuse and requests for the medication from different physicians on varying pretexts. On questioning, the patient admitted that for ≥9 months he had been crushing and insufflating 3–4 600-mg gabapentin tablets at 2-hour intervals in bingeing episodes. He described the "high" he achieved as characterized by increased focus, energy, and productivity, followed by a calm/relaxation similar to opioid intoxication. Abrupt discontinuation resulted in withdrawal symptoms. The patient denied misuse of his

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other psychotropic medications, and a urine screen for illicit drugs was negative.

Gabapentin is widely used off label as adjunctive treatment for several psychiatric disorders including bipolar disorder, anxiety, PTSD, and depression. It has also shown potential for treatment of withdrawal and craving in alcohol, benzodiazepine, opioid, and cocaine dependence. The drug is well tolerated, has few interactions with other drugs, and is relatively inexpensive. Because it is presumed to have no abuse potential, it is currently not scheduled as a controlled substance. However, there have been other reports of gabapentin abuse and misuse, mainly among patients with a history of substance abuse and psychiatric comorbidity. The pharmacologic properties that underlie gabapentin's abuse potential are unknown. Increasing rates of diversion, comparable to those with oxycontin, have also been documented. Although the present patient denied "cutting" heroine or buprenorphine with gabapentin, there have been reports of gabapentin being used illicitly in combination with opioids and to potentiate the effects of buprenorphine–naloxone. Gabapentin misuse by patients with opioid use disorder is especially concerning, given the recent increases in opioid-related mortality and evidence linking gabapentin use with increased risk of accidental opioid-related overdose deaths. Prescribers should be aware of the potential for gabapentin abuse in at-risk populations and should closely monitor these patients.

Khalid Z, Hennen M-A, Aldana-Bernier L: Gabapentin abuse by nasal insufflation: a case report [letter]. *Journal of Clinical Psychopharmacology* 2018; doi 10.1097/JCP.0000000000000983. From Rutgers New Jersey Medical School, Newark; and VA NJ Healthcare System, East Orange. **The authors declared no competing interests.**

Common Drug Trade Names*: buprenorphine–*Subutex*; naloxone—*Suboxone*; divalproex—*Depakene, Depakote*; gabapentin—*Neurontin, Gralise*; sertraline—*Zoloft*; trazodone—*Desyrel, Oleptro

Contraceptives and Ovarian Cancer

Combined hormonal contraceptives have been shown to reduce ovarian cancer risk; however, most evidence concerns older, relatively high-dose formulations. According to a population-based cohort study, the benefit extends to contemporary, lower-dose contraceptives and the risk reduction persists after discontinuation, although the length of time is not known.

Methods: Data were collected as part of the ongoing Danish Sex Hormone Register Study. The present analysis included all women aged 15–49 years between 1995 and 2014, excluding those with preexisting cancer, venous thrombosis, or infertility. The cohort of nearly 1.9 million women was followed until the occurrence of ovarian cancer or age 50 years. Women were categorized as current or recent users of hormonal contraceptives, former users (stopping ≥1 year ago), and never-users.

Results: A large majority of contraceptive use (86%) consisted of combined oral preparations. The remaining women used either non-oral combinations or progestogen-only products. There were 1249 incident cases of ovarian cancer, including 478 cases in women who had ever used a hormonal contraceptive. Risk of ovarian cancer was reduced in women who were currently using or had ever used hormonal contraceptives. (See table.) Risk reduction was evident in users of combined oral agents and, by a smaller margin, users of progestogen-only formulations. There was little evidence of important differences between combined oral contraceptives containing different progestogens.

Adjusted relative risk of ovarian cancer		
Use category	**Incidence**	**Relative risk***
Never use	7.5	1.00
Ever use	4.3	0.66
Former use	5.0	0.77

Relative risk of ovarian cancer was lower the longer that women used hormonal contraceptives, reaching a low point of 0.26 in women who had used the contraceptives for >10 years. Women who had stopped taking the contraceptives >10 years in the past had a similar level of risk reduction as women who stopped using them more recently. Protection appeared to wane more rapidly in women who discontinued contraceptives after shorter periods of use.

The investigators estimated that hormonal contraception prevented 21% of the ovarian cancers that would have occurred in this population.

Iversen L, et al: Association between contemporary hormonal contraception and ovarian cancer in women of reproductive age in Denmark: prospective, nationwide cohort study. *BMJ* 2018; doi 10.1136/bmj.k3609. From the University of Aberdeen, U.K.; and the University of Copenhagen, Denmark. **Funded by the Novo Nordisk Foundation. Three of 6 study authors disclosed financial relationships with commercial sources including Novo Nordisk; the remaining authors declared no competing interests.**

***See Reference Guide.**

Adverse Events with SGLT2 Inhibitors

In patients receiving second- or third-tier medication for type 2 diabetes, use of a sodium glucose cotransporter 2 (SGLT2) inhibitor was associated with increased risk of lower limb amputation and diabetic ketoacidosis, compared with use of a glucagon-like peptide 1 (GLP1) receptor agonist. Whether these adverse events are a class-wide effect of these drugs remains unknown.

Background: Previous clinical trials have demonstrated increased rates of lower limb amputation and bone fracture in users of SGLT2 inhibitors. There have also been reports of other serious adverse effects. Venous thromboembolism is a theoretical concern because these agents increase blood viscosity by inducing diuresis. There have been no previous large-scale, methodologically valid studies covering the entire spectrum of suspected adverse events of SGLT2 inhibitors.

Methods: The analysis used combined data from nationwide registers in Sweden and Denmark from July 2013 to December 2016. All patients aged ≥35 years who received a first prescription for an SGLT2 inhibitor were compared with patients who received a GLP1 receptor agonist. Patients from the 2 groups were individually matched with controls using a 66-item propensity score.* The primary outcomes were 7 adverse effects suspected to be associated with SGLT2 inhibitors: lower limb amputation, bone fracture, diabetic ketoacidosis, acute knee injury, serious urinary tract infection, venous thromboembolism, and acute pancreatitis.

Results: The study population consisted of >21,000 patients with a new prescription for an SGLT2 inhibitor and >27,000 patients given a GLP1 receptor agonist. Of those who received an SGLT2 inhibitor, 61% were prescribed dapagliflozin, 38% empagliflozin, and 1% canagliflozin. Patients given an SGLT2 inhibitor were older, more likely to be men and to use a dipeptidyl peptidase 4 (DPP4) inhibitor, and less likely have obesity or to require insulin. Propensity score matches were made for about 17,000 pairs of patients, resulting in 2 well balanced groups.

Among patients receiving an SGLT2 inhibitor, risks were significantly elevated for lower limb amputation (hazard ratio,* 2.32) and diabetic ketoacidosis (hazard ratio, 2.14). Risks of the other adverse events were not increased in SGLT2 inhibitor users. Subgroup analyses did not identify any clinical group in which risks differed from the population at large.

Discussion: The mechanisms associated with the potential adverse events are not known. Class-wide mechanisms that could explain some of the suspected associations include volume depletion, increased levels of phosphate, and non-insulin-dependent glucose lowering leading to diabetic ketoacidosis. However, an analysis of individual agents was not conducted and future research should evaluate each agent separately.

Ueda P, et al: Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *BMJ* 2018; doi 10.1136/bmj.k4365. From Karolinska University Hospital, Stockholm, Sweden; and other institutions. **Funded by the Swedish Heart-Lung Foundation; and other sources. Three of 10 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: canagliflozin—*Invokana*; dapagliflozin—*Farxiga*; empagliflozin—*Jardiance

***See Reference Guide.**

Baloxavir Efficacy

A single dose of the newly-approved antiviral drug baloxavir reduced the duration of influenza symptoms as well as viral load in randomized, active- and placebo-controlled trials. Its mechanism of action distinguishes baloxavir from existing anti-influenza drugs, to which recent influenza strains are developing resistance.

Methods: A phase II trial, conducted in Japan, enrolled patients aged 20–64 years who were randomly assigned a single dose of baloxavir (10, 20, or 40 mg) or placebo. A phase III trial, conducted in Japan and the U.S., enrolled patients aged 12–64 years. Those aged ≥20 years received a single weight-based dose of baloxavir (40 or 80 mg), oseltamivir 75 mg b.i.d. for 5 days, or placebo. All adult patients in this study received a 5-day regimen, with placebos as appropriate. Patients aged 12–19 years received a single dose of baloxavir or placebo.

For both trials, patients were enrolled if they had been experiencing fever (axillary temperature, ≥100.4), ≥1 systemic symptom, and ≥1 respiratory symptom for ≤48 hours. Twice a day, patients rated the severity of 7 influenza symptoms on a 4-point scale. The primary study endpoint was alleviation of flu symptoms, defined as ratings of mild or absent for all 7 symptoms for ≥21.5 hours.

Results: A total of 389 patients completed the phase II study. The median time to symptom

alleviation ranged from 49.5 hours to 54.2 hours in the 3 baloxavir dosage groups, compared with 77.7 hours in the placebo group. All 3 dosage groups showed greater reductions than the placebo group in influenza virus titers on days 2 and 3.

A total of 1064 patients were included in the efficacy analysis of the phase III trial. The median time to alleviation of symptoms was 65.4 hours with baloxavir and 88.6 hours with placebo. Symptoms were alleviated 38.6 hours earlier with baloxavir than placebo in adolescents and 25.6 hours earlier in adults. The effects of baloxavir were greater in the 53% of patients who started treatment within 24 hours of symptom onset. The median time to symptom resolution was similar with baloxavir and oseltamivir. Baloxavir was associated with more rapid declines in viral load than oseltamivir or placebo.

Discussion: Baloxavir targets the viral polymerase complex that binds to the cap of host cell RNA as a step in transcribing viral messenger RNA. Several other agents in this category are in clinical development. Two other classes of antiviral drugs are widely available, but circulating influenza viruses are largely resistant to 1 class and developing resistance to the other. Viral variants with reduced susceptibility to baloxavir were detected in 2% of patients in the phase II trial and nearly 10% in the phase III trial. Nevertheless, baloxavir may provide an option for patients with infections caused by viruses resistant to other drugs.

Hayden F, et al: Baloxavir marboxil for uncomplicated influenza in adults and adolescents. *NEJM* 2018;379 (September 6):913–923. From the University of Virginia College of Medicine, Charlottesville; and other institutions. **Funded by Shionogi. Thirteen of 16 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Common Drug Trade Names*: baloxavir marboxil—*Xofluza*; oseltamivir—*Tamiflu

Prucalopride for Constipation

The serotonin-4 receptor agonist prucalopride (*Motegrity*) has received FDA approval for the treatment of chronic idiopathic constipation in adults. The first serotonin agonist approved for the indication, prucalopride works by enhancing colonic peristalsis to increase bowel motility.

In clinical trials, significantly more patients taking prucalopride than placebo achieved normalization of bowel movement frequency. Response was rapid, in some cases as early as week 1, with improvement maintained over 12 weeks of treatment. In the trials, the most common adverse reactions were headache, abdominal pain, nausea, diarrhea, abdominal distension, dizziness, vomiting, flatulence, and fatigue. Suicides, suicide attempts, and suicidal ideation were also reported. Although a causal association with prucalopride has not been established, treated patients should be monitored for persistent worsening of depression or the emergence of suicidal thoughts and behaviors. Prucalopride is contraindicated in patients with intestinal perforation or obstruction due to a structural or functional disorder of the gut wall, obstructive ileus, or severe inflammatory conditions of the intestinal tract (e.g., Crohn's disease, ulcerative colitis, and toxic megacolon/megarectum). The manufacturer will be required to conduct postmarketing studies evaluating the pharmacokinetics, efficacy, and safety of prucalopride in pediatric patients and in pregnant and lactating women.

FDA approves Shire's Motegrity™ (prucalopride), the only serotonin-4 receptor agonist for adults with chronic idiopathic constipation (CIC) [press release]: Cambridge, MA; Shire: December 17, 2018. Available at www.shire.com/en/newsroom/2018/december/qmmwqk.

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.

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.