PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XXXVI / January 2015 / Number 1 www.alertpubs.com

Metformin and Vitamin B Deficiency

According to results of a meta-analysis, metformin therapy is associated with reduced serum concentrations of vitamin B_{12} and a 2-fold increased prevalence of vitamin B_{12} deficiency.

Background: Malabsorption of vitamin B_{12} is a known effect of long-term metformin treatment, and annual measurement of vitamin B_{12} is recommended in patients receiving long-term metformin. However, previous studies have not established the link between metformin use and reduced serum B_{12} levels to an increased prevalence of B_{12} deficiency, due in part to small sample sizes and retrospective designs.

Methods: The analysis included published studies, and 1 unpublished study by the authors, that compared vitamin B_{12} status in patients with type 2 diabetes who received treatment with metformin versus a comparison group with diabetes. The studies were either retrospective or prospective cohort studies or randomized controlled trials. Vitamin D deficiency was defined as a serum level <203 pg/mL.

Results: A total of 29 studies were identified: 18 retrospective cohort studies and 11 randomized controlled trials, with a total enrollment of >8000 patients. A total of 15 studies, with >4000 subjects, reported the effects of metformin on average vitamin B_{12} levels. Concentrations were reduced by an overall average of 89 pg/mL (p<0.00001). The effect was smaller and lost its statistical significance when the analysis was restricted to the 10 randomized clinical trials, with about 900 patients. A total of 18 studies, with >7500 participants, reported vitamin B_{12} deficiency as a primary or secondary study outcome. Deficiency in these studies was present in 11% of metformin patients and 6% of controls (odds ratio,* 2.45; p<0.0001). Results of this analysis were essentially unchanged when only the randomized controlled trials were included.

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

Niafar M, et al: The role of metformin on vitamin B12 deficiency: a meta-analysis review. *Internal and Emergency Medicine* 2014; doi 10.1007/s11739-014-1157-5. From Tabriz University of Medical Sciences, Iran; and the University at Buffalo, State University of New York. **Source of funding not stated. The authors declared no conflicts of interest.**

Drug Trade Names*: metformin—*Fortamet, Glucophage, Glumetza, Riomet

***See Reference Guide.**

Antidiabetics: Comparative Effectiveness

Despite treatment guidelines, less than two-thirds of patients received metformin as their initial oral drug for type 2 diabetes in an observational comparative-effectiveness study.[1] Compared with the other options, metformin was associated with reduced subsequent treatment intensification, and without increased rates of hypoglycemia or other adverse events.

Methods: The study was a retrospective analysis of claims data from a large nationwide health insurer for a cohort of patients who were given a prescription for their first oral glucose-lowering medication in 2009–2013. The analysis was limited

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to patients newly initiating treatment with metformin, a sulfonylurea, a thiazolidinedione, or a dipeptidyl peptidase 4 (DPP-4) inhibitor. The glucagon-like peptide 1 agonists (e.g., exenatide, liraglutide) were not included in the analysis because they were not approved as monotherapy early in the study period and they can be used off-label for weight loss. To exclude nonadherent or intolerant patients, the analysis was further limited to those who filled a second prescription for the same agent. The primary study outcome was time to treatment intensification, defined as the initiation of another class of oral glucose-lowering medication or insulin.

Results: Of >15,500 patients included in the analysis, 58% received metformin as their initial medication, 23% received a sulfonylurea, 6% a thiazolidinedione, and 13% a DPP-4 inhibitor. Median follow-up was about 1 year. Rates of treatment intensification during follow-up were 25% for patients started on metformin and 36–40% for the other drug classes. In multivariate analyses adjusted for comorbidity and other factors, rates of intensification were associated with odds ratios* ranging from about 1.60 to 1.80 for the 3 other drug classes, relative to metformin ($p<0.001$ for all 3 comparisons). The second drug added was metformin in half or more of patients, which suggests metformin was not contraindicated in most of those who initially received other drugs.

Sulfonylureas were associated with increased risk of cardiovascular complications and congestive heart failure compared with metformin (hazard ratios,* 1.16 and 1.19, respectively), but there was no evidence of increased risk with the other 2 drug classes. Only 72 patients had an episode of hypoglycemia during follow-up. Sulfonylurea was associated with an almost 3-fold higher risk of hypoglycemia than metformin. The other 2 drug classes were associated with very low rates of hypoglycemia, which did not differ statistically from metformin. Treatment adherence during follow-up was higher for DPP-4 inhibitors (42%) than for the 3 other drug classes (28–33%).

Editorial.[2] The cohort understandably excluded patients who received the newest class of medications, the sodium-dependent glucose cotransporter 2 inhibitors (e.g., canagliflozin, dapagliflozin), because the first of these agents did not receive FDA approval until 2013. Less understandable, according to the editorial, is the exclusion of the glucagon-like peptide 1 agonist class despite their availability since 2005 and the approval of exenatide as monotherapy in 2009. In addition, the slow dosage titration required for metformin may have biased the analysis to show a longer delay in treatment intensification. According to the editorial, the most compelling rationale for the present study is the use of intensification of therapy as an outcome indicative of treatment failure.

[1]Berkowitz S, et al: Initial choice of oral glucose-lowering medication for diabetes mellitus: a patient-centered comparative effectiveness study. *JAMA Internal Medicine* 2014;174 (December):1955–1962. From Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and other institutions. **Funded by CVS Health. One study author disclosed potential conflicts of interest.**

[2]Segal J, et al: Initial therapy for diabetes mellitus [editorial]. *JAMA Internal Medicine* 2014;174 (December):1962–1963.

Drug Trade Names*: canagliflozin—*Invokana*; dapagliflozin—*Farxiga*; exenatide—*Byetta, Bydureon*; liraglutide—*Victoza*; metformin—*Glucophage

***See Reference Guide.**

Liraglutide Injection for Weight Loss

The FDA has approved a new glucagon-like peptide-1 receptor agonist injection, liraglutide (*Saxenda*), for weight management in patients with obesity and in those who are overweight with weight-related risk factors (e.g., hypertension, diabetes, dyslipidemia). *Saxenda* contains the same active ingredient (liraglutide) as *Victoza*, approved for treatment of type 2 diabetes, and the agents should not be used together. Patients taking *Saxenda* should be evaluated after 16 weeks, and treatment should be discontinued in those who have not lost ≥4% of their baseline body weight, as the likelihood of achieving and sustaining clinically meaningful weight loss with continued use is low.

Saxenda may be associated with tumors of the thyroid gland and should not be used in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2. In clinical trials, serious adverse effects of treatment included pancreatitis, gallbladder disease, renal impairment, and suicidal thoughts. The agent can also increase resting heart rate. Less serious, but common, adverse effects included nausea; diarrhea; constipation; vomiting; hypoglycemia; and decreased appetite.

FDA approves weight-management drug Saxenda. FDA News Release: Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements.

Ondansetron for IBS with Diarrhea

In a placebo-controlled trial, ondansetron (*Zofran*) improved symptoms of diarrhea related to irritable bowel syndrome. A serotonin 5-HT3 receptor antagonist currently approved as an antiemetic, ondansetron is safe, inexpensive, and widely available.

Methods: The study enrolled patients from multiple IBS clinics in the U.K. Participants were adults, aged 18–75 years, who met standardized diagnostic criteria for IBS and had other causes of diarrhea ruled out by colonoscopy, colonic biopsy, and other tests. Patients taking serotonergic antidepressants were allowed to enroll if they had been on medication for ≥3 months. Beginning with a 1-week baseline assessment, patients recorded their symptoms in a daily stool diary. Then each patient received active treatment or placebo in a randomized crossover fashion for 5 weeks, separated by a 2- to 3-week washout. The dosage was titrated based on response for the first 3 weeks and held stable during the final 2 weeks. The primary endpoint, stool form, was measured using the 7-point Bristol Stool Form scale and averaged over the last 2 weeks of treatment.

Results: Of 120 patients who were randomized and began treatment, 98 received both treatments and were included in the intent-to-treat analysis.* A total of 90 completed the study according to protocol. Ondansetron was associated with a significant improvement in stool consistency (0.9 points on the Bristol scale; $p<0.001$). Ondansetron had the greatest effect in patients with less severe diarrhea. There was very little placebo response, and the onset and loss of treatment effect were rapid, occurring within the first week on average.

Secondary efficacy measurements also showed larger effects with ondansetron than placebo. Active treatment was associated with significantly fewer days per week with urgency and bloating (but not pain), reductions in stool frequency, and increases in gut transit time. Patients were nearly 5 times as likely to prefer ondansetron than placebo. The only frequent side effect was constipation, which occurred in 9% of ondansetron-treated patients and 2% of those who received placebo.

Discussion: Treatment of IBS-related diarrhea is an important unmet need. The known abnormalities of serotonin metabolism in IBS-related diarrhea make 5-HT3 antagonists a logical treatment choice. Patients in the present study showed a marked preference for ondansetron despite its lack of effect on pain, which suggests urgency and loose stools are more troubling symptoms. Higher doses might have reduced pain but might also have increased constipation, which patients wished to avoid.

Garsed K, et al: A randomised trial of ondansetron for the treatment of irritable bowel syndrome with diarrhoea. *Gut* 2014;63 (October):1617–1625. From Queens Medical Centre, Nottingham, U.K.; and other institutions. **Funded by the National Institute for Health Research. Two study authors disclosed relationships with commercial sources.**

***See Reference Guide.**

Neurotoxicity of Antimicrobials

According to a literature review, delirium and psychosis are among the neurotoxic adverse events that may occur with fluoroquinolone, macrolide, sulfonamide, nitrofuran, and β-lactam antimicrobial therapy. These events are underrecognized and may be mistaken for symptoms of an underlying neurologic disorder or for worsening of the infection.

Fluoroquinolones. Neurotoxicity occurs in 1–2% of patients taking a fluoroquinolone. Mania has been reported with ciprofloxacin, ofloxacin, and norfloxacin, and delirium has been associated with ciprofloxacin and levofloxacin. Onset of neuropsychiatric effects typically occurs within 1 week of starting therapy, and symptoms typically resolve with discontinuation.

Macrolides. CNS toxicity has been reported with both erythromycin and clarithromycin. There have also been several cases of azithromycin-associated delirium in geriatric patients with no psychiatric history.

β-lactams. Penicillins are generally considered safe in the elderly, but neurotoxicity has been reported with piperacillin–tazobactam, particularly in older people with advanced renal insufficiency. This side effect is rare when the agent is dosed appropriately for renal dysfunction and the patient does not have a CNS infection. Neurologic adverse events have been reported with all 4 generations of cephalosporins. The most frequently implicated agents are cefepime ceftazidime, cefuroxime, and cefazolin. Risk factors for cephalosporin-associated neurotoxicity include renal insufficiency, preexisting neurologic

disease, and advanced age. Cases of delirium and a psychosis-like syndrome with hallucinations and delusions have been reported with the carbapenems. Linezolid has been reported to cause neurologic toxicities including peripheral neuropathy, which can persist for months after drug discontinuation or even become permanent. Risk may be increased in patients with preexisting neurologic disease, alcohol abuse, diabetes, chemotherapy, or concomitant antiviral therapy.

Nitrofurans and Sulfonamides. Most reported cases of neurotoxicity from nitrofurans have occurred in the elderly. Underlying renal dysfunction may be a contributing factor. Trimethoprim-sulfamethoxazole has been associated with many reports of psychosis and hallucinations in the elderly, a growing concern with the increasing survival of HIV-positive patients into advanced age.

Mattappalil A, Mergenhagen K: Neurotoxicity with antimicrobials in the elderly: a review. *Clinical Therapeutics* 2014;36 (November):1489–1511. From Rutgers, the State University of New Jersey, Piscataway; and the Veterans Affairs Western New York Healthcare System, Buffalo. **Source of funding not stated. The authors declared no conflicts of interest.**

Drug Trade Names*: azithromycin—*Zithromax*; cefazolin—*Ancef, Kefzol*; cefepime—*Maxipime*; ceftazidime—*Fortaz, Tazicef*; cefuroxime—*Ceftin, Zinacef*; ciprofloxacin—*Cipro*; clarithromycin—*Biaxin*; linezolid—*Zyvox*; ofloxacin—*Ocuflox*; norfloxacin—*Noroxin*; piperacillin–tazobactam—*Zosyn*; trimethoprim–sulfamethoxasole—*Bactrim, Septra

New ADHD Treatment in Development

A novel dopamine and norepinephrine reuptake inhibitor (DNRI), dasotraline, appears to be an effective treatment for adults with ADHD, according to results of a study presented at the American College of Neuropsychopharmacology Annual Meeting. The agent, still in development, inhibits pre-synaptic dopamine and norepinephrine reuptake and has a half-life suggestive of extended steady state plasma concentrations and therapeutic effects over a 24-hour dosing interval.

In the first randomized, placebo-controlled trial, 4 weeks of dasotraline treatment at dosages of 4 and 8 mg/day improved ADHD Rating Scale–IV total scores as well as scores on both the inattentive and hyperactivity/impulsivity subscales. Results for the higher dose were statistically significant, while the lower dose was numerically but not statistically superior to placebo. The most common adverse effect leading to dasotraline discontinuation was insomnia, followed by anxiety, and panic attacks. None of these adverse effects were recorded in the placebo group.

Investigational drug dasotraline significantly improved symptoms of attention deficit hyperactivity disorder (ADHD) in a placebo-controlled study in adults [press release]. Marlborough, MA: Sunovion Pharmaceuticals, Inc.; December 11, 2014.

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 one group has half the risk of the other group.

Intent-to-Treat Analysis (ITT): An analysis based on initial treatment intent, not on the treatment actually administered or completed. In an ITT analysis, everyone who begins treatment is regardless of treatment completion. ITT analyses are done to avoid the effects of crossover, drop-out, and other factors that could alter the results or inflate the magnitude of effects.

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 have been posted at www.alertpubs.com.

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Volume XXXVI / February 2015 / Number 2 www.alertpubs.com

Generic Nexium

Ivax Pharmaceuticals has received FDA approval to market the first generic version of the proton pump inhibitor *Nexium* (esomeprazole) to treat gastroesophageal reflux disease (GERD) in adults and children aged ≥1 year. Esomeprazole is also approved to treat gastric ulcers associated with NSAID use, *H. Pylori*, and other conditions that produce excessive stomach acid. The generic will be available in 20- and 40-mg strengths.

FDA approves first generic esomeprazole. FDA News Release: Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements.

Technosphere Inhaled Insulin

The rapid-acting inhaled human insulin powder Technosphere insulin (*Afrezza*), approved in July 2014, is an alternative to injected insulin for type 1 and type 2 diabetes. Potential advantages include greater acceptability to patients who are averse to injecting themselves and possibly a lower risk of hypoglycemia.

Afrezza is contraindicated in patients with COPD or asthma because limited evidence suggests it may produce a transient but significant decline in forced expiratory volume. In addition, *Afrezza* carries a black box warning for patients with these conditions because it was associated with bronchoconstriction, wheezing, and asthma exacerbation in a phase I study in 5 of 17 nondiabetic patients with asthma. Based on limited safety and efficacy data, *Afrezza* insulin is not recommended for current smokers or those who have recently quit.

In pooled data from phase II and III trials, *Afrezza* was associated with a higher rate of pulmonary adverse events than control treatments: 45% vs. about 33%. *Afrezza* was also associated with small, reversible declines in forced expiratory volume. For this reason, pulmonary function tests are required at the start of treatment, again after 6 months, and then annually. Discontinuation should be considered in patients who have a ≥20% decline in forced expiratory volume.

Afrezza powder is supplied in 4- and 8-unit single-use cartridges. The manufacturer provides 30 cartridges in a single dispensed foil package. Unopened packages should be stored in the refrigerator. Once opened, *Afrezza* cards, which contain 15 cartridges, are stable at room temperature for 10 days. If an individual cartridge is opened it should be used within 3 days. One inhaler is provided with each card and should be used for 15 days and then discarded.

Nuffer W, Trujillo J, Ellis S: Technosphere insulin (*Afrezza*): a new, inhaled prandial insulin. *Annals of Pharmacotherapy* 2015:49 (January):99–106. From the University of Colorado Skaggs School of Pharmacy, Aurora. **This review was conducted without funding. The authors declared no conflicts of interest.**

New GLP-1 Agonist for Diabetes

Dulaglutide, a once-weekly injected glucagon-like peptide-1 receptor agonist (GLP-1 RA), was approved for treatment of type 2 diabetes in late 2014. It is the fifth GLP-1 RA to be introduced and the third once-weekly injected agent in this class. Dulaglutide is an attractive option because of its glucose-lowering and weight-loss effects,

Primary Care Drug Alerts® (ISSN 1061-0359) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: kasey@alertpubs.com. Periodical-class postage is paid at Butler, NJ, and at additional mailing offices. POSTMASTER: Send address changes to Primary Care Drug Alerts, 45 Carey Avenue, Ste 111, Butler, NJ 07405. Subscription $99.00 a year in the U.S.; $107.50 Canada; $117.50 elsewhere; $151 institutional. Back issues and single copies, $10.00 each; prepaid. Institutional multicopy discounts are available.

acceptable tolerability and safety, and once-weekly dosing, according to a literature review.

A search identified all available published articles and abstracts and other information supplied by the manufacturer; the review included pharmacology, pharmacokinetics, efficacy, and safety. Data on the cost-effectiveness of dulaglutide are not yet available. Head-to-head efficacy comparisons with the other once-weekly injected GLP-1 RAs have not been conducted.

Like other agents in its class, dulaglutide has multiple clinical effects. It stimulates insulin secretion and suppresses glucagon secretion, resulting in enhanced glycemic control. It delays gastric emptying, resulting in greater satiety and weight loss. The GLP-1 RAs differ from one another with regard to pharmacokinetics and pharmacodynamics, which leads to differences in clinical effects and adverse events.

Dulaglutide is administered using a pen device. Peak drug concentrations occur within 24–72 hours, and the half-life is about 4–5 days. Steady-state concentrations are reached after 2–4 weeks of once-weekly administration. It is available in 2 doses, 0.75 mg/0.5mL and 1.5 mg/0.5 mL, with therapy initiated at the lower dose. No dosage adjustment is needed for renal or hepatic dysfunction. Because dulaglutide slows gastric emptying, levels of concomitant oral medications with a narrow therapeutic index should be monitored.

Two studies compared dulaglutide with orally administered GLP-1 RAs. Dulaglutide resulted in greater glucose-lowering and similar weight loss compared with twice-daily exenatide. Compared with once-daily liraglutide, dulaglutide had similar glucose-lowering and lesser weight-loss effects. Adverse effects were predominantly gastrointestinal, similar to other GLP-1 RAs, and were usually transient.

Thompson A, Trujillo J: Dulaglutide: the newest GLP-1 receptor agonist for the management of type 2 diabetes. *Annals of Pharmacotherapy* 2015; doi 10.1177/1060028014564180. From the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora. **This review was conducted without funding. The authors declared no conflicts of interest.**

Drug Trade Names*: dulaglutide—*Trulicity*; exenatide—*Byetta, Bydureon*; liraglutide—*Victoza

ADHD Medications and Pregnancy

In a population-based cohort study, treatment with ADHD medications was associated with increased rates of some adverse pregnancy outcomes, but these were largely explained by the effects of ADHD itself. Among multiple outcomes investigated, only low Apgar scores were associated with medications, independently of the underlying disorder.

Methods: Registry data were analyzed from a cohort of nearly 1 million pregnancies in Danish women over a 12-year period. The data included all diagnoses of ADHD and all prescriptions for methylphenidate or atomoxetine that were filled beginning 30 days before the estimated date of conception, until birth, stillbirth (weeks 22–28), or spontaneous abortion (before week 22). Adverse pregnancy outcomes included low birth weight (<5.5 lbs.), preterm birth (before 37 weeks), small size for gestational age (<10th percentile), Apgar scores <10 at 5 minutes, and major congenital malformations.

Results: The study population included 186 women who were taking ADHD medications and 275 with ADHD who did not use medications. Compared with those without ADHD, women with ADHD were younger, less well educated, lower-income, and more likely to be single and nulliparous; they also had higher rates of concomitant medication, comorbidity, and smoking.

Women with ADHD had about a 55% increased risk of spontaneous abortion compared with those without ADHD, after adjustment for maternal age, education, cohabitation, comorbidity, and co-medication. This association was present regardless of medication use. Women taking ADHD medication had a significantly higher adjusted proportion of newborns with low Apgar scores than comparison women (adjusted relative risk,* 2.06), but unmedicated women with ADHD did not (relative risk, 0.99). Unmedicated women with ADHD, but not medicated women, had elevated adjusted rates of preterm births compared with controls. Other study outcomes occurred too infrequently in women taking ADHD medications to be analyzed statistically: preterm birth, small for gestational age, low birth weight, and congenital malformations.

Discussion: Animal studies have shown methylphenidate associated with high rates of congenital anomalies, but this finding has not been replicated in humans. A few human studies suggest ADHD medications may be associated with adverse pregnancy outcomes. Confounding

by indication—the contribution of risk from the underlying disease—is a persistent challenge in pharmacoepidemiological studies. The present study indicates that at least part of the increase in spontaneous abortion associated with ADHD medications may be due to the disorder itself, while low Apgar scores appear to be a direct effect of the drugs.

Bro S, et al: Adverse pregnancy outcomes after exposure to methylphenidate or atomoxetine during pregnancy. *Clinical Epidemiology* 2015;7:139–147. From Aarhus University and Aarhus University Hospital, Denmark. **Funded by the Danish Epilepsy Foundation. The authors declared no competing interests.**

Drug Trade Names*: atomoxetine—*Strattera*; methylphenidate—*Ritalin

***See Reference Guide.**

Aromatase Inhibitors and Breast Cancer

Clinical trial evidence suggests aromatase inhibitors are an effective alternative for breast cancer prevention in high-risk postmenopausal women with contraindications to selective estrogen receptor modulators (SERMs).

Aromatase inhibitors block the endogenous conversion of androgens to estrogens and are currently used to treat locally advanced or metastatic breast cancers that are hormonally sensitive. They are not FDA-approved for breast cancer risk reduction, but evidence supporting exemestane and anastrozole has led the National Comprehensive Cancer Network to issue a recommendation for their use in risk reduction for postmenopausal women with risk factors and a life expectancy of ≥10 years.

Exemestane was investigated in an international randomized, placebo-controlled trial in >4500 postmenopausal women with ≥1 breast cancer risk factor. Women who received exemestane had a 65% annual reduction in the incidence of invasive breast cancer. Most of the cancers that developed were estrogen-receptor positive but node-negative and HER2/neu-negative. The number needed to treat* (NNT) to prevent 1 case of invasive breast cancer in a 5-year period was 26. Early discontinuation for adverse effects occurred in 15% of the exemestane group and 11% of the placebo group ($p<0.001$). Hot flashes and arthritis occurred more often with exemestane than placebo, but there was no difference between groups in skeletal fractures, new osteoporosis, cardiovascular events, or most aspects of quality of life. Menopause-specific quality-of-life scores were lower in women who received exemestane.

Anastrozole was evaluated for breast cancer prevention in a study of nearly 4000 postmenopausal women at high risk of breast cancer but with no history of breast cancer or ongoing hormone replacement therapy. Incidence of invasive breast cancer was reduced by 53% with anastrozole, with a NNT of 36 women in 7 years. Anastrozole reduced the frequency of high-grade tumors more than low-grade ones and also reduced the occurrence of colorectal and skin cancers. Anastrozole was associated with more musculoskeletal adverse events than placebo (64% vs. 58%) and more vasomotor symptoms (57% vs. 49%), but similar frequencies of fractures.

Olin J, et al: Aromatase inhibitors in breast cancer prevention. *Annals of Pharmacotherapy* 2014;48 (December):1605–1610. From Wingate University School of Pharmacy, NC. **This review was conducted without funding. The authors declared no conflicts of interest.**

Drug Trade Names*: anastrozole—*Arimidex*; exemestane—*Aromasin

***See Reference Guide.**

Finafloxacin Otic Suspension

A new fluoroquinolone antimicrobial, finafloxacin otic suspension (*Xtoro*), has received FDA approval for treatment of acute otitis externa associated with *Pseudomonas aeruginosa* or *Staphylococcus aureus*. Otitis externa, commonly known as swimmer's ear, causes inflammation of the ear canal, along with pain, swelling, redness of the ear, and discharge. In clinical trials, patients who received treatment with finafloxacin demonstrated clearing of bacteria on culture and reduced pain; 70% of patients achieved clinical cure of otitis externa.

FDA approves Xtoro to treat swimmer's ear. FDA News Release: Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements.

Teixobactin

According to the CDC, drug-resistant bacteria infect ≥2 million people per year in the U.S., and 23,000 people die each year from these infections. In addition, drug-resistant strains of many diseases are evolving faster than new antibiotics can be formulated. An unusual method of producing antibiotics, which extracts the drugs from bacteria that lie in dirt, may present a solution to this problem. This novel method for the

first time allows the microbes that produce these compounds to be grown in the laboratory and has the potential to open the door to other compounds that could fights infections and cancer.

Although not yet tested in humans, a new antibiotic, teixobactin, has been shown to cure several types of infection in mice, with no adverse effects. Laboratory studies indicated the new drug kills various strains of staph and strep, as well as anthrax and tuberculosis. Gram-negative infections, such as pneumonia and gonorrhea, were not affected by teixobactin. Research also suggests that teixobactin attacks bacteria by blocking fatty molecules needed to build cell walls, a method different from available antibiotics. This could make it unlikely that bacteria will become resistant to it.

Preliminary research appears to be promising, but human studies will not begin for several more years and potential approval and widespread use is likely ≥5 years away.

From a pile of dirt, hope for a powerful new antibiotic. (2015, January 8). *New York Times*. Available at http://www.nytimes.com.

Sertraline-Associated Maculopathy

Within 2 weeks of starting treatment with sertraline (*Zoloft*), a 23-year-old man presented with worsening bilateral blurred vision and metamorphopsia, a type of distorted vision in which a grid of straight lines appears wavy and parts of the grid may appear blank.[1] The patient had no previous ocular issues or family history of eye disease. Intraocular pressure was normal, but dilated fundal examination showed Bull's eye-type maculopathy similar in appearance to that which occurs in chloroquine toxicity. Optical coherence tomography showed intermittent outer segment defects and thickening of the retinal pigment epithelium. Sertraline was discontinued. At 1-month follow-up, the patient reported some visual improvement.

Most adverse effects of sertraline and other selective serotonin reuptake inhibitors (SSRIs) are well documented; however, the incidence of adverse ocular effects appears to be unknown. Reports of SSRI-associated adverse ocular effects including mydriasis, increased intraocular pressure, glaucoma, and oculogyric crisis are anecdotal and few in number. There appears to be only 1 previous report of maculopathy developing in association with sertraline treatment. The previous patient was a 58-year-old woman in whom symptoms developed within 4 months of starting treatment.[2]

[1]Ewe S, Abell R, Vote B: Bilateral maculopathy associated with sertraline. *Australasian Psychiatry* 2014; doi 10.1177/1039856214556327. From Tasmanian Eye Institute, Australia. **The authors declared no conflicts of interest.**

[2]Sener E, Kirath H: Presumed sertraline maculopathy. *Acta Ophthalmologica Scandinavica* 2001;79:428–430.

Reference Guide

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 is 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.

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PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XXXVI / March 2015 / Number 3 www.alertpubs.com

Guideline: Drug Treatment of Obesity

Medications approved for weight loss can be useful adjuncts to diet and exercise, the first-line treatment in patients with obesity, according to a clinical practice guideline from the Endocrine Society. Weight loss drugs do not "work on their own," but may amplify adherence to diet, ameliorate comorbidities, and allow for greater physical activity.

In addition to drugs that help with weight loss, the guidelines cover medications used for other indications that cause weight gain, generally recommending the use of alternate drugs when possible in individuals with obesity. The recommendations are based on body mass index (BMI) thresholds determined by the FDA for use in product labeling, despite relatively little evidence supporting these thresholds.

Medications, as an adjunct to diet, exercise, and lifestyle modification, are recommended for patients with a BMI of ≥30, or ≥27 with ≥1 comorbid condition, such as hypertension, dyslipidemia, type 2 diabetes, or obstructive sleep apnea. The efficacy and safety of weight loss medications should be assessed at least monthly for the first 3 months, and then at least every 3 months. Effective medications—those that produce a loss of ≥5% of body weight at 3 months—should be continued if they are safe and well tolerated. Dose escalation should be based on efficacy and tolerability and should not exceed the maximum approved dose. If medication is not safe, tolerated, or sufficiently effective, it should be discontinued and other medications or referral for alternative treatments should be considered. The sympathomimetic drugs phentermine and diethylpropion should be avoided in patients with uncontrolled hypertension or heart disease; instead, nonsympathomimetic agents such as lorcaserin and orlistat are preferred. For patients with type 2 diabetes, antidiabetic medications with additional weight-loss effects, such as GLP-1 analogs or SGLT-2 inhibitors, should be added to first-line metformin.

The guidelines do not recommend specific weight-loss medications but rather list advantages and disadvantages of each. The treatment with the greatest known weight loss efficacy is the phentermine–topiramate combination, followed by phentermine and naltrexone–bupropion. Side effects were listed as a disadvantage for these medications and for orlistat. Lorcaserin and liraglutide, agents with a favorable side effect profiles, were also the most expensive. Off-label agents should be reserved for research or for clinicians who are expert in weight management and who are dealing with a well-informed patient.

Apovian C, et al: Pharmacological management of obesity: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2015; doi 10.1210/jc.2014-3415. From Boston University Medical Center, MA; and other institutions. **Funded by the European Society of Endocrinology; and the Obesity Society. Three study authors disclosed relationships with commercial sources; the remaining 5 authors declared no conflicts of interest.**

Drug Trade Names*: liraglutide—*Victoza*; lorcaserin—*Belviq*; metformin—*Glucophage*; naltrexone–bupropion—*Contrave*; orlistat—*Xenical*; phentermine—*Adipex-P*, *Suprenza*; phentermine–topiramate—*Qsymia

Primary Care Drug Alerts® (ISSN 1061-0359) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: kasey@alertpubs.com. Periodical-class postage is paid at Butler, NJ, and at additional mailing offices. POSTMASTER: Send address changes to Primary Care Drug Alerts, 45 Carey Avenue, Ste 111, Butler, NJ 07405. Subscription $99.00 a year in the U.S.; $107.50 Canada; $117.50 elsewhere; $151 institutional. Back issues and single copies, $10.00 each; prepaid. Institutional multicopy discounts are available.

Probiotic Yogurt for Antibiotic Diarrhea

In a randomized controlled trial, probiotic yogurt was highly effective in preventing antibiotic-induced diarrhea in children.

Methods: Study subjects were 70 children, aged 1–12 years, given a broad-spectrum oral antibiotic. Participants were randomly assigned to receive either probiotic or ordinary pasteurized yogurt. The active treatment contained *Lactobacillus (L.) rhamnosus GG*, presumed to be the strain active against diarrhea, and 2 other types of bacteria, *Bifidobacterium lactis* and *L. acidophilus*. Symptoms were rated using the Bristol Stool Scale for children.

Results: Use of probiotic yogurt was associated with a markedly lower risk of diarrhea of all degrees of severity (hazard ratios,* 0.04–0.18; p≤0.01, based varying definitions of diarrhea). None of the 34 children who ingested the probiotic yogurt experienced severe diarrhea, compared with 6 of the 36 children (17%) in the placebo group. A single child in the probiotic group experienced mild diarrhea, compared with 21 in the placebo group (3% vs. 58%).

Discussion: As many as 30% of children who receive treatment with oral antibiotics develop diarrhea, depending in part on how diarrhea is defined. Probiotics are often recommended for prevention, but different formulations have different effects. *L. rhamnosus GG* yogurt has previously shown efficacy in adults, and non-yogurt *L. rhamnosus GG* supplements in children.

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

Fox M, et al: Can probiotic yogurt prevent diarrhoea in children on antibiotics? A double-blind, randomised, placebo-controlled study. *BMJ Open* 2015; doi 10.1136/bmjopen-2014-006474. From the University of Tasmania, Launceston, Australia. **Funded by Parmalat Australia. The authors declared no conflicts of interest.**

***See Reference Guide.**

BP Lowering with Dietary Nitrate

In a randomized phase II trial, nitrate supplementation for 4 weeks reduced blood pressure in a group of patients with hypertension.

Methods: Study participants were 68 patients, aged 18–85 years, with BP >130/85 mm Hg; 34 were receiving pharmacotherapy for their hypertension, and 34 were drug-naïve. Treatment consisted of unmodified, nitrate-rich beet juice or placebo (nitrate-depleted beet juice), consumed in a single drink every morning. Patients recorded their BP daily using a standardized device and had 24-hour ambulatory BP, vascular function, and saliva, urine, and blood samples tested at the start of treatment, after 4 weeks, and again after a 2-week treatment washout.

Results: Nitrate-containing beet juice was associated with significant reductions from baseline in clinic measurements of BP: 7.7 mm Hg systolic (p<0.001) and 2.4 mm Hg diastolic (p=0.05). BP was unchanged in the placebo group. The beet juice was also associated with a similar magnitude of decreases in 24-hour ambulatory BP and in home BP measurements. BP began returning to previous levels after discontinuation of active treatment. Treatment had similar effects in unmedicated patients and those taking BP medications.

Discussion: The BP lowering effect of nitric oxide is due to its potent vasodilator activity. Use of dietary nitrate to lower BP is based on understanding of a newly discovered, alternative metabolic pathway. It is now known that a significant proportion of orally ingested nitrate is extracted from the blood by salivary glands, reduced to nitrite by bacteria in the mouth, re-ingested, and converted to nitrous oxide in the circulation. Although 4 weeks is too short a time to claim any clinical cardiovascular benefit, the magnitude of BP reductions observed in the present study are potentially important. Supplementation of medication with a nitrate-rich diet can be a cost-effective and favorable public health recommendation.

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

Kapil V, et al: Dietary nitrate provides sustained blood pressure lowering in hypertensive patients: a randomized, phase 2, double-blind, placebo-controlled study. *Hypertension* 2015;65 (February):320–327. From Queen Mary University of London, U.K. **Funded by the British Heart Foundation. One study author declared a potentially relevant financial relationship; the remaining 4 authors declared no conflicts of interest.**

***See Reference Guide.**

Folate Supplements for Stroke Prevention

Folic acid supplementation was associated with reduced risk of a first stroke in a randomized trial of patients with hypertension.[1]

Methods: Study participants, aged 45–75 years, were recruited from 2 Chinese provinces and were required to have a BP of ≥140 mm Hg systolic or 90 mm Hg diastolic on 2 consecutive visits or to be taking antihypertensive medication. They were

randomly assigned to receive either a combination tablet of 10 mg enalapril (*Vasotec*) plus 0.8 mg folic acid or a tablet containing enalapril alone. The primary study outcome was a first stroke.

Results: More than 20,000 patients were randomly assigned to treatment, and about 70% took most of their assigned medication. About 14% of patients discontinued their study medication but remained in follow-up. The study population was a mean age of 60 years and had low rates of self-reported hyperlipidemia (3%) and diabetes (3%). The study was designed to run for 5 years but was terminated after a median of 4 years of treatment when the primary efficacy endpoint was met.

A first stroke occurred in 2.7% of the enalapril–folic acid group and 3.4% of the group that received enalapril alone, a 21% reduction in risk (hazard ratio,* 0.79; p=0.003). The number needed to treat* to prevent 1 stroke over 4.5 years was 141. Results were similar using a secondary endpoint that combined stroke with all-cause mortality and in a separate analysis of ischemic stroke, but not hemorrhagic stroke.The effects of folic acid were more pronounced in participants with lower baseline folate levels.

Discussion: Because of its careful design and execution and precisely targeted endpoint, this study resolves a longstanding controversy about the effect of folate supplementation on cardiovascular health.[2] Many previous studies of this question have had null results, which might be attributed to factors such as the decrease in the prevalence of folate deficiency and the widespread use of background medications. In the present study, very few patients were taking lipid-lowering or anti-platelet drugs. It is likely that the study underestimated the preventive effects of folate because adherence was imperfect and because serum folate levels increased substantially in the control group, probably reflecting improvements in diet or use of supplements.

[1]Huo Y, et al: Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA* 2015; doi: 10.1001/jama.2015.2774. From Peking University First Hospital, Beijing, China; and other institutions. **Funded by Shenzhen AUSA Pharma Co. Ltd.; and other sources. Five study authors declared potentially relevant financial relationships; the remaining 26 authors declared no conflicts of interest.**

[2]Stampfer M, Willett W: Folate supplements for stroke prevention: targeted trial trumps the rest [Editorial]. *JAMA* 2015; doi: 10.1001/jama.2015.1961. **The authors declared no conflicts of interest.**

***See Reference Guide.**

Antidepressants and Cognitive Decline

In a large, nationally representative sample of older adults followed for 6 years, antidepressant use did not modify the well-established association between depression and cognitive decline.

Methods: The Health and Retirement Study is an ongoing study of U.S residents, aged >50 years at enrollment in 1992. Alternate-year interviews of participants include assessments of depression and cognitive function. Prescription drug data were also available beginning in 2005. The sample for the present analysis (n=3714) consisted mostly of people who were aged ≥65 years in 2007, community-dwelling, and able to participate in cognitive-function tests. Cognitive function was tested on 4 occasions between 2004 and 2010, using a 27-point scale based on a battery of memory and computational tests. Cognitive function was classified as normal, impaired function, or dementia based on these scores. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression (CES-D) Scale.

Results: At baseline, 12% of the study participants were taking an antidepressant. Depressive symptoms were associated with reduced baseline cognitive function, but there was no difference in cognitive function at baseline between those taking or not taking antidepressants. During the 6-year follow-up, both users and nonusers of antidepressants experienced a decline in cognitive function, which did not differ between the groups. In an analysis that was adjusted for sociodemographic variables, functional impairment, comorbidity, depressive symptom burden, and the anticholinergic activity of the antidepressant, rates of cognitive decline still did not differ between users and nonusers of antidepressants.

Discussion: Because antidepressant use does not appear to protect against cognitive decline in older patients with depression, adding nonpharmacological approaches that may be associated with cognition, such as social engagement, physical activity, and diet, should be considered for these patients.

Saczynski J, et al: Antidepressant use and cognitive decline: the Health and Retirement Study. *American Journal of Medicine* 2015; doi 10.1016/j.amjmed.2015.01.007. From the University of Massachusetts Medical School, Worcester; and other institutions. **Funded by the National Institute on Aging; and other sources. The authors declared no conflicts of interest.**

SSRI plus Stimulant in Geriatric Depression

In elderly patients with chronic depression, the combination of citalopram and methylphenidate resulted in a more robust antidepressant response than either agent alone.

Methods: This randomized trial was carried out in 143 older adults (average age, 70 years) with major depression and no or minimal cognitive impairment. Patients were seen in the clinic, at first weekly for 4 weeks of methylphenidate titration, and then every 2 weeks until the 16-week endpoint. Methylphenidate was dosed flexibly at 5–40 mg/day, with response defined as a Clinical Global Impression–Improvement (CGI-I) rating of at least much improved. Citalopram was also flexibly dosed in the 20- to 60-mg/day range. Patients in the 2 monotherapy groups received a placebo for the alternate drug. The primary outcome measure was change from baseline on the Hamilton Rating Scale for Depression (HAM-D). Remission was defined as a HAM-D score of ≤6. The rate of HAM-D reduction by the fourth week of treatment was also evaluated. Neuropsychological tests of cognitive function were carried out at baseline and study end.

Results: Patients had a history of 3–4 depressive episodes on average, with a mean duration of nearly 4 years for the present episode. About 40% met criteria for treatment resistance.

By 16 weeks, combination therapy was associated with a significantly larger average reduction in HAM-D score than citalopram alone (p=0.02) or methylphenidate alone (p=0.005). During the first 4 weeks of treatment, combination therapy was associated with greater improvement than citalopram monotherapy (p=0.03), but not methylphenidate alone. Efficacy did not differ significantly between the monotherapy groups. After week 4, improvement was significantly more rapid with combination therapy than with methylphenidate (p=0.04); improvement was not more rapid with combination therapy than with citalopram. By week 16, remission occurred in 62% of the combination therapy group, compared with 42% of patients who received citalopram alone (p=ns), and 29% of the methylphenidate group (p=0.003).

CGI-I ratings of much improved or better were noted in 84% of the combined therapy group, 57% of the citalopram group, and 39% of the methylphenidate group (p=0.001 for the combined group vs. each monotherapy). Cognitive outcomes of treatment were variable, with greater improvement in some areas of cognitive function observed in the 2 groups receiving citalopram. The treatment groups did not differ in any measure of tolerability or adverse effects.

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

Lavretsky H, et al: Citalopram, methylphenidate, or their combination in geriatric depression: a randomized, double-blind, placebo-controlled trial. *American Journal of Psychiatry* 2015; doi 10.1176/appi.ajp. 2014.14070889. From the University of California, Los Angeles. **Funded by the NIH. Two study authors disclosed financial relationships with commercial sources; the remaining 4 authors declared no conflicts of interest.**

Drug Trade Names*: citalopram—*Celexa*; methylphenidate—*Ritalin

***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 one group has half the risk of the other group.

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 is the treatment.

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 have been posted at www.alertpubs.com.

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XXXVI / April 2015 / Number 4 www.alertpubs.com

Aflibercept for Diabetic Retinopathy

The most common diabetic eye disease and a leading cause of blindness, diabetic retinopathy affects up to one-third of patients with diabetes. Following an expedited review, the FDA has expanded the indications for aflibercept (*Eylea*) injection to include diabetic retinopathy in patients with diabetic macular edema. *Eylea* should be administered as a monthly intraocular injection for 5 months, followed by injections every other month, and should be used in conjunction with therapies to control blood sugar, cholesterol, and blood pressure. Common adverse effects of *Eylea* injections include conjunctival bleeding; eye pain; cataracts; floaters; increased intraocular pressure; and vitreous detachment. Endophthalmitis and retinal detachment can also occur.

FDA News Release: FDA approves new treatment for diabetic retinopathy in patients with diabetic macular edema. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements.

Adult Sinusitis Guideline

Based on new evidence from multiple systematic reviews and randomized controlled trials, the American Academy of Otolaryngology—Head and Neck Surgery Foundation has updated its clinical practice guideline for adult rhinosinusitis.

The new guideline includes information on differential diagnosis and use of radiographic imaging, as well as treatment recommendations. For viral rhinosinusitis, analgesics, intranasal steroids, and/or nasal saline irrigation are recommended for symptom relief. Initial management of uncomplicated bacterial rhinosinusitis should consist of either 7 days of watchful waiting with symptom-relief-focused treatment (i.e., analgesics, intranasal steroids, and/or nasal saline irrigation) or antibiotic therapy. First-line antibiotic therapy should be amoxicillin with or without clavulanate for 5–10 days. If improvement is not evident within 7 days or if symptoms worsen, the antibiotic should be switched, or initiated after watchful waiting. Chronic rhinosinusitis has been defined as symptom presence for ≥12 weeks of ≥2 of the following symptoms: mucopurulent drainage, congestion, facial pain or pressure, decreased sense of smell, in addition to documented inflammation. Chronic disease should be treated with saline nasal irrigation and/or intranasal corticosteroids. Antifungal therapy should not be prescribed for chronic rhinosinusitis.

Rosenfeld R, et al: Clinical practice guideline (update): adult sinusitis executive summary. *Otolaryngology—Head and Neck Surgery* 2015;152 (4):598–609. From the American Academy of Otolaryngology. **Funded by the American Academy of Otolaryngology—Head and Neck Surgery Foundation. Six of 9 study authors disclosed potentially relevant financial relationships.**

Glyburide Safety in Pregnancy

According to results of a large cohort study in women with gestational diabetes, glyburide is associated with increased risk of adverse pregnancy outcomes compared with insulin.[1]

Methods: The study cohort consisted of patients in a large database of employer-sponsored private health insurance plans in 2000–2011. The cohort included all women who had gestational diabetes,

Primary Care Drug Alerts® (ISSN 1061-0359) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: kasey@alertpubs.com. Periodical-class postage is paid at Butler, NJ, and at additional mailing offices. POSTMASTER: Send address changes to Primary Care Drug Alerts, 45 Carey Avenue, Ste 111, Butler, NJ 07405. Subscription $99.00 a year in the U.S.; $107.50 Canada; $117.50 elsewhere; $151 institutional. Back issues and single copies, $10.00 each; prepaid. Institutional multicopy discounts are available.

filled their first prescription for glyburide or insulin within 150 days of delivery, and gave birth to a single live infant. The analysis excluded women who had a diagnosis of diabetes before becoming pregnant and those treated for diabetes in the first months of pregnancy. Study outcomes included a range of adverse maternal and neonatal outcomes. Patients were propensity-score matched* based on risk factors for the outcomes of interest and for factors that might influence the choice of glyburide or insulin.

Results: About 8% of the >110,000 women in the cohort received treatment for gestational diabetes; of these, 4982 (54%) received glyburide and 4191 (46%) received insulin. The proportion of the cohort that received glyburide increased from 9% in 2000 to 64% in 2011. The 2 groups were comparable with regard to baseline covariates.

Compared with insulin, newborns exposed to glyburide had increased risk of several adverse birth outcomes, with relative risk (RR)* increases in the 35–63% range. (See table.) Rates of other adverse outcomes—obstetric trauma, preterm birth, and jaundice—were not increased with glyburide use. Glyburide was associated with a 3% lower risk of cesarean delivery.

Adverse maternal and neonatal outcomes			
	Incidence		Adjusted RR
	Glyburide	Insulin	
NICU admission	10.2%	7.2%	1.41
Large for gestational age	4.7%	3.2%	1.43
Respiratory distress	2.9%	1.7%	1.63
Birth injury	2.2%	1.6%	1.35
Neonatal hypoglycemia	1.9%	1.3%	1.40

Editorial.[2] The increasing use of glyburide for gestational diabetes stems from studies suggesting that glyburide, unlike other sulfonylureas, does not cross the placenta, and from a single randomized clinical trial showing no increase in risk of adverse pregnancy outcomes. However, those findings have been challenged by recent research showing clinically significant fetal plasma glyburide concentrations in exposed pregnancies. The results of the present study suggest that the role of glyburide in managing gestational diabetes should be reconsidered.

[1]Castillo W, et al: Association of adverse pregnancy outcomes with glyburide vs insulin in women with gestational diabetes. *JAMA Pediatrics* 2015; doi 10.1001/jamapediatrics.2015.74. From the University of Maryland, Baltimore; and other institutions. **Funded by the Agency for Healthcare Research and Quality; and other sources. Four study authors declared potentially relevant financial relationships; the remaining 2 authors declared no conflicts of interest.**

[2]Holt R: Glyburide for gestational diabetes: time for a pause for thought [editorial]. *JAMA Pediatrics* 2015; doi 10.1001/jamapediatrics.2015.144. From the University of Southampton, U.K. **The author declared no competing interests.**

Drug Trade Names*: glyburide—*Diabeta, Glynase

***See Reference Guide.**

Long-Term Nicotine Replacement

In a randomized trial, using nicotine patches for 24 weeks was associated with higher smoking cessation rates than the standard 8-week regimen, but treatment beyond 24 weeks did not confer additional efficacy.

Methods: Study participants (n=525) were adults who smoked ≥10 cigarettes per day and were interested in smoking cessation. They were randomly assigned to treatment with 21-mg transdermal nicotine patches (*Nicoderm CQ*) for 8 weeks (standard), 24 weeks (extended), or 52 weeks (maintenance). In addition, all participants were offered 12 counseling sessions, including an in-person pre-cessation visit and periodic telephone coaching throughout the study year. The primary efficacy outcome was self-reported 7-day abstinence, confirmed with breath levels of carbon monoxide at weeks 24 and 52. Patients who withdrew from the study were counted as smokers.

Results: About 40% of subjects withdrew from the study before 1 year, but retention rates were similar in the 3 treatment arms. The 24-week analysis compared cessation rates between standard 8-week treatment and the combined groups receiving longer treatment. Rates of abstinence were similar, 22% and 27%, respectively. The odds ratio* for cessation at week 24 was significant in a multivariate model (1.70; p=0.04). In the 52-week analysis, the standard and extended treatment arms were combined for comparison with 52-week maintenance treatment. Rates of abstinence were 24% and 20%, respectively. Analysis of secondary outcomes—e.g., prolonged abstinence, time to relapse, number of abstinent days, and

number of cigarettes per day—generally favored the 24-week regimen over 8 weeks. Maintenance treatment was well tolerated and did not result in additional adverse effects over extended treatment. Adherence to patch use was similar in the extended and maintenance treatment groups during the first 24 weeks and diminished somewhat afterward in the maintenance group.

Discussion: Although long-term nicotine patch use appears safe, whether there is any clinical benefit of this or other nicotine replacement treatments beyond 6 months requires further study. This study confirms previous research in supporting the current FDA labeling of the patch to permit extended use.

Schnoll R, et al: Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Internal Medicine* 2015;175 (April):504–511. From the University of Pennsylvania, Philadelphia; and other institutions. **Funded by the National Institute on Drug Abuse; and the National Cancer Institute. Two study authors disclosed potentially relevant financial relationships; the remaining 7 authors declared no conflicts of interest.**

***See Reference Guide.**

Congenital Malformations with Statins

Statins are contraindicated in pregnancy based on animal data indicating teratogenic potential at high doses; clinical experience with their use in pregnancy is rare. In a large epidemiologic study, statin use during the first trimester of pregnancy did not increase risk of major congenital malformations, suggesting that inadvertent use during the first trimester may not be as worrisome as the contraindication suggests.

Methods: The study cohort consisted of all Medicaid-covered pregnancies (representing about 40% of all U.S. births) in 2000–2007. A total of nearly 887,000 women, aged 12–55 years, who gave birth to live infants and did not receive known teratogenic drugs were included. Statin use was defined as a prescription filled at any time between the last menstrual period and the 90th day of pregnancy. The primary study outcome was the presence of an organ-specific congenital malformation in the infant. The analysis was adjusted for 4 groups of potential confounders: maternal demographic characteristics/conditions, comorbid medical conditions, obstetric characteristics, and other drugs dispensed to the mother.

Results: A total of 1152 women, 0.13% of the cohort, received a statin during the first trimester. Compared with the rest of the cohort, women who received statins were older, had a higher prevalence of all of the comorbid conditions considered (nearly half had diabetes), and were more likely to use non-statin prescription drugs. The crude rate of congenital malformations was nearly twice as high in pregnancies with statin exposure as unexposed pregnancies. However, after adjustment for all potential confounders, there was no increase in risk associated with statin use (relative risk,* 1.04). When each category of organ-specific anomaly was analyzed separately, statin-exposed pregnancies were associated with elevated crude risk for central nervous system and cardiac malformations, but adjustment removed the association.

Discussion: Because about half of pregnancies in the U.S. are unplanned, inadvertent statin exposure does occur. Furthermore, statins are now being investigated clinically as a potential treatment for preeclampsia. Results of this study suggest the FDA's classification of statins as pregnancy category X should be reevaluated.

Bateman B, et al: Statins and congenital malformations: cohort study. *BMJ* 2015; doi 10.1136/bmj.h1035. 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 & Human Development of the NIH; and other sources. Two study authors disclosed potentially relevant financial relationships; the remaining 9 authors declared no conflicts of interest.**

***See Reference Guide.**

Intraarticular Treatments for Osteoarthritis

The commonly used pharmacologic treatments for knee osteoarthritis all produced pain relief with small differences among treatments, according to a network meta-analysis.* Intraarticular (IA) therapies were superior to oral medications.

Methods: This analysis included all identifiable randomized controlled trials conducted in patients with clinically or radiologically confirmed knee osteoarthritis that compared ≥2 treatments. Based on current worldwide treatment guidelines, the treatments of interest included oral acetaminophen, diclofenac, ibuprofen, naproxen, and celecoxib; IA corticosteroids and hyaluronic acid; and oral and IA placebo. The primary analysis evaluated pain relief. Although stiffness and function were also considered, there were substantially fewer trials evaluating these outcomes and they are not included.

Results: The analysis was based on 137 studies with >33,000 participants. Pain was reported as an outcome in 129 trials in >32,000 patients. All interventions were superior to oral placebo, with effect sizes* ranging from 0.18 for acetaminophen to 0.29 for IA placebo to 0.63 for IA hyaluronic acid. Naproxen, ibuprofen, diclofenac, IA hyaluronic acid, and IA corticosteroids were significantly superior to acetaminophen. All treatments except acetaminophen met prespecified criteria for clinically significant effects. IA treatments were superior to oral treatments.

Oral nonselective NSAIDs were poorly tolerated compared with other treatments, with a larger proportion of treatment withdrawals due to adverse events. Few trials reported on cardiovascular adverse events, probably because the trials were of short duration. Most adverse events with the IA therapies were local and transient. There was only 1 case of septic joint in about 9500 injections.

Discussion: The efficacy of IA treatments was surprising, given the widespread belief that IA hyaluronic acid is minimally effective. IA placebo was superior to oral placebo, and none of the oral NSAIDs was superior to IA placebo. It is possible that the IA method itself may induce a strong placebo response, or that injecting fluid into the knee joint itself produces pain relief. Thus trials comparing an IA therapy to IA placebo may underestimate the true benefit of active IA therapies. Another surprising finding was that celecoxib, the most frequently studied oral therapy, was not superior to the least effective agent, acetaminophen. Celecoxib was not significantly inferior to nonselective NSAIDs, but these results call into question the rationale for its use.

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

Bannuru R, et al: Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Annals of Internal Medicine* 2015;162 (January 6):46–54. From Tufts University, Boston, MA; and Brown University School of Public Health, Providence, RI. **Funded by the Agency for Healthcare Research and Quality. Three study authors disclosed potentially relevant financial relationships; the remaining 3 authors declared no conflicts of interest.**

Drug Trade Names: **celecoxib—*Celebrex*; diclofenac—*Cataflam, Voltaren*; naproxen—*Aleve, Anaprox, Naprosyn***

***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.

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

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.

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 have been posted at www.alertpubs.com.

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XXXVI / May 2015 / Number 5 www.alertpubs.com

Statin-Associated Plantar Warts

Plantar warts are a common dermatological presentation of the human papilloma virus (HPV) and may be associated with statin use. Emerging literature suggests an association between statin use and proliferation of HPV via an increase in regulatory T cells, which have immunosuppressive action.

A 67-year-old man presented with a long-term history of plantar warts that had been resistant to several lines of treatment. The patient had no relevant medical history but was undergoing secondary prevention of cardiovascular disease with clopidogrel, perindopril, and simvastatin. He was also taking quinine sulfate for treatment of leg cramps. Photodynamic therapy was scheduled, but the warts resolved prior to the treatment. The only change in the patient's medical status, treatment, or environment was discontinuation of simvastatin. Resolution of the warts in this patient appears likely due to a decrease in T-cell production upon simvastatin discontinuation.

Werham A, et al: A case of recalcitrant plantar warts associated with statin use. *Case Reports in Dermatological Medicine* 2015; doi 10.1155/2015/320620. From Sandwell and West Birmingham NHS Trust, U.K. **The authors declared no conflicts of interest.**

Drug Trade Names: **clopidogrel—*Plavix*; perindopril—*Aceon*; simvastatin—*Zocor***

Pediatric Pill-Swallowing Interventions

Inability to swallow pills can be an important barrier to treatment in children and adolescents, but there has been very little research on effective techniques to improve pill swallowing. The limited evidence indicates that several different approaches are effective.

Methods: A literature search identified all English-language studies published since 1987 that were conducted in patients, aged 0–21 years, with pill swallowing difficulties not attributable to dysphagia or conditions such as severe developmental disability.

Results: The 5 identified studies included 4 cohort studies and 1 case series; no randomized trials were identified. Sample sizes ranged from 11 to 67. Two studies were limited to children aged ≤13 years, 2 also included adolescents up to age 17 years, and 1 included patients as old as 21 years. A behavioral intervention that included shaping and modeling was used in 2 studies. The remaining 3 studies evaluated the effects of: swallowing instructions, a flavored spray that lubricated the mouth and tongue, and an education intervention that included information about the esophagus, 5 different head positions to try, and reassurance.

In all of the studies, most or nearly all patients learned to swallow pills, usually after only 1 practice session. Continued ability to swallow pills was demonstrated in 1 study of patients with HIV at 3- and 6-month follow-up using pill counts, CD4+ T-cell percentage, and viral load. Two other studies assessed ongoing compliance with telephone calls or other methods.

Discussion: The present review identified a number of methods that clinicians can use to

Primary Care Drug Alerts® (ISSN 1061-0359) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: kasey@alertpubs.com. Periodical-class postage is paid at Butler, NJ, and at additional mailing offices. POSTMASTER: Send address changes to Primary Care Drug Alerts, 45 Carey Avenue, Ste 111, Butler, NJ 07405. Subscription $99.00 a year in the U.S.; $107.50 Canada; $117.50 elsewhere; $151 institutional. Back issues and single copies, $10.00 each; prepaid. Institutional multicopy discounts are available.

facilitate pill-swallowing skills. Children as young as 2 years were helped; in fact, younger children needed less training than older ones, perhaps because they had fewer previous negative experiences.

Patel A, et al: Effectiveness of pediatric pill swallowing interventions: a systematic review. *Pediatrics* 2015;135 (May):883–889. From the University of North Carolina School of Medicine, Chapel Hill; and other institutions. **This study was conducted without external funding. The study authors declared no conflicts of interest.**

Vitamin D for Statin Intolerance

In a longitudinal study, vitamin D supplementation successfully resolved statin intolerance due to myalgia or myositis in patients with low levels of vitamin D.

Methods: Study subjects (n=146; mean age, 59 years) had been referred to a specialty clinic after experiencing myalgia, myositis, myopathy, and/or myonecrosis with ≥2 statins. Patients who had experienced rhabdomyolysis were excluded. Serum 25-hydroxyvitamin D levels were measured at the first visit, and patients with levels below the laboratory's normal limit (<32 ng/mL) received supplementation at 50,000 or 100,000 units per week. After 3 weeks, all patients were started on a statin—most frequently 10–20 mg/day rosuvastatin (*Crestor*), or other agents depending on insurance coverage. Other supplemental vitamins were not permitted, and patients were instructed to stop taking the statin immediately if intolerable symptoms occurred. Vitamin D and cholesterol levels were measured every 3 months for 1 year, and then every 4 months thereafter for up to 2 years. The vitamin D dose was adjusted to keep levels in the mid-normal range (approximately 50–80 ng/mL), and the statin dose was adjusted to achieve LDL-cholesterol levels according to the Adult Treatment Panel III guideline.

Results: The median vitamin D dose was 50,000 units/week throughout the 2 years of follow-up. Patients had average increases in serum 25-hydroxyvitamin D, with levels reaching normal in about 90%. Of 134 patients who had a 6-month follow-up visit, 118 (88%) were free of muscle symptoms, as were 94 of 103 (91%) seen at 12 months and 78 of 82 (95%) seen at 24 months. Median LDL cholesterol fell from about 165 mg/dL at the beginning of treatment to 97 mg/dL at last follow-up.

Discussion: Severe vitamin D deficiency can cause reduced muscle function and the same muscle symptoms as statin intolerance. Various retrospective and cross-sectional studies have linked statin intolerance with low levels of vitamin D, and there have been previous case reports of reversal of statin intolerance with vitamin D. A limitation of the present study is its primary use of rosuvastatin, which is associated with less myalgia than some other statins.

Khayznikov M, et al: Statin intolerance because of myalgia, myositis, myopathy, or myonecrosis can in most cases be safely resolved by vitamin D supplementation. *North American Journal of Medical Sciences* 2015;7 (March):86–93. From the Jewish Hospital of Cincinnati, OH. **Funded by the Jewish Hospital of Cincinnati; and other sources. The authors declared no conflicts of interest.**

Statins and Dementia Risk

According to results of a cohort study in elderly patients, statin therapy reduces the risk of dementia. Higher dosages of statins and use of agents with greater lipid-lowering potency appear to confer the greatest benefit.

Background: Accumulating evidence suggests cholesterol may be implicated in the pathogenesis of dementia, but the role of statins in prevention has been unclear.

Methods: A national health insurance registry in Taiwan was used to identify nearly 60,000 patients, aged >65 years, without a history of dementia in 1997–98. Patients were followed until 2009 for the development of senile or presenile dementia, classified according to ICD-9 codes. Statin use was determined from prescription claims, and the different statins were assigned an equivalent daily dose. More than 15,000 patients received statins, but to balance comparison groups of users and nonusers according to multiple covariates, the investigators assigned propensity scores* for statin use and were able to match 2003 pairs of statin users and non-users.

Results: Throughout the study, the most commonly used agent was atorvastatin (>50%), followed by simvastatin and lovastatin. After a median follow-up of nearly 12 years, 5516 patients received a diagnosis of dementia. Risk estimates were adjusted for age, gender, major comorbidities, major risk factors, and use of several relevant medications. Statin use during follow-up was associated with a highly statisti-

cally significant reduction in the risk of dementia compared with non-use (p<0.001). Results of the propensity score-matched analysis demonstrated a significant protective effect in the highest tertile of accumulated statin dose (>542 mg; hazard ratio [HR],* 0.38), mean daily dose (>0.99 mg; HR, 0.49), days of taking statins (>830 days; HR, 0.49), and percentage of days of statin use (>21%; HR, 0.64). Lesser degrees of statin exposure were not associated with reduced risk.

Dementia risks with different statins were estimated using atorvastatin as the reference. Rosuvastatin had a stronger protective effect than atorvastatin (HR, 0.20; p<0.001). Effects of pravastatin and simvastatin were similar to atorvastatin; fluvastatin and lovastatin had weaker protective effects.

Discussion: The potency of statins rather than their solubility (i.e., hydrophilic vs. lipophilic) appears to be the major influence on dementia risk. High-potency statins such as atorvastatin and rosuvastatin have not only greater cholesterol-lowering effects, but also greater anti-inflammatory effects.

Wu C-K, et al: Statin use reduces the risk of dementia in elderly patients: a nationwide data survey and propensity analysis. *Journal of Internal Medicine* 2015;277: 343–352. From National Taiwan University College of Medicine and Hospital and other institutions, Taipei. **Source of funding not stated. The authors declared no conflicts of interest.**

Drug Trade Names: **atorvastatin—*Lipitor*; fluvastatin—*Lescol*; lovastatin—*Altoprev, Mevacor*; pravastatin—*Pravachol*; rosuvastatin—*Crestor*; simvastatin—*Zocor***

***See Reference Guide.**

Neuropeptide for Alzheimer's Disease

A neurotrophic supplement, Cerebrolysin, has positive effects on cognition in patients with Alzheimer's disease, according to a meta-analysis.[1]

Background: Cerebrolysin is a biotechnologically prepared peptide that stimulates neurotrophic regulation in the central nervous system.[2] It is used in many countries, but not the U.S., for treatment of ischemic and hemorrhagic stroke, traumatic brain injury, dementia (i.e., vascular dementia, Alzheimer's disease), and other cognitive disorders and to prevent cognitive decline after brain injuries. Cerebrolysin is administered by injection or infusion.

Methods: All randomized, double-blind, parallel-group, placebo-controlled trials of Cerebrolysin for the treatment of mild-to-moderate Alzheimer's disease were identified by literature search. The included studies were ≥4 weeks in duration and used a variety of primary cognitive efficacy endpoints, such as the Alzheimer's Disease Assessment Scale–cognitive subscale and mini-mental state examination. To compensate for the variety of outcome measures, mean changes in cognitive function were standardized and the effect size* estimated using the standardized mean difference (SMD).*

Results: In 6 separate trials, patients received 30 mg/day Cerebrolysin in 20 infusions over the first 4 weeks; 1 study had an additional treatment cycle that started 8 weeks after the end of the first; and 1 study extended treatment with 2 weekly injections for a further 8 weeks. Data on cognitive function was available for 763 patients at 4 weeks and for 519 patients at 6 months.

After 4 weeks, there was a 0.4-point SMD for measures of cognitive function in favor of Cerebrolysin over placebo (p=0.003). The 6-month follow-up showed a difference of similar size, but without statistical significance. Cerebrolysin produced significantly more global clinical change than placebo, with odds ratios* of 3.32 (p=0.02) at 4 weeks and 4.98 (p=0.015) at 6 months. The number needed to treat* for 1 patient to benefit was 3 at both time intervals. Global benefit was estimated as a combined effect of global clinical change and cognitive function. At both follow-up time points, the effect size of Cerebrolysin was >0.57, indicating more than a small superiority to placebo (p=0.0006 for 4 weeks and 0.0010 for 6 months).

Cerebrolysin and placebo were associated with similar rates of adverse events. Patients who received Cerebrolysin had slightly higher rates of headache, vertigo, and hyperhidrosis. Rates of discontinuation due to adverse effects were similar in the Cerebrolysin and placebo groups: 34% and 35%, respectively.

Discussion: Compared with meta-analyses of other Alzheimer's-disease treatments, this study places the effect size of Cerebrolysin between the smaller effects of memantine and the larger effects of donepezil. However, further study is needed to determine the effects of Cerebrolysin on functioning and behavior.

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

[1]Gauthier S, et al: Cerebrolysin in mild-to-moderate Alzheimer's disease: a meta-analysis of randomized controlled clinical trials. *Dementia and Geriatric Cognitive Disorders* 2015; doi 10.1159/000377672. From the McGill Center for Studies in Aging, Montreal, Canada; and other institutions including EVER Neuro Pharma GmbH, Unterach, Austria. **Source of funding not stated. Four study authors disclosed potentially relevant financial relationships; the remaining 2 authors declared no conflicts of interest.**

[2]Cerebrolysin. Everpharma website: www.everpharma.com/products/cerebrolysinr.

Drug Trade Names*: donepezil—*Aricept*; memantine—*Namenda

***See Reference Guide.**

Ivabradine Approved for Heart Failure

The FDA has approved ivabradine (*Corlanor*) to reduce hospitalization in patients with chronic heart failure.[1] The agent belongs to a novel class of cardiac drug that regulates heart rate through selective inhibition of the I_f current in the sino-atrial node, the body's cardiac pacemaker, inhibiting spontaneous depolarization in the sinus node. As such, its effects are highly specific, lowering heart rate without affecting other aspects of cardiac function or inducing hypotension.[2]

Ivabradine is indicated for patients who have symptoms of heart failure that are stable and a normal heartbeat with a resting rate of ≥70 beats per minute, who are also taking beta blockers at the highest tolerated dose. The agent was reviewed under the FDA's priority review program, which provides for expedited review of drugs intended to treat a serious disease or condition and that may provide a significant improvement over available therapy. It was also granted fast track designation, which helps facilitate the development and expedite the review of drugs to treat serious or life-threatening conditions and fill an unmet medical need.

In a clinical trial in >6500 patients, ivabradine reduced the time to re-hospitalization for worsening heart failure. The most common adverse effects were bradycardia, hypertension, atrial fibrillation, and temporary vision disturbance. Ivabradine poses fetal risks, and women should not become pregnant while taking the drug.

[1]FDA News Release: FDA approves Corlanor to treat heart failure. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements.

[2]Lally J, et al: Ivabradine, a novel treatment for clozapine-induced sinus tachycardia: a case series. *Therapeutic Advances in Psychopharmacology* 2014;4:117–122.

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 one group has half the risk of the other group.

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 is the treatment.

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.

Standardized Mean Difference: The difference between two normalized means—the mean values divided by an estimate of the within-group standard deviation. The standardized mean difference is used for comparison of data obtained using different scales.

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

Volume XXXVI / June 2015 / Number 6 www.alertpubs.com

Combination COPD Drug Approved

The FDA has approved the combination of the anticholinergic tiotropium bromide plus the long-acting beta$_2$-adrenergic agonist (LABA) olodaterol (*Stiolto Respimat*) for the treatment of chronic bronchitis and emphysema. Approval was based on the results of 2 clinical trials that showed the combination improved lung function to a greater degree than either of its components alone. Common adverse effects included back pain, cough, and common cold. Serious adverse effects can include allergic reactions; shortness of breath; irregular heartbeat; increased BP; narrow-angle glaucoma; urinary symptoms; lowered potassium levels; and increased blood sugar. Tiotropium–olodaterol is an inhalation spray designed to be used daily; it is not intended to replace rescue inhalers. Like all LABAs, it will carry a boxed warning about increased risk of asthma-related death.

Drug Trials Snapshots: Stiolto Respimat. Available at www.fda.gov/drugs.

Oral Contraceptives and VTE

Newer combined oral contraceptives are associated with higher risk of venous thromboembolism than older, second-generation preparations, according to a large population-based study based on prescribing practices in the U.K. Risks were significantly increased for formulations containing gestodene, desogestrel, drospirenone, and cyproterone.

Methods: Data were analyzed from 2 research databases comprising >1300 general practices in the U.K. Cases of VTE were identified among women, aged 15–49 years, who received treatment in 2001–2013 and had no history of VTE. Each case patient was matched with up to 5 age- and practice-matched controls. Odds ratios* for VTE were calculated for each of the 7 combined oral contraceptives that were the most commonly prescribed in the U.K. (i.e., cyproterone; desogestrel; drospirenone; gestodene; levonorgestrel; norethisterone; norgestimate). Results were adjusted for medical conditions affecting risk of VTE and other risk factors such as obesity, smoking, and alcohol consumption.

Results: The analysis was based on >10,500 patients who experienced VTE and >42,000 control subjects who did not. Results were broadly similar for the 2 databases. About 58% of the VTE cases were recorded as deep vein thrombosis only, one-third were pulmonary embolism, and about 10% were other types. In the year before the index date, 30% of case patients and 18% of control patients received a prescription for ≥1 oral contraceptive. Preparations containing levonorgestrel accounted for nearly half of all oral contraceptive prescriptions in both groups.

Use of any combined oral contraceptive in the previous year was associated with a significantly increased risk of VTE (adjusted odds ratio, 2.97) compared with no exposure. The risk varied among different agents, resulting in a clear division into 2 categories. One group—desogestrel, gestodene, drospirenone, and cyproterone—was associated with about a 4-fold increase in risk. The others—norethisterone, levonorgestrel, and

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norgestimate—were associated with about 2.5 times the risk. The numbers needed to harm* to produce 1 additional case of VTE over 1 year ranged from >700 (cyproterone) to about 1700 (levonorgestrel). The number of extra VTE cases per 10,000 women treated per year ranged from 6 or 7 (norethisterone, levonorgestrel, and norgestimate) to 11–14 (the others).

The overall pattern of risk was similar for older and younger women and for those with idiopathic VTE versus those with risk factors. Patterns of risk were inconsistent with regard to estrogen dose and duration of exposure.

Vinogradova Y, Coupland C, Hippisley-Cox J: Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ* 2015; doi 10.1136/bmj.h2135. From the University of Nottingham, U.K. **This study was conducted without external funding. The authors declared no relevant financial relationships.**

***See Reference Guide.**

New Treatment Options for IBS

Two new treatments, eluxadoline (*Viberzi*) and rifaximin (*Xifaxan*), have received FDA approval for treatment of adults with irritable bowel syndrome with diarrhea (IBS-D).

Eluxadoline activates receptors in the nervous system that can reduce bowel contractions. It is to be taken twice daily with food. Safety and efficacy of the agent in patients with IBS-D were established in 2 controlled trials in nearly 2500 patients who received treatment for 26 weeks. In the trials, eluxadoline was more effective than placebo at both reducing abdominal pain and improving stool consistency. Constipation, nausea, and abdominal pain were the most commonly reported adverse effects of eluxadoline. However, there is a risk for eluxadoline to produce spasms in the sphincter of Oddi, which can result in pancreatitis. Eluxadoline should not be used by patients with a history of bile duct obstruction, pancreatitis, severe liver impairment, or severe constipation, or by patients who drink >3 alcoholic beverages per day.

Rifaximin is an antibiotic derived from the previously approved rifampin. Rifaximin should be taken 3 times/day for 14 days for the treatment of abdominal pain and diarrhea in patients with IBS-D. Patients who experience symptom recurrence can be retreated with ≤2 additional 14-day treatment courses. The exact mechanism by which rifaximin improves IBS-D is unknown, but it is believed to be related to alteration in GI tract bacterial content. Safety and efficacy of rifaximin in IBS-D were demonstrated in 3 controlled trials: 2 that evaluated a 14-day treatment period followed by a 10-week treatment-free period, and 1 that evaluated two 14-day repeat courses separated by 10 weeks in patients with recurrent symptoms. More patients who received rifaximin than placebo reported improvements in abdominal pain and stool consistency. Common adverse effects of rifaximin included nausea and increased alanine aminotransferase levels. The agent should be used with caution in patients with severe liver impairment.

FDA News Release: FDA Approves two therapies to treat IBS-D. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements.

Oral Medications for Type 2 Diabetes

In the last decade, multiple medications have received FDA approval for the treatment of type 2 diabetes. There are now 9 distinct classes of oral medications and a variety of insulin and noninsulin injectables available. According to a comprehensive review, metformin remains the first-line treatment for most patients, and other options should be selected based on patient characteristics.

Oral Antidiabetics by Class
Sulfonylureas (2nd generation) Glimepiride, Glipizide, Glyburide
Biguanides Metformin
α-Glucosidase Inhibitors Acarbose, Miglitol
Meglitinides Nateglinide, Repaglinide
TZDs Pioglitazone, Rosiglitazone
DPP-4 Inhibitors Alogliptin, Linagliptin, Saxagliptin, Sitagliptin
Bile Acid Sequestrants Colesevelam
Dopamine Receptor Agonists Bromocriptine
SGLT2 Inhibitors Canagliflozin, Dapagliflozin, Empagliflozin

First-Line Therapy. Treatment of patients with type 2 diabetes should follow current guidelines,

such as those of the American Diabetes Association, which recommend lifestyle modification as the initial step. Metformin is recommended as first-line pharmacotherapy for most patients because of its efficacy, low hypolycemia risk, and potential to produce weight loss. Metformin has also been associated with a 36–40% reduction in mortality compared with conventional therapy with a sulfonylurea or insulin. Alternate first-line treatments include sulfonylureas; thiazolidinediones (TZDs); dipeptidyl peptidase 4 (DPP-4) inhibitors; sodium-glucose cotransporter 2 (SGLT2) inhibitors; injectable glucagon-like peptide-1 (GLP-1) agonists; or basal insulin. Patients with an initial A1c >9% may be started on insulin or dual therapy.

Second-Line Therapy. A1c should be monitored every 3 months to assess the effectiveness of hypoglycemic medication. Dual therapy is recommended if the patient is not at goal by 3 months. The same alternate first-line treatments already mentioned can be added to metformin. Agents should not be combined if they have similar mechanisms of action—for example, sulfonylureas and meglitinides or DPP4-inhibitors and GLP-1 antagonists; there is insufficient information on the safety and efficacy of these combinations. Metformin and TZDs are both insulin sensitizers but act via different mechanisms and may be used together. Treatment guidelines do not include several classes of drugs as second-stage therapy: α-glucosidase inhibitors, meglitinides, dopamine receptor agonists, and colesevelam.

Third-Line Therapy. If A1c remains above goal after 3 months of dual therapy, a third agent should be added. In patients already on basal insulin, adding a GLP-1 agonist or prandial insulin should be considered.

Safety. Metformin should be used with caution in patients at risk for lactic acidosis, including the elderly; patients with excessive alcohol intake, hepatic disease, dehydration, or sepsis; and those undergoing surgery. For some second- and third-line options, safety concerns are an issue. For example, TZDs are associated with weight gain, edema, and adverse changes in lipids; patients taking TZDs require monitoring of liver function; and the agents affect bone homeostasis, increasing fracture risk. The possibility that DPP4-inhibitors are associated with acute pancreatitis and risk of pancreatic cancer is under investigation. SGLT2 inhibitors are associated with increased risk of mycotic infections, bladder infections, and possibly bladder cancer.

Tran L, et al: Pharmacologic treatment of type 2 diabetes: oral medications. *Annals of Pharmacotherapy* 2015;49 (May):540–556. From the Chalmers P. Wylie Veterans Affairs Ambulatory Care Center, Columbus, OH. **This review was conducted without funding. The authors declared no conflicts of interest.**

Drug Trade Names*: acarbose—*Precose*; alogliptin—*Nesina*; bromocriptine—*Cycloset*, *Parlodel*; canagliflozin—*Invokana*; colesevalam—*Welchol*; dapagliflozin—*Farxiga*; empagliflozin—*Jardiance*; glipizide—*Glucotrol*; glimepiride—*Amaryl*; glyburide—*Diabeta, Glynase*; metformin—*Glucophage*; miglitol—*Glyset*; nateglinide—*Starlix*; pioglitazone—*Actos*; repaglinide—*Prandin*; rosiglitazone—*Avandia*; saxagliptin—*Onglyza*; sitagliptin—*Januvia

New Class of Cholesterol Lowering Drugs

An FDA advisory committee has recommended approval of alirocumab (*Praluent*) and evolocumab (*Repatha*), 2 new monoclonal antibodies that target proprotein convertase subtilisin/kexin type 9 (PCSK9) for cholesterol lowering.[1,2] However, several committee members suggested that use be limited to high-risk patients such as those with familial hypercholesterolemia. The PCSK9-inhibitors are a new class of cholesterol lowering drugs that block the protein PCSK9, which interferes with the liver's ability to clear LDL cholesterol from the blood. The agents are injectables administered either monthly or every 2 weeks. The new drugs could help patients who cannot tolerate statins or whose cholesterol levels are not adequately reduced with statin therapy.

In most alirocumab clinical trials, cholesterol levels were reduced by about 40–60% and the agent did not appear to be related to increased rates of death or serious adverse events. Memory impairment occurred more frequently in patients taking alirocumab, but it was not considered to be serious. Hepatic adverse effects were also more common with alirocumab, affecting about 2.5% of patients (vs. 1.8% with placebo).

Evolocumab clinical trials demonstrated similar efficacy (average LDL cholesterol reduction, 60%), but the primary studies lasted only 12 weeks and whether the drug reduces cardiovascular events is unclear. Common adverse effects included nasopharyngitis, respiratory tract infections, and back

pain.[3] As with alirocumab, evolocumab did not appear to be associated with increased rates of death or serious adverse events. Potential safety issues with evolocumab include risk of pancreatitis, new-onset type 2 diabetes, and injection site reactions.

The FDA is not required to follow the panel's recommendations, but they typically do so.

[1]Burton T: FDA panel backs cholesterol drug, but raises concerns. *Wall Street Journal* June 09, 2015. Available at http://online.wsj.com.

[2]Burton T: FDA Panel backs Amgen's cholesterol-lowering drug. *Wall Street Journal* June10, 2015. Available at http://online.wsj.com.

[3]Repatha approval status. Drugs.com. Available at www.drugs.com/history/repatha.html.

Botulinum Toxin for Chronic Migraine

OnabotulinumtoxinA was effective and well tolerated in a clinical series of patients with treatment-resistant chronic migraine.[1]

Background: OnabotulinumtoxinA is approved for use in migraine only in tandem with the PREEMPT treatment protocol.[2] The objective of this study was to analyze the results of treatment with OnabotulinumtoxinA in a population with less strict selection criteria than clinical trials, in order to reflect a clinical setting.

Methods: Study patients (n=52) received onabotulinumtoxinA injections at an outpatient headache clinic following the PREEMPT protocol. Participants were required to have had a history of headaches resulting in a significant disruption to quality of life that had been refractory to topiramate or another neuromodulator and to ≥1 other preventive therapy. Patients kept headache diaries and rated the results of treatment after each session as excellent, good, partial, or no effect.

Results: At baseline, 43 patients (83%) had symptomatic overuse of analgesics or combined medication, and 44 (85%) were receiving preventive therapy. They had a mean of 23 monthly headache days and 14 monthly migraine days.

After the first cycle of treatment, patients had a mean reduction of about 50% in the number of headache days, migraine days, and days of acute medication or triptan intake ($p<0.001$ for each of the 4 variables). Twelve patients reported a lack of efficacy after the first treatment, and 4 of these refused additional treatment. A total of 39 patients received a second set of injections after 3 months. This group experienced a 73% reduction in migraine days from baseline after the second treatment ($p<0.001$) and smaller reductions in the other study outcomes. No patient discontinued onabotulinumtoxinA because of adverse effects.

[1]Pedraza M, et al: OnabotulinumtoxinA treatment for chronic migraine: experience in 52 patients treated with the PREEMPT paradigm. *SpringerPlus* 2015;. doi 10.1186/s40064-015-0957-z. From the Hospital Clinico Universitario Valladolid, Spain. **This study was conducted without financial support. One study author declared relevant financial relationships with commercial sources; the remaining 6 authors declared no conflicts of interest.**

[2]Facts and Comparisons eAnswers: http://online.factsandcomparisons.com.

Drug Trade Names*: onabotulinumtoxinA—*Botox*; topiramate—*Topamax

Reference Guide

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.

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

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XXXVI / July 2015 / Number 7 www.alertpubs.com

Strengthened NSAID Warnings

Both prescription and over-the-counter NSAIDs already carry label warnings about increased risk of heart attack and stroke. Based on the results of a comprehensive safety review, the FDA will now require these warnings to be stronger. The prescription products will now be required to include the following information:

• The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.

• The risk appears greater at higher doses.

• It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.

• NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.

• In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors because they have a higher risk at baseline.

• Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.

• There is an increased risk of heart failure with NSAID use.

Non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs): Drug safety communication FDA strengthens warning of increased chance of heart attack or stroke. Available at www.fda.gov.safety/medwatch.

Esmirtazapine for Insomnia

In a multicenter, placebo controlled trial, esmirtazapine, an investigational enantiomer of the antidepressant mirtazapine (*Remeron*), improved sleep parameters in patients with chronic primary insomnia without producing residual morning effects.

Background: Mirtazapine has sleep-promoting properties believed to be due to its binding of serotonin and histamine-1 receptors. The enantiomer esmirtazapine has a shorter half-life than the racemic compound, suggesting a smaller risk for residual sedative effects the next day.

Methods: Study participants (n=398) were adults, aged 18–65 years, with a diagnosis of primary insomnia. Patients were randomly assigned to esmirtazapine (3.0 or 4.5 mg) or placebo, to be taken 30 minutes before bedtime. The primary endpoint was wake time after sleep onset, measured at days 1, 15, and 36. Latency to persistent sleep was the key secondary endpoint.

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Rebound was assessed during a 1-week discontinuation period. Patients also completed the Withdrawal Symptom Questionnaire.

Results: Esmirtazapine was associated with about a 50- to 55-minute decrease in wake time after sleep onset, compared with about 25 minutes for placebo. Both doses of esmirtazapine were superior to placebo at each of the 3 time points. Esmirtazapine was also associated with a significant decrease in sleep latency: about 30 minutes versus about 15 minutes for placebo at all 3 time points. Active treatment was also associated with an increase in total sleep time (about 80 minutes vs. 35 minutes for placebo), fewer nighttime awakenings, and more time spent in slow-wave sleep. There were no significant differences in efficacy between the 2 esmirtazapine doses.

There was no evidence of rebound or withdrawal effects when esmirtazapine was discontinued. Compared with baseline, all treatment groups including placebo showed improvement in tests of daytime alertness and in patient-reported energy levels and ability to work. The predominant adverse effects of esmirtazapine were somnolence and headache. Five patients stopped taking esmirtazapine because of somnolence. Four reported mild–to-moderate weight gain.

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

Ivgy-May N, et al: Esmirtazapine in non-elderly adult patients with primary insomnia: efficacy and safety from a randomized, 6-week sleep laboratory trial. *Sleep Medicine* 2015;16 (July):838–844. From Merck & Co., Kenilworth, NJ; and other institutions. **Funded by Organon, a subsidiary of Merck. All study authors disclosed financial relationships with commercial sources.**

***See Reference Guide.**

Orlistat-Associated Pancreatitis

A 54-year-old man with a history of hypertension, for which he had been taking irbesartan for 7 years, presented to the emergency department with abdominal pain, nausea, and vomiting 7 days after starting orlistat for obesity. Laboratory studies found marked elevated levels of white blood cells (12,600), C-reactive protein (136 mg/l), lactate dehydrogenase (835 U/l), and serum amylase (2409 U/l). Serum calcium and lipid levels were in the normal range. Based on the laboratory findings and an abdominal CT scan, the patient received a diagnosis of early-stage pancreatitis. All medications and oral intake were stopped. Symptoms improved, and serum amylase levels normalized over 3 days.

Alcohol use and gallstones are the cause for the majority of cases of acute pancreatitis; only about 2% of cases are drug-induced. Orlistat is a pancreatic lipase inhibitor, and due to the increased prevalence of obesity, its use is increasing. Controlled trials of the drug found no association with pancreatitis, but there have been 4 previous cases reported. The mechanism by which the drug causes the reaction is unknown. However, pancreatitis should be considered when a patient newly started on orlistat presents with onset of abdominal pain. Orlistat should be prescribed with caution in patients with risk factors for the condition.

Kose M, et al: An unexpected result of obesity treatment: orlistat-related acute pancreatitis. *Case Reports in Gastroenterology* 2015;9 (May-August):152–155. From Istanbul University, Turkey. T**he authors declared no conflicts of interest.**

Drug Trade Names*: irbesartan—*Avapro*; orlistat—*Xenical

Drug Combination for Alzheimer's Disease

Results of 2 preliminary studies in healthy adults suggest a single-capsule, fixed-dose combination of donepezil and memantine is bioequivalent to coadministered commercially available versions of the 2 drugs.[1] Food intake and sprinkling the capsule contents on applesauce did not affect bioavailability of the combination pill.

Background: Patients with moderate-to-severe Alzheimer's disease take an average of 6 different medications each day, and medication nonadherence has been reported in about 40% of patients with the disease. Nonadherence may be caused by forgetfulness, high caregiver burden, high pill burden, complex medication regimens, or swallowing difficulties. Combining 2 of the most commonly prescribed medications into a single daily capsule has the potential to improve treatment adherence, and the ability to administer the drugs sprinkled on soft foods can further increase compliance and safety in patients who have difficulty swallowing.

Methods: The fixed-dose combination of 28 mg extended-release memantine and 10 mg donepezil, which received FDA approval in late 2014,[2] was evaluated in 2 groups of healthy men and women, aged 18–45 years. Pharmacokinetics of the fixed-dose combination were compared with coadministered commercially available donepezil and

memantine in 38 participants. Treatments were administered in a single dose, in a randomized crossover fashion, with a 21-day washout between tests. In the second study, 36 patients received 3 treatments in randomized order, again separated by a 21-day washout: an intact fixed-dose combination capsule taken while fasting, a capsule taken following a high-fat meal, and the capsule contents sprinkled on applesauce and taken while fasting.

Results: In the first trial, the fixed-dose combination was bioequivalent to the commercially available drugs, as indicated by the area under the concentration-time curve*. Peak concentrations, time to peak, half-life, and plasma concentration-time profiles did not differ between treatments. In the second study, most pharmacokinetic parameters were similar for the 3 types of administration. For memantine, the half-life after administration of an intact capsule while fasting was significantly longer than the other 2 methods (24 vs. 14 hours). For donepezil, administration with a high-fat meal was associated with a later time-to-peak concentration. All 3 methods were bioequivalent. In both studies, adverse events were similar with all treatments; the most common being nausea, dizziness, feeling hot, vomiting, headache, and abdominal discomfort.

[1]Boinpally R, et al: A novel once-daily fixed-dose combination of memantine extended release and donepezil for the treatment of moderate to severe Alzheimer's disease: two phase I studies in healthy volunteers. *Clinical Drug Investigation* 2015; doi 10.1007/s40261-015-0296-4. From Forest Research Institute, Jersey City, NJ; and Adamas Pharmaceuticals, Emeryville, CA. F**unded by Forest Laboratories, Inc. All 6 study authors declared financial relationships with commercial sources including Forest Laboratories or Adamas Pharmaceuticals.**

[2]Actavis and Adamas announce FDA approval of Namzaric™, a fixed-dose combination of memantine extended-release and donepezil hydrochloride [Press Release]. Dublin and Emeryville, CA: Actavis PLC and Adamas Pharmaceuticals Inc.; December 24, 2014.

Drug Trade Names*: donepezil—*Aricept*; donepezil–memantine—*Namzaric*; memantine—*Namenda

***See Reference Guide.**

Antidiabetics and Ketoacidosis

Health Canada has initiated a safety review of the possible association between ketoacidosis and the sodium-glucose cotransporter-2 (SGLT2) inhibitors dapagliflozin and canagliflozin. Ketoacidosis occurs when insulin levels are too low and is typically associated with high blood sugar levels in patients with type 1 diabetes. The condition has been reported in patients taking the SGLT2 inhibitors who had only slight increases in blood sugar. Symptoms of ketoacidosis include difficulty breathing; extreme thirst; abdominal pain; nausea; vomiting; loss of appetite; confusion; and tiredness. Patients taking an SGLT2 inhibitor who present with these symptoms should be evaluated for ketoacidosis regardless of blood sugar levels. Treatment should be discontinued if ketoacidosis is confirmed.

Information Update Forxiga, Invokana: Health Canada begins safety review of diabetes drugs known s SGLT2 inhibitors and risk of ketoacidosis. Available at www.hc-sc.gc.ca.

Drug Trade Names*: canagliflozin—*Invokana*; dapagliflozin—*Forxiga

Quetiapine Abuse

Concern about quetiapine (*Seroquel*) misuse has emerged from the existence of street names and markets for the drug, reports of patients feigning symptoms to obtain it, and reports of intravenous or intranasal use. Quetiapine has reportedly been used to self-medicate insomnia and anxiety, to get drunk without the hangover, as a sedative after using stimulants or crack cocaine, to zone out, and to substitute for other drugs.

Methods: Data were collected from the Drug Abuse Warning Network (DAWN), a surveillance system of emergency department visits that acts as an indirect measure of drug use, abuse, and misuse. DAWN data are based on a sample of 250–350 hospitals, depending on the year, and come from abstracting of emergency department records. The present report examined visits in patients aged ≥12 years for 3 types of drug-related problems: adverse events, suicide attempts, and misuse and abuse—the latter defined as use by a person for whom the drug was not prescribed, or use not according to medical instructions, such as in larger amounts or more often.

Results: The nationally representative estimate of quetiapine-related visits increased from about 35,600 in 2005 to 67,500 in 2011. The number of visits for misuse or abuse increased from about 19,000 to 32,000, and visits for suicide attempts increased from about 8600 to 16,000. Quetiapine accounted for about half of all visits involving an antipsychotic agent and 62% of visits involving an atypical. Proportions of visits for suicide attempts were the same: quetiapine accounted for 52% of antipsychotics and 62% of atypicals. Among

patients taking drug combinations, quetiapine was typically used with anxiolytics, sedatives, or hypnotics for both misuse/abuse and suicide attempts. Alcohol was involved in about one-third of misuse/abuse or suicide visits, and illicit drugs in about one-fourth.

Discussion: It is possible that the increasing rate of quetiapine misuse may be the result of its greater availability; it is among the most widely prescribed antipsychotics. Regardless of the reasons, the data from DAWN suggest that concerns about the misuse and abuse of quetiapine are warranted. Clinicians should be particularly cautious about quetiapine in patients with comorbid mental health and substance abuse issues.

Mattson M, et al: Emergency department visits involving misuse and abuse of the antipsychotic quetiapine: results from the Drug Abuse Warning Network (DAWN). S*ubstance Abuse Research and Treatment* 2015; doi 10.4137/SART.S22233. From the Substance Abuse and Mental Health Services Administration (SAMHSA), Rockville, MD; and other institutions. **Funded by SAMHSA. The authors declared no conflicts of interest.**

Methylphenidate Skin Changes

According to a warning issued by the FDA, permanent loss of skin color can occur with use of the methylphenidate transdermal system (*Daytrana*).

The skin condition, known as chemical leukoderma, is not physically harmful but is disfiguring. In addition, the condition is not reversible, which can cause patients' emotional distress. The lightened skin sites associated with the methylphenidate patch were reportedly as large as 8 inches in diameter. *Daytrana* labeling has been updated to reflect the risk.

Patients and caregivers should monitor users for new areas of lightened skin, particularly under where the patch has been applied, and alternate treatments should be considered for patients who experience skin color changes.

Daytrana Patch (methylphenidate transdermal system): Drug safety communication—Permanent skin color changes. Available at www.fda.gov/safety/medwatch.

Reference Guide

Area Under the Concentration-Time Curve (AUC): A pharmacokinetic measure useful when trying to determine whether 2 formulations of the same dose (for example a capsule and a tablet) release the same dose of drug to the body. AUC can range from zero to infinity, and it represents the total drug exposure over time. AUC is proportional to the total amount of drug absorbed by the body (i.e., the total amount of drug that reaches the blood circulation).

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 XXXVI / August 2015 / Number 8 www.alertpubs.com

Brilinta, Brintellix Name Confusion

The FDA has released a drug safety communication regarding prescribing and dispensing errors involving the antiplatelet agent *Brilinta* (ticagrelor) and the antidepressant *Brintellix* (vortioxetine). The primary reason for the errors appears to be the similarity of the drugs' brand names. Prescribers can reduce the risk of these errors by including the generic name as well as the indication for treatment on all prescriptions for these agents. Patients should be reminded to check their prescriptions to ensure the proper medication was dispensed.

Brintellix (vortioxetine) and Brilinta (ticagrelor): drug safety communication–name confusion. Available at www.fda.gov/Safety/MedWatch.

New Cardiovascular Agents

Two new cardiovascular drugs have recently received FDA approval: a combination antihypertensive for patients with heart failure and an antiplatelet agent to be used during percutaneous coronary intervention (PCI).

Sacubitril–valsartan (*Entresto*) was evaluated under the priority review program and received fast-track approval for treatment of heart failure. It was shown in a clinical trial of >8000 patients to reduce the rates of death and heart failure-related hospitalization further than enalapril. Common adverse effects included hypotension, hyperkalemia, and renal impairment. Angioedema was also reported, and sacubitril–valsartan should not be used with an ACE inhibitor as coadministration increases this risk.

Cangrelor (*Kengreal*) is an IV antiplatelet drug recently approved to reduce the risk of serious clotting complications during PCI. In a clinical trial of >10,000 patients, cangrelor significantly reduced heart attacks, the need for further procedures, and stent thrombosis compared with clopidogrel. However, while the absolute rates were low, serious bleeding occurred more frequently with cangrelor than clopidogrel: about 1 in 170 patients vs. 1 in 275 clopidogrel patients.

[1]FDA news release: FDA approves new drug to treat heart failure. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements.

[2]FDA news release: FDA approves new antiplatelet drug used during heart procedure. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements.

Drug Trade Names*: cangrelor—*Kengreal*; clopidogrel—*Plavix*; enalapril—*Vasotec*; sacubitril–valsartan—*Entresto

Impact of New Statin Guidelines

According to the results of a large cohort study, the new American College of Cardiology/American Heart Association (ACC/AHA) guidelines for cholesterol management are more accurate in identifying patients who would benefit from statin therapy than the older guidelines from the National Cholesterol Education Program (ATP III). The new guidelines appear to be particularly useful in patients at intermediate risk of cardiovascular disease.

Background: The 2013 ACC/AHA guidelines have raised concerns about a large increase in the number of patients who would receive statins, compared with the previous ATP III cholesterol

Primary Care Drug Alerts® (ISSN 1061-0359) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: kasey@alertpubs.com. Periodical-class postage is paid at Butler, NJ, and at additional mailing offices. POSTMASTER: Send address changes to Primary Care Drug Alerts, 45 Carey Avenue, Ste 111, Butler, NJ 07405. Subscription $99.00 a year in the U.S.; $107.50 Canada; $117.50 elsewhere; $151 institutional. Back issues and single copies, $10.00 each; prepaid. Institutional multicopy discounts are available.

guidelines. To determine if the new guidelines improve identification of patients at higher risk of cardiovascular events, the 2 guidelines were compared in a subset of second- and third-generation participants in the Framingham Heart Study.

Methods: Study subjects (n=2435) were men aged ≥35 years and women aged ≥40 years who weighed ≤350 pounds, did not have cardiovascular disease, and were not taking lipid-lowering medications at baseline. Participants had a mean age of 51 years at baseline and a mean Framingham risk score (10-year cardiovascular risk) of 6.7%. Each patient's eligibility for statin therapy was determined using both sets of guidelines, and they were followed for an average of >9 years. The primary study outcome was incident coronary heart disease (CHD) events (MI or death due to CHD) or cardiovascular (CVD) events (CHD events plus ischemic stroke). All patients also underwent cardiac CT imaging for coronary artery calcification, a secondary outcome.

Results: At baseline, 39% of study subjects were eligible for statin therapy according to the ACC/AHA guidelines, compared with 14% according to ATP III guidelines. During follow-up, there were 40 nonfatal MIs, 31 nonfatal strokes, and 3 cardiac deaths, for a total of 74 (3%) incident CVD events and 43 (1.8%) incident CHD events. In statin eligible versus noneligible patients, hazard ratios* for incident cardiovascular disease (6.8) and major CHD (8.6) were higher with the ACC/AHA guidelines (3.1 and 3.3, respectively), indicating that these guidelines are better able than ATP III to discriminate risk of disease events between statin-eligible versus non-eligible participants. These results were not attenuated by adjusting the analysis to account for prescription of statin therapy at subsequent examinations.

About one-third of the study population was at intermediate risk of CVD at baseline, based on a Framingham Risk Score of 6–20%. Most patients (80%) at intermediate risk were eligible for statin therapy according to the ACC/AHA guidelines, but only 27% according to the ATP III guidelines. The older guidelines did not discriminate between patients who did or did not experience an adverse outcome. Statin-eligible patients according to ACC/AHA were significantly more likely to have a CVD event than ineligible patients (hazard ratio, 9.3; p=0.03).

Pursnani A, et al: Guideline-based statin eligibility, coronary artery calcification, and cardiovascular events. *JAMA* 2015;314 (July 14):134–141. From Massachusetts General Hospital and Harvard Medical School, Boston; and other institutions. **Funded by the National Heart, Lung, and Blood Institute. One study author disclosed financial relationships with commercial sources.**

***See Reference Guide.**

Isavuconazole: New Systemic Antifungal

The FDA recently approved isavuconazole (*Cresemba*), a new broad-spectrum triazole antifungal. According to a review, isavuconazole has several advantages over other antifungals, and it provides a useful alternative to voriconazole for treating invasive aspergillosis.

Mortality from invasive antifungal infections is high, and the incidence of these infections is increasing. There is an urgent need for better antifungals, including ones with activity against resistant strains and the widening range of important fungal pathogens. Existing antifungals are limited by adverse effects; drug interactions; limited spectrum of coverage; resistance; and the lack of an oral formulation. Isavuconazole is a second-generation triazole antifungal with oral and IV dosage forms. It was approved in March 2015 for treatment of invasive aspergillosis and invasive mucormycosis in adults, and it is under investigation for numerous other fungal infections.

Isavuconazole is administered as a prodrug, which is rapidly and almost completely converted to the active compound. Following oral administration, isavuconazole reaches peak concentrations in about 2 hours and the elimination half-life is 77 hours. The oral and IV doses are equivalent due to high oral bioavailability. There is no clinically relevant food effect. Like other azoles, isavuconazole works by interfering with the synthesis of the fungal cell membrane. In vitro, isavuconazole shows antifungal activity against most *Aspergillus*, *Cryptococcus*, and *Candida* species; *Trichosporon*; several rare yeasts; Mucorales; and filamentous and dimorphic fungi.

Clinical trials support its efficacy in oropharyngeal and esophageal candidiasis and in aspergillosis. In subanalyses from these studies, there is promising evidence of efficacy in other invasive mold infections that are typically associated with high morbidity and mortality. Ongoing studies are

investigating the role of isavuconazole in invasive candida infections and against emerging invasive fungal pathogens.

Isavuconazole is well tolerated, with fewer skin, eye, and hepatobiliary adverse events than voriconazole. Primary adverse effects are GI symptoms, rash, elevated liver function tests, cough, conjunctivitis, and dizziness. Unlike other azoles, it has not been associated with QTc prolongation. It has a drug-interaction profile that is similar to fluconazole or itraconazole, with fewer drug interactions than voriconazole.

Pettit N, Carver P: Isavuconazole: a new option for the management of invasive fungal infections. *Annals of Pharmacotherapy* 2015;49:825–842. From the University of Chicago, IL; and the University of Michigan, Ann Arbor. **This review was conducted without funding. One study author disclosed financial relationships with commercial sources; the other author declared no competing interests.**

Drug Trade Names*: fluconazole—*Diflucan*; isavuconazole—*Cresemba*; itraconazole—*Onmel, Sporanox*; voriconazole—*Vfend

Weight Loss with Liraglutide

Liraglutide, marketed as *Saxenda*, is a recent addition to the list of drugs FDA approved to treat obesity. Like the other agents, liraglutide is an effective adjunctive treatment, recommended for patients who do not achieve sufficient weight loss with diet and increased exercise. According to this review, advantages of liraglutide are once-daily administration and a lower discontinuation rate than some other weight-loss treatments; disadvantages are high cost and daily injections.

Liraglutide is a GLP-1 agonist already approved (as *Victoza*) for treatment of type 2 diabetes. For weight loss, it works by increasing satiety and delaying gastric emptying. As *Saxenda*, it will be available in prefilled injection pens, with a range of doses for titration; however, the highest dose, 3 mg, is the only dose approved for long-term use in obesity management. Like the other obesity medications, liraglutide should be used according to current treatment guidelines: as adjunctive treatment in patients with obesity (body mass index [BMI], >30) or who are overweight (BMI, >27) with comorbid conditions such as diabetes, hypertension, and/or hyperlipidemia.

In clinical trials of obesity medications, the FDA criteria for effectiveness are a mean 5% loss in body weight from baseline, after subtracting weight loss in the placebo group; at least 35% of patients with a ≥5% weight loss; or twice as many patients with a 5% weight loss as placebo. For this review, 3 clinical trials were identified of liraglutide for obesity published through March 2015, all of which met the FDA criteria. The first enrolled 564 patients with obesity (BMI, 30–40), randomly assigned to 4 different liraglutide doses, orlistat as an active comparator, or placebo. After 20 weeks of treatment, patients in all liraglutide dosage groups lost weight, with averages of 11–16 pounds, while the placebo group lost 6 pounds and the orlistat group 9 pounds on average. In the 2 highest dosage groups, more than twice as many patients lost 5% of their initial weight as the in placebo group (61% and 76%, respectively, vs. 30%).

The second trial was an extension of the first, with 268 patients continuing maintenance treatment with orlistat or liraglutide for up to 2 years. Patients who continued liraglutide for 2 years had an average 23-pound weight loss from baseline. In patients who had lost ≥5% of their initial body weight with diet and exercise, 50% of patients who received 3 mg/day liraglutide lost an additional 5% of their initial body weight.

It has also shown promising effects in 2 smaller studies: in overweight patients with prediabetes and in overweight women with polycystic ovary syndrome. Because most study participants were white and otherwise healthy, it is unknown if liraglutide is equally effective in African American or Hispanic patient populations or in people with multiple comorbidities or extreme obesity. Effects of long-term treatment are unknown. Liraglutide is currently being evaluated in a series of ongoing studies, called the SCALE studies (see next article in this issue), in various clinical groups.

Clements J, Shealy K: Liraglutide: an injectable option for the management of obesity. *Annals of Pharmacotherapy* 2015;49 (August):938–944. From Presbyterian College, Clinton, SC. **This review was conducted without funding. The authors declared no competing interests.**

Drug Trade Names*: liraglutide—*Saxenda, Victoza*; orlistat—*Alli, Xenical

More on Liraglutide Weight Loss

In a large, multicenter, randomized trial conducted by the Satiety and Clinical Adiposity—Liraglutide Evidence in Nondiabetic and Diabetic Individuals (SCALE) Study Group, liraglutide (*Saxenda*) was associated with weight loss and improved glycemic control when combined with

lifestyle modification in patients with obesity and in those who were overweight with additional risk factors.

Methods: The trial, conducted in 27 countries on 6 continents, enrolled nondiabetic patients with a BMI of ≥30, or ≥27 in patients with dyslipidemia or hypertension. Patients (n=3731) were randomly assigned in a 2:1 ratio to receive 3 mg/day liraglutide or placebo in addition to counseling about diet and exercise. Treatment was administered once daily via a preloaded injection pen. The 56-week trial had 3 co-primary endpoints: weight change from baseline and the proportion of patients who lost ≥5% and >10% of baseline body weight.

Results: Study patients had a mean initial body weight of 234 lbs. and a mean BMI of 38. Nearly two-thirds met criteria for prediabetes. Most patients—72% in the liraglutide group and 64% in the placebo group—completed the 56 weeks of treatment. Results were superior for liraglutide for the 3 primary endpoints. (See table.) Overall, about 92% of patients in the liraglutide group and 65% of the placebo group lost weight.

The liraglutide group also had larger decreases in BMI and waist circumference and in glycated hemoglobin, fasting glucose, and insulin levels, although these metabolic differences were sometimes modest. Measures of insulin resistance and beta-cell function were improved in the liraglutide group. The prevalence of prediabetes was lower at end of study in the liraglutide group (about 38% vs. 88% of the placebo group), and more patients in the placebo group had onset of type 2 diabetes (odds ratio,* 8.1). Liraglutide was associated with significantly greater BP lowering and improvement in the fasting-lipid profile.

Primary endpoints at 56 weeks			
Endpoint	**Liraglutide**	**Placebo**	**Significance**
Mean weight loss	19 lbs.	6 lbs.	p<0.001
Percent losing ≥5% of baseline weight	63%	27%	p<0.001
Percent losing >10% of baseline weight	33%	11%	p<0.001

Pi-Sunyer X, et al: A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *NEJM* 2015;373 (July 2):11–22. From Columbia University, New York, NY; and other institutions. **Funded by Novo Nordisk. Nine study authors declared financial relationships with commercial sources; the remaining 2 authors declared no conflicts of interest.**

***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.

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PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XXXVI / September 2015 / Number 9 www.alertpubs.com

Fracture Risk with Canagliflozin

The sodium-glucose cotransporter-2 (SGLT2) canagliflozin has been linked to reduced bone mineral density at the hip and lower spine, as well as increased fracture risk as early as 12 weeks after starting treatment. Prescribers should consider other factors that affect fracture risk before starting a patient on canagliflozin, and patients should be counseled about these factors. To address the safety concerns, the FDA is requiring label changes strengthening the warning about fracture risk and updating information on bone mineral density effects. In addition, the agency is evaluating risk with other drugs in the SGLT2 class (e.g., dapagliflozin, empagliflozin).

FDA MedWatch Alert: Invokana and Invokamet (canagliflozin): drug safety communication – new information on bone fracture risk and decreased bone mineral density. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm461876.htm.

Drug Trade Names*: canagliflozin—*Invokana*; canagliflozin–metformin—*Invokamet*; dapagliflozin—*Farxiga, Xigduo XR*; empagliflozin—*Jardiance, Glyxambi, Synjardy

Rapid Dabigatran Reversal

In a prospective cohort study, idarucizumab rapidly, completely, and safely reversed the anticoagulant activity of dabigatran (*Pradaxa*) in patients requiring an antidote to the anticoagulant.[1] Idarucizumab is an investigational monoclonal antibody fragment that binds dabigatran and neutralizes its activity.

Background: A previous review of the FDA Adverse Event Reporting System data found an increased fatality rate with dabigatran relative to warfarin, potentially because dabigatran bleeding could not be reversed.[2]

Methods: This report presents an interim analysis of data on the first 90 patients (of an expected ≤300) enrolled in a multinational study. The study enrolled 2 groups of patients taking dabigatran: those with overt, uncontrollable bleeding that required a reversal agent, and those who needed a surgery/procedure that required normal hemostasis and could not be delayed for 8 hours. All patients received a total of 5 mg IV idarucizumab in 2 infusions, ≤15 minutes apart. The primary study endpoint was the maximum percentage reversal of the anticoagulant effect of dabigatran from the end of the first infusion to 4 hours after the second. Reversal was assessed using the dilute thrombin time or ecarin clotting time.

Results: Nearly all study patients (median age, 77 years) were receiving dabigatran for stroke prevention in the context of atrial fibrillation. A total of 51 patients required reversal for uncontrollable bleeding: 20 with GI bleeding, 18 with intracranial hemorrhage, 9 with trauma, and 11 with other causes; and 39 patients required reversal for surgery. Median time since last dabigatran dose was 15 hours.

In the patients who could be assessed, the median maximum percentage reversal of anticoagulation was 100%, with reversal evident in the blood sample taken after first infusion. In

Primary Care Drug Alerts® (ISSN 1061-0359) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: kasey@alertpubs.com. Periodical-class postage is paid at Butler, NJ, and at additional mailing offices. POSTMASTER: Send address changes to Primary Care Drug Alerts, 45 Carey Avenue, Ste 111, Butler, NJ 07405. Subscription $99.00 a year in the U.S.; $107.50 Canada; $117.50 elsewhere; $151 institutional. Back issues and single copies, $10.00 each; prepaid. Institutional multicopy discounts are available.

these early blood samples, levels of unbound dabigatran were associated with negligible anticoagulant effects in all but 1 patient. At 12 and 24 hours, the dilute thrombin time was below the upper limit of normal in 90% of patients with bleeding who could be evaluated, and in 81% of those undergoing surgery. Similar results were evident with other measures of anticoagulation.

In 35 patients with uncontrolled bleeding who could be assessed, bleeding was stopped after a median of 11 hours. Of 36 patients who underwent surgery, normal intraoperative hemostasis was reported in 33.

One patient had a thrombotic event within 72 hours of idarucizumab administration. A total of 18 patients died as a result of the index event or coexisting conditions. There were no safety concerns, including in the patients who were given idarucizumab on clinical grounds but later found to have normal clotting times.

[1]Pollack C Jr, et al: Idarucizumab for dabigatran reversal. *NEJM* 2015;373 (August 6):511–520. From Pennsylvania Hospital, Philadelphia; and other institutions including Boehringer Ingelheim Pharmaceuticals, Ridgefield, NJ and other locations. **Funded by Boehringer Ingelheim. Sixteen of the 18 study authors declared financial relationships with commercial sources; the remaining 2 authors declared no competing interests.**

[2]McConeghy K, et al: Evaluation of dabigatran bleeding adverse reaction reports in the FDA Adverse Event Reporting System during the first year of approval. *Pharmacotherapy* 2014; doi 10.1002/phar.1415. See *Primary Care Drug Alerts* 2014;35 (April):13–14.

Prasugrel vs. Clopidogrel

In patients receiving antiplatelet therapy for coronary artery disease, the increased risk of a major adverse cardiac event with clopidogrel far outweighs risk of major bleeding with prasugrel, according to results of a meta-analysis.

Background: The newer antiplatelet agent prasugrel is known to have more rapid, robust, and consistent antiplatelet actions than clopidogrel, but increased risk of major bleeding has been a concern. The present study was undertaken to clarify the comparative risks of prasugrel and clopidogrel.

Methods: A systematic literature search identified all studies, published through the end of 2014, comparing prasugrel and clopidogrel in patients with coronary artery disease. Studies (n=9; >25,000 patients) were included in the analysis if patients were randomly assigned to prasugrel or clopidogrel and the study reported the outcomes of major adverse cardiac events and major or minor bleeding. Major adverse cardiac event was defined as a composite of cardiovascular deaths, myocardial infarction, and ischemic stroke.

Results: Compared with standard-dose clopidogrel, prasugrel was associated with significantly lower risk of major adverse cardiac events, but a higher incidence of bleeding. (See table.) The risk of major adverse cardiac event far outweighed that of major bleeding (odds ratio,* 7.48; p<0.0001), as well as the risk of minor bleeding (odds ratio, 3.77; p<0.001). The results were not substantially altered by limiting the analysis to trials of standard-dose clopidogrel. For double-dose clopidogrel, results were numerically similar to the overall analysis but did not reach statistical significance.

Adverse Outcomes in Patients on Antiplatelet Therapy

Outcome	Number of cases		Odds ratio prasugrel vs. clopidogrel
	Prasugrel	Clopidogrel	
Major adverse cardiac events	1385	1595	0.86; p<0.0001
Major bleeding	242	183	1.33; p=0.004
Minor bleeding	210	163	1.29; p=0.02

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

Chen H-B, et al: Meta-analysis of randomized controlled trials comparing risk of major adverse cardiac events and bleeding in patients with prasugrel versus clopidogrel. *American Journal of Cardiology* 2015; doi 10.1016/j.amjcard.2015.04.054. From Nanfang Hospital, Southern Medical University, Guangzhou, China. **Funded by the National Nature Science Foundation of China. The authors declared no conflicts of interest.**

Drug Trade Names*: clopidogrel—*Plavix*; prasugrel—*Effient

***See Reference Guide.**

Flibanserin for Hypoactive Sexual Desire

The FDA has approved the first treatment for acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women. HSDD is characterized by low sexual desire that causes marked distress. Flibanserin (*Addyi*) acts as a serotonin 1A receptor agonist and a serotonin 2A receptor antagonist. The mechanism by which it improves sexual desire and related distress is unclear. However, in clinical trials, women who received treatment with 100 mg flibanserin reported an increase in sexual desire, an increased number of satisfying sexual events, and reduced distress associated with HSDD.

Common adverse effects of flibanserin include dizziness; somnolence; nausea; fatigue; insomnia; and dry mouth. The agent is approved with a risk evaluation and mitigation strategy (REMS) program and will be available only from certified physicians and pharmacies. It will carry a Black Box Warning about the potential for severe hypotension and syncope in patients who drink alcohol or who use moderate-to-strong CYP3A4 inhibitors and in those with liver impairment. Bedtime dosing is recommended to reduce the risk for these serious adverse effects. Patients who do not experience improved sexual desire and reduced distress after 8 weeks of treatment should discontinue flibanserin.

FDA news release: FDA approves first treatment for sexual desire disorder. Available at http://www.fda.gov /newsevents/newsroom/pressannouncements.

Antidepressants and Stroke Mortality

The most common neuropsychiatric complication after stroke is post-stroke depression. In a population-based study, early antidepressant treatment during hospitalization for an ischemic stroke was associated with a large decrease in mortality in the subsequent month.

Methods: Registry data was collected for nearly 6000 Danish adults (mean age, 70 years; 44% women) who were admitted during a 7-year period for a first ischemic stroke. Antidepressants were prescribed for post-stroke depression or for pathological crying, another relatively common neurologic complication of stroke. The present analysis was based on 955 patients newly prescribed an antidepressant for these indications and an equal number of propensity-matched controls who had no antidepressant treatment. The primary study endpoint was mortality within 30 days.

Results: Antidepressants were started a median of 5 days after admission (range, 2–11 days). During the 30-day follow-up, 30 deaths occurred in patients who received antidepressants and 318 in the untreated group (adjusted odds ratio,* 0.28). The effects of antidepressant treatment did not differ according to patient age or gender. Antidepressants were beneficial at all levels of stroke severity but had larger effects with greater stroke severity. For example, in patients with very severe stroke, the odds ratio for death was 0.08.

Discussion: These results suggest early antidepressant use is a safe approach to poststroke depression, and there may be no need to wait for the full 14 days of depressive symptom duration before initiating treatment. It should be noted that information on specific antidepressants was not available for the study. However, selective serotonin reuptake inhibitors (SSRIs) are the recommended first-line treatment and likely account for the majority of antidepressant prescriptions. Possible underlying mechanisms for the benefit of antidepressants include anti-inflammatory effects, restoration of capillary blood flow, antiplatelet effects of SSRIs, and earlier recovery from depression, promoting participation in rehabilitation and faster mobilization. Randomized trials are now in progress to replicate these results.

Mortensen J, et al: Early antidepressant treatment and all-cause 30-day mortality in patients with ischemic stroke. *Cerebrovascular Diseases* 2015; doi 10.1159/000435819. From Aarhus University Hospital, Aarhus, Denmark. **Funded by the Tryg Foundation; and other institutions. The authors declared no conflicts of interest.**

***See Reference Guide.**

Effectiveness of *H. Pylori* Treatments

Treatment approaches to eradicate *Helicobacter pylori* have multiplied since the development of resistance to the standard triple treatment (i.e., proton pump inhibitor [PPI] and clarithromycin plus amoxicillin or metronidazole). According to a network meta-analysis, the standard treatment remains effective, but most of the newer regimens have even greater efficacy. Tolerability of the different regimens is similar.

Methods: A literature search identified all full-text, published, randomized, controlled trials, in any language, comparing treatments for *H. pylori* eradication. These included a total of 14 different

treatment regimens (see table); data for each regimen were pooled for comparison. The primary efficacy outcome was the rate of eradication according to an intention-to-treat analysis. Adverse event rates were the secondary outcome.

Results: The efficacy analysis included 143 studies in >32,000 patients. All commonly used treatments were the subject of ≥1 comparison. The eradication rate for 7-day triple therapy (the basis for comparison) was 73%. For the comparison treatments, all were effective in terms of eradication with the most effective being: 7 days concomitant treatment with a PPI and 3 antibiotics (94%); 10 or 14 days concomitant (91%); 10 or 14 days levofloxacin with a PPI plus a second antibiotic (90%); 10 or 14 days of a probiotic plus standard triple treatment (90%); and hybrid treatment with 7 days PPI plus amoxicillin, followed by 7 days PPI plus 3 antibiotics (89%). Only 2 treatments—7 days of levofloxacin (plus PPI inhibitor and a second antibiotic) and 7 days of bismuth (plus PPI and 2 antibiotics)—had an eradication rate that was not statistically superior to standard triple therapy. Longer regimens, lasting 10–14 days, were generally more effective than 7-day treatments. This was not true for concomitant treatments (PPI plus 3 antibiotics) and ranitidine bismuth-based triple treatments, for which shorter and longer durations were equally effective.

The frequency of adverse events did not differ among most treatments but was statistically superior for 2 treatment options: 7 days of probiotic-supplemented triple treatment and 7 days of levofloxacin-based triple treatment. Not surprisingly, shorter regimens had fewer side effects.

Li B-Z, et al: Comparative effectiveness and tolerance of treatments for *Helicobacter pylori*: systematic review and network meta-analysis. *BMJ* 2015; doi 10.1136/bmj.h4052. From Anhui Medical University, China; and other institutions. **Funded by the Chinese national high level personnel special support plan. The authors declared no competing interests.**

Drug Trade Names*: metronidazole—*Flagyl*; ranitidine—*Zantac*; ranitidine bismuth citrate (not available in U.S.)—*Tritec

Treatment Regimens for *H. Pylori* Eradication	
Standard triple therapy	7 days simultaneous PPI+clarithromycin+(amoxicillin or metronidazole)
Concomitant treatment	7 days simultaneous PPI+3 antibiotics (often amoxicillin, clarithromycin, and a 5-nitroimidazole)
Sequential treatment	5 or 7 days simultaneous PPI+amoxicillin, followed by 5 or 7 days simultaneous PPI+clarithromycin+(a 5-nitroimidazole or amoxicillin)
Triple therapy	10 or 14 days simultaneous PPI+clarithromycin+(amoxicillin or metronidazole)
Bismuth	7, 10, or 14 days simultaneous PPI+bismuth compounds+2 antibiotics
Concomitant	10 or 14 days simultaneous PPI+3 antibiotics (often amoxicillin, clarithromycin, and a 5-nitroimidazole)
Probiotic	7, 10, or 14 days standard triple treatment supplemented with probiotics
Ranitidine bismuth	7, 10, or 14 days simultaneous ranitidine bismuth citrate+any 2 of amoxicillin, clarithromycin, and metronidazole
Levofloxacin	7, 10, or 14 days simultaneous PPI+levofloxacin+1 antibiotic
Hybrid	7 days simultaneous PPI+amoxicillin, followed by 7 days simultaneous PPI+amoxicillin+clarithromycin+a 5-nitroimidazole

Reference Guide

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

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

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

Volume XXXVI / October 2015 / Number 10 www.alertpubs.com

GI Bleeding with Newer Anticoagulants

Overall risk of GI bleeding was not elevated in patients taking newer oral anticoagulants compared with those taking warfarin, according to results of a very large cohort study. However, risk with novel agents was elevated in patients aged >65 years and was "particularly concerning" in those aged >75 years.

Background: Randomized trials have identified elevated GI-bleeding risk with dabigatran and rivaroxaban, but there have been few real-world studies comparing bleeding risk with warfarin.

Methods: The present analysis was based on a medical claims database with >100 million enrolled members from geographically diverse areas across the U.S. Plan members were included if they were newly prescribed warfarin, dabigatran, or rivaroxaban between November 2010 and September 2013, with no other anticoagulant prescription in the prior year. Patients with mechanical heart valves, dialysis recipients, and a few other risk groups were excluded. The rate of bleeding with each of the 2 newer agents was separately compared with warfarin using propensity score matching* of pairs receiving each anticoagulant. Separate analyses were carried out for patients with or without atrial fibrillation (AF).

Results: The cohort consisted of nearly 93,000 patients, of whom 73% received warfarin, 18% rivaroxaban, and 9% dabigatran. No difference was found in the overall risk of GI bleeding or in upper or lower GI bleeding between patients taking either of the newer anticoagulants and warfarin, regardless of the presence or absence of AF. However, risk began to increase with the newer agents as patients reached age 65 years. Risk with the newer agents exceeded that with warfarin only in patients aged ≥76 years. Among patients in this age group with AF, hazard ratios* (HR) for GI bleeding were 2.91 for rivaroxaban and 2.49 for dabigatran. In those without AF, the HR was 4.58 for dabigatran, but the risk with rivaroxaban was similar to warfarin.

Discussion: This study supports the general safety of novel anticoagulants in younger patients but highlights the need to carefully consider their safety in older patients.

Abraham N, et al: Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population-based cohort study. *British Medical Journal* 2015; doi 10.1136/bmj.h1857. From the Mayo Clinic, Scottsdale, AZ; and other institutions. **Funded by the Mayo Clinic. The study authors declared no competing interests.**

Drug Trade Names: **dabigatran—*Pradaxa*; rivaroxaban—*Xarelto***

***See Reference Guide.**

Dabigatran Reversal

Accelerated FDA approval has been granted for the only dabigatran-reversal agent, idarucizumab (*Praxbind*). The agent is indicated for rapid reversal of dabigatran anticoagulation during emergency situations when bleeding cannot be controlled. Idarucizumab is an intravenous injection that works by binding to dabigatran to

Primary Care Drug Alerts® (ISSN 1061-0359) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: kasey@alertpubs.com. Periodical-class postage is paid at Butler, NJ, and at additional mailing offices. POSTMASTER: Send address changes to Primary Care Drug Alerts, 45 Carey Avenue, Ste 111, Butler, NJ 07405. Subscription $99.00 a year in the U.S.; $107.50 Canada; $117.50 elsewhere; $151 institutional. Back issues and single copies, $10.00 each; prepaid. Institutional multicopy discounts are available.

neutralize its effects. Reversing anticoagulant effects is necessary in certain situations but can increase risk of blood clots and stroke due to the underlying condition; anticoagulation should be resumed as soon as medically appropriate.

FDA News Release (October 16, 2015): FDA approves *Praxbind*, the first reversal agent for the anticoagulant *Pradaxa*. Available at http://www.fda.gov/newsevents/newsroom/pressannouncements. See related story in *Primary Care Drug Alerts* 2015;36 (September):33–34.

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

Sertraline for Premenstrual Symptoms

Results of a multisite, placebo-controlled trial suggest that initiating sertraline (*Zoloft*) treatment at symptom onset can improve some symptoms of premenstrual dysphoric disorder (PMDD).

Background: Evidence supports the use of selective serotonin reuptake inhibitors, either as daily treatment or during the luteal phase, to manage the entire luteal phase of the menstrual cycle. However, symptoms are typically present for only 4–7 days per month. Previous small studies have suggested that treatment for only 1 week or only at symptom onset may be effective. The present randomized trial was undertaken to evaluate efficacy of symptom-onset dosing of sertraline in women with PMDD.

Methods: Study participants were 252 women, aged 18–48 years, who met diagnostic criteria for PMDD during a ≥2-month pretrial assessment period. Women were randomly assigned to 6 months of double-blind treatment with either sertraline or placebo and instructed to take study medication beginning on the day they first noticed onset of premenstrual symptoms and to stop within a few days of menstrual flow, when their symptoms typically abated. Sertraline was started at 50 mg/day and could be increased to 100 mg/day with nonresponse. Women whose symptoms did not respond to treatment after 2 months were offered rescue treatment with daily sertraline. The primary outcome measure was the Premenstrual Tension Scale (PMTS), a 10-item measure of mood, physical, and functional symptoms of PMDD. Symptoms were rated 5–7 days after onset of menses during 6 menstrual cycles of treatment.

Results: A total of 188 study subjects completed the trial, including 3 women in the sertraline group and 9 in the placebo group who received rescue treatment. Women began taking their study medication after about 2 symptomatic days each month and took it for an average of about 7 days per cycle. Change from baseline in mean PMTS score did not differ significantly between the groups receiving sertraline or placebo. However, significant differences favoring sertraline were found on the Inventory of Depressive Symptomatology, clinician-rated version (p=0.02). Rates of response (Clinical Global Impression–Improvement [CGI-I] rating of ≤2) and remission (CGI-I score of 1) also favored the sertraline group, although with statistical significance only for response. (See table.) On the Daily Record of Severity of Problems, which measures 11 symptoms of PMDD, sertraline was associated with statistically significantly greater improvement in the Anger/Irritability subscale (p<0.01), but not the Depressive Symptoms or Physical Symptoms subscales. There was no evidence of withdrawal symptoms after cessation of treatment each month.

Rates of response and remission with sertraline or placebo

	Sertraline	Placebo
Response	67%	52%
Remission	42%	32%

Discussion: The present study suggests irritability symptoms may be most responsive to symptom-onset sertraline, in line with the hypothesis that anger and irritability are the hallmark of the disorder. Although the primary efficacy measure did not show a significant advantage of sertraline over placebo, the authors suggest the finding may be related to the large placebo response, which was likely driven by expectations of improvement arising from repeated counseling.

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

Yonkers K, et al: Symptom-onset dosing of sertraline for the treatment of premenstrual dysphoric disorder: a randomized clinical trial. *JAMA Psychiatry* 2015; doi 10.1001/jamapsychiatry.2015.1472. From Yale University School of Medicine, New Haven, CT; and other institutions. **Funded by the NIMH. One study author disclosed financial relationships with pharmaceutical-industry sources. The remaining 5 authors declared no competing interests.**

***See Reference Guide.**

Best Treatments for Chronic Sinusitis

Evidence supports topical corticosteroids with daily saline irrigation as first-line maintenance treatment for chronic sinusitis, according to a systematic literature review. Subsequent therapies are based on the patient's polyp status and symptom severity.

Methods: A comprehensive literature search identified 29 studies (12 meta-analyses, 13 systematic reviews, and 4 randomized controlled trials) of chronic sinusitis treatment in adults. Diagnostic criteria for chronic sinusitis varied across individual studies. Each treatment was assigned a score based on the quality of evidence or consensus and on the usefulness of the treatment.

Results: Topical corticosteroids have the highest level of support for maintenance therapy, and high-volume irrigations that deliver >100 ml of solution into the nasal cavity appear to be more effective than low-volume spray techniques. However, firm recommendations on the delivery method await further research. Saline irrigations are also highly effective when used with intranasal corticosteroids, and less so when used alone. Isotonic and hypertonic irrigations are equally effective in improving symptoms, and high-volume (>100 ml) saline irrigation is superior to low-volume nasal sprays. Modest evidence supports the use of adjunctive oral leukotriene pathway antagonists, such as montelukast (*Singulair*), in patients with nasal polyps. Antihistamines and allergy immunotherapy are not effective for the specific management of sinusitis but they may be useful for concurrent allergic rhinitis.

Rudmik L, Soler Z: Medical therapies for adult chronic sinusitis: a systematic review. *JAMA* 2015;314 (September):926–939. From the University of Calgary, Canada; and the Medical University of South Carolina, Charleston. **Source of funding not stated. One study author declared financial relationships with commercial sources; the remaining author declared no competing interests.**

New Long-Acting Insulin Formulations

Two new long-acting insulin preparations, insulin degludec injection (*Tresiba*) and insulin degludec/insulin aspart injection (*Ryzodeg* 70/30), have received FDA approval for treatment of type 1 or type 2 diabetes mellitus in adults. *Tresiba* is a long-acting insulin analog, administered subcutaneously once daily at any time. *Ryzodeg 70/30* is a combination of insulin degludec and a rapid-acting human insulin analog. Both agents, when used in combination with mealtime insulin, reduced HbA1c levels with similar efficacy to previously approved long-acting or pre-mixed insulins. Common adverse effects associated with both agents include hypoglycemia; allergic reactions; injection-site reactions; lipodystrophy; itching; rash; edema; and weight gain. Neither agent should be used in patients with diabetic ketoacidosis or with increased blood or urine levels of ketones. Patients should be closely monitored if changes are made to their insulin regimen.

FDA News Release (September 25, 2015): FDA approves two new drug treatments for diabetes mellitus. Available at http://www.fda.gov/newsevents/newsroom/pressannouncements.

Dextromethorphan–Quinidine in Alzheimer's

In a preliminary, manufacturer-sponsored trial, the combination of dextromethorphan and quinidine (*Nuedexta*) reduced agitation in patients with Alzheimer's disease.[1]

Background: Safe, effective treatments are lacking for agitation in patients with Alzheimer's disease. Dextromethorphan–quinidine is currently approved for treatment of pseudobulbar affect, and research has shown the agent reduces agitation in patients with the disorder.

Methods: The study was conducted at 42 U.S. treatment sites, including outpatient Alzheimer's disease clinics and assisted living and nursing facilities. Study participants (n=220; 126 women) were aged ≥50 years and met diagnostic criteria for probable Alzheimer's disease. They had clinically significant agitation, defined as poorly organized and purposeless psychomotor activity characterized by verbal or physical aggression or nonaggressive physical behaviors such as pacing or restlessness. Patients receiving Alzheimer's medication (e.g., memantine or a cholinesterase inhibitor) were not excluded provided the dosage had been stable for ≥2 months. Participants were randomly assigned to 5 weeks of either dextromethorphan–quinidine or placebo. After 5 weeks, nonresponding patients in the placebo group were re-randomized to receive active medication or placebo for another 5 weeks. Those who had received active treatment during the first 5 weeks continued with no change. Dextromethorphan–quinidine was titrated to a maximum dosage of 30/10 mg b.i.d. The primary efficacy outcome was change from baseline in the Agitation/Aggression domain of

the Neuropsychiatric Inventory (NPI), which measures the frequency and severity of behaviors and is scored from 0 (no symptoms) to 12 (daily symptoms, with marked severity).

Results: The efficacy analysis included 218 patients, of whom 88% completed the study. Nearly 90% of participants were outpatients. Baseline Clinical Global Impression–Severity (CGI-S) ratings for agitation were moderate in 66%, marked in 30%, and severe or extreme in 4%.

The mean baseline NPI Agitation/Aggression score of 7 was reduced to 3.8 in the active treatment group at the 5-week evaluation ($p<0.001$ for change from baseline), compared with 5.3 in the placebo group ($p<0.001$ for between-group comparison). In stage 2, mean NPI Agitation/Aggression scores decreased from 5.8 to 3.8 in the dextromethorphan–quinidine group and from 6.7 to 5.8 in the placebo group ($p=0.02$ for between-group comparison). Stratification by baseline mini-mental state exam scores, CGI-S scores for agitation, and background treatment with cholinesterase inhibitors or other psychotropic medications did not alter the findings. Secondary outcome measures, including caregiver distress, generally favored the active treatment.

Discussion: An accompanying editorial called the results of this study encouraging but modest and difficult to interpret.[2] However, given the limited existing treatment options, it called for further development of dextromethorphan–quinidine as an off-label treatment for agitation. The editorial also noted that the treatment was well tolerated, with no increases in sedation or QTc prolongation, falls, or diarrhea, no detrimental effects on cognition or activities of daily living, and no increase in mortality. This safety profile contrasts favorably with atypical antipsychotics, the usual pharmacologic treatment for agitation in dementia. However, the study may have been too small and short in duration to observe the less common of these effects.

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

[1]Cummings J, et al: Effect of dextromethorphan-quinidine on agitation in patients with Alzheimer disease dementia: a randomized clinical trial. *JAMA* 2015;314 (September 22/29):1242–1254. From the Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV; and other institutions. **Funded by Avanir Pharmaceuticals Inc. Twelve of the study authors declared financial relationships with commercial sources, including Avanir; the remaining author declared no competing interests.**

[2]Ballard C, Sharp S, Corbett A: Dextromethorphan and quinidine for treating agitation in patients with Alzheimer disease dementia [editorial]. JAMA 2015;314 (September 22/29):1233–1235. From King's College London, U.K. One author declared financial relationships with commercial sources; the remaining 2 authors declared no competing interests.

Drug Trade Names: memantine—*Namenda*; dextromethorphan–quinidine—*Nuedexta*

***See Reference Guide.**

Reference Guide

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

Propensity Score Matching: Selection bias can be problematic when using observational data, making causal relationships difficult to establish. Propensity score matching is 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

Volume XXXVI / November 2015 / Number 11 www.alertpubs.com

Epinephrine Auto-Injector Recalled

A voluntary recall has been issued for several lots of epinephrine injection (*Auvi-Q*), which is used to treat severe, life-threatening allergic reactions. The affected lots, expiring between March and December 2016, have been found to have potentially inaccurate dosage delivery, which could lead to death in cases of anaphylaxis. No deaths have been reported, but prescriptions should be given for an alternate epinephrine auto-injector, and patients should be directed to use the *Auvi-Q* injector only if another auto-injector is not available.

FDA News Release (October 29, 2015): Auvi-Q (epinephrine injection, USP): recall–potential inaccurate dosage delivery. Available at http://www.fda.gov/safety/recalls /ucm469980.htm.

Amphetamine Oral Suspension

The FDA has approved the first extended-release oral amphetamine suspension (*Dyanavel XR*) for use in children aged ≥6 years.[1] The agent, developed using the patented LiquiXR™ technology, comprises both immediate- and extended-release amphetamine. The approval was based on a phase III randomized, placebo-controlled, laboratory classroom study in 108 children, aged 6–12 years, with ADHD. The study included a 5-week, open-label, dose optimization phase, followed by a 1-week, double-blind treatment period. Participants demonstrated improvements beginning 1 hour post dose and continuing through 13 hours. Nose bleed, allergic rhinitis, and upper abdominal pain were the most common adverse effects of treatment.

Dyanavel XR joins methylphenidate extended-release oral solution (*Quillivant XR*),[2] approved in 2012, as the only available liquid stimulant preparations.

[1]Tris Pharma receives FDA approval of Dyanavel XR (amphetamine) CII as once-daily liquid for treatment of ADHD in children [press release]. Monmouth Junction, NJ: Tris Pharma, Inc.; October 20, 2015.

[2]NextWave Pharmaceuticals receives FDA approval of Quillivant XR for once daily treatment of ADHD [press release]. Cupertino, CA: PRNewswire; October 1, 2012.

HPV Vaccine Safety

According to the results of a review by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee, the evidence does not support an association between the HPV vaccine (*Gardasil*) and development of complex regional pain syndromes (CRPS) or postural orthostatic tachycardia syndrome (POTS) in young women. The review found no increase in risk for either syndrome above that reported for the general population—about 150 per million for each. Some symptoms of CRPS and POTS may overlap those of chronic fatigue syndrome (CFS), and many of the reported cases also have features of or a concurrent diagnosis of CFS. Because the vaccine is expected to prevent precancerous growths, cervical and anal cancer, and genital warts, the benefits were judged to outweigh the risks.

European Medicines Agency News Release (November 5, 2015): Review concludes evidence does not support that HPV vaccines cause CRPS or POTS. Available at http://www.ema.europa.eu.

Primary Care Drug Alerts® (ISSN 1061-0359) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: kasey@alertpubs.com. Periodical-class postage is paid at Butler, NJ, and at additional mailing offices. POSTMASTER: Send address changes to Primary Care Drug Alerts, 45 Carey Avenue, Ste 111, Butler, NJ 07405. Subscription $99.00 a year in the U.S.; $107.50 Canada; $117.50 elsewhere; $151 institutional. Back issues and single copies, $10.00 each; prepaid. Institutional multicopy discounts are available.

Spironolactone for Resistant Hypertension

A randomized, head-to-head, comparison trial found spironolactone to be the most effective treatment for hypertension resistant to ≥3 other BP-lowering drugs. Previously, little evidence was available on the best treatment for resistant hypertension.

Methods: The PATHWAY-2 study enrolled patients with a seated systolic BP of ≥140 mm Hg (≥135 mm Hg in the presence of comorbid diabetes) despite treatment for ≥3 months with maximum tolerated doses of an ACE inhibitor or angiotensin II receptor blocker, a calcium channel blocker, and a diuretic. Add-on therapy with spironolactone, a mineralocorticoid receptor blocker, was compared with placebo, the α1-adrenoreceptor blocker doxazosin, and the β-blocker bisoprolol. Patients received treatment with all 4 medications, in randomized order, with 6 weeks at a lower dose followed by forced titration to a higher dose for an additional 6 weeks. The primary outcome was average home systolic BP, which was measured twice a day on the 4 consecutive days before the study visit at the end of each treatment phase.

Results: A total of 314 patients were randomized and followed for ≥1 treatment phase; 230 patients completed treatment with all 4 agents. The mean reduction from baseline in systolic BP was significantly greater with spironolactone (-12.8 mm Hg) than with the other agents: -8.7 mm Hg with doxazosin, -8.3 mm Hg with bisoprolol, and -4.1 mm Hg with placebo ($p<0.001$ for all comparisons). Blood pressure control, defined as a mean home systolic BP <135 mm Hg, was achieved with spironolactone in 58% of patients, significantly higher than rates for the other treatments.

A secondary aim of the study was to clarify whether resistant hypertension was caused largely by sodium retention or by any of a mixed group of patient-specific mechanisms. Baseline plasma renin, an inverse marker of sodium status, was low in many patients despite treatment with 3 agents that tend to elevate renin. Spironolactone was more effective than other treatments across the entire distribution of plasma renin but especially at lower levels, which suggests sodium retention is a major mechanism of resistant hypertension.

All 3 drugs were well tolerated, with low rates of adverse effects. Notably, spironolactone was not associated with discontinuation due to renal impairment, hyperkalemia, or gynecomastia.

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

Williams B, et al: Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015; doi 10.1016/S0140-6736(15)00257-3. From University College London, UK; and other institutions.
Funded by the British Heart Foundation; and the National Institute for Health Research. Several study authors declared financial relationships with commercial sources.

Common Drug Trade Names*: bisoprolol—*Zebeta*; doxazosin—*Cardura*; spironolactone—*Aldactone

***See Reference Guide.**

Sustained-Release Peppermint Oil for IBS

In a manufacturer-sponsored, placebo-controlled trial, patients with non-constipated irritable bowel syndrome experienced symptomatic relief with a novel peppermint-oil formulation (*IBgard*) designed for sustained release in the small intestine.

Methods: Study participants (n=72) were adults who met diagnostic criteria for mixed-type or diarrhea-predominant IBS with at least moderate average daily abdominal pain. After exclusion of organic disease and washout of medications that could affect gastrointestinal symptoms, patients were randomly assigned to receive peppermint oil or placebo. Both the active medication and placebo consisted of triple-coated beads of the same size, which contained either 60% fiber with 90 mg peppermint oil (active) or 100% fiber (placebo). Patients were instructed to take 2 capsules 3 times a day, 30–90 minutes before each meal. Symptoms were assessed at baseline, after 24 hours, and again at 28 days. The primary endpoint was change from baseline to day 28 in the Total IBS Symptom Score (TISS), which rates the intensity and frequency of 8 different symptoms.

Results: After 28 days of treatment, mean TISS total scores decreased by 40% with peppermint oil, compared with a 24% decrease with placebo ($p=0.03$). Improvement with peppermint oil was rapid. At 24 hours, differences between the 2 treatments were statistically significant, with a 20% reduction with peppermint oil and 10% with placebo ($p=0.009$). At 4 weeks, peppermint oil was associated with statistically significantly greater improvement than placebo in 4 of the 8 individual IBS symptoms: abdominal pain or discomfort,

abdominal bloating or distention, pain at evacuation, and urgency of bowel movements. The number of symptoms rated as severe or unbearable decreased by 67% with peppermint oil and 35% with placebo (p=0.03).

Dyspepsia, reported by 1 patient, was the only treatment-related adverse event observed in the peppermint-oil group. No patient reported smelling menthol on the breath, on flatus, or after bowel movements.

Discussion: Other peppermint-oil formulations are available as liquid-filled enteric-coated capsules, which can rupture in the stomach, causing heartburn and nausea. Delayed release of peppermint oil from these capsules may be associated with an anal burning sensation. The formulation evaluated in this study was designed to dissolve at the intestinal pH and release peppermint oil over 4 hours in the small intestine, avoiding unpredictable delivery problems. Patients' rapid improvement at 24 hours suggests the agent has potential as an on-demand therapy. The trial was limited to patients with non-constipation-predominant IBS, because few treatment options are available for these types.

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

Cash B, et al: A novel delivery system of peppermint oil is an effective therapy for irritable bowel syndrome symptoms. *Digestive Diseases and Sciences* 2015; doi 10.1007/s10620-015-3858-7. From the University of South Alabama, Mobile; and other institutions. **Funded by IM HealthScience, LLC. All study authors declared financial relationships with commercial sources including, IM HealthScience.**

***See Reference Guide.**

Influenza Vaccination and Pneumonia

According to results of a case-control study, influenza vaccination appears to protect patients from hospitalization due to influenza-associated pneumonia.

Methods: Study subjects were adults and children hospitalized for pneumonia at 8 U.S. hospitals in 2010–12. Nasopharyngeal or oropharyngeal swabs were collected within 72 hours of admission and were analyzed for influenza and other respiratory viruses. Case patients were those whose pneumonia was laboratory-confirmed as related to influenza. Comparison subjects had pneumonia associated with other causes. Vaccination status was verified, and for inclusion as a case patient, it was required to have occurred >14 days before the hospitalization. Patients who were previously living in an institution, aged <6 months, or severely immunosuppressed were excluded, as were partially vaccinated children and patients who became ill outside the flu season.

Results: The 162 case patients had confirmed influenza, and the 2605 controls tested positive for other respiratory viruses or negative for any virus. A total of 29% of patients with pneumonia had been vaccinated during the current flu season. Vaccinated patients were older and more likely to be white than unvaccinated patients and had a higher prevalence of chronic medical conditions such as cardiovascular disease, diabetes, and COPD. Mortality in both vaccinated and unvaccinated groups was 1%. Rates of vaccination during prior influenza seasons were 17% in patients with influenza-associated pneumonia and 29% in those with other types (adjusted odds ratio,* 0.43).

In subgroup analyses, the adjusted odds of prior vaccination was most favorable in children aged <4 years (odds ratio, 0.16). Odds ratios were more modest in older children and adults. The odds ratio of vaccination was significant in patients without immunosuppression (0.27) but not significant in immunosuppressed individuals (1.22).

Discussion: This study extends previous observations that vaccination is effective at reducing hospitalization for influenza-associated acute respiratory infections. Few prior studies have addressed the effectiveness of vaccination in preventing complications of influenza infections, such as pneumonia.

Grijalva C, et al: Association between hospitalization with community-acquired laboratory-confirmed influenza pneumonia and prior receipt of influenza vaccination. *JAMA* 2015; doi 10.1001/jama.2015.12160. From Vanderbilt University School of Medicine, Nashville, TN; and other institutions. **Funded by the CDC. Ten of 19 study authors declared financial relationships with commercial sources.**

***See Reference Guide.**

New Asthma Treatment Approved

Mepolizumab (*Nucala*), a humanized interleukin-5 antagonist monoclonal antibody produced by recombinant DNA technology, has received FDA approval as add-on therapy for patients aged ≥12 years with severe asthma not controlled by current medications. Mepolizumab works by reducing eosinophil levels and is administered as a monthly subcutaneous injection. In controlled trials, patients receiving mepolizumab experienced fewer asthma exacerbations that required

emergency visits or hospitalization as well as a longer time to first exacerbation. In addition, these patients were able to maintain asthma control with reduced doses of their daily maintenance corticosteroid. Mepolizumab did not improve lung function. Common adverse effects included headache, injection-site reactions, back pain, and fatigue. Herpes zoster infections were also reported. Hypersensitivity reactions can occur within hours or days of injection.

FDA News Release (November 4, 2015): FDA approves Nucala to treat severe asthma. Available at http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm471031.htm.

Methylphenidate/Acetaminophen Interaction

A 6-year-old boy with ADHD had been receiving 18 mg/day OROS methylphenidate (*Concerta*) for 2 months with significant improvement in behavior. The only reported adverse effect was appetite suppression. He presented with a 1-week history of anxiety, fearfulness, and refusal to leave his parents. After he started 120 mg/day acetaminophen suspension following a flu-like illness, the patient reported visual hallucinations. Because hallucinations had not occurred with methylphenidate monotherapy, it was presumed not to be the cause. Acetaminophen was discontinued, and the hallucinations resolved. They did not recur during 6 months of follow-up with continued methylphenidate monotherapy.

Methylphenidate is generally safe and well tolerated but has reportedly caused psychotic symptoms in a small number of young patients. It is unclear whether the acetaminophen alone or the combination of the drugs precipitated the hallucinations. However, it was speculated that concomitant use of acetaminophen and methylphenidate led to excessive brain levels of dopamine that then resulted in the hallucinations. It is also possible that acetaminophen elevated the patient's serum methylphenidate concentrations, increasing the risk of adverse effects.

Herguner S, Ozayhan H: Visual hallucinations with methylphenidate and acetaminophen in combination. *Journal of Child and Adolescent Psychopharmacology* 2015;25 (September):598–599. From Necmettin Erbakan University, Konya; and Konya Training and Research Hospital, Turkey. **The authors declared no competing interests.**

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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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(Required by 39 U.S.C. 3685) 1. Publication Title: Primary Care Drug Alerts. 2. Publication No.:7090-30. 3. Filing Date: 09/30/15. 4. Issue Frequency: Monthly. 5. No. of Issues Published Annually: 12. 6. Annual Subscription Price: $99.00 in U.S.A. 7. Complete Mailing Address of Known Office of Publication: 45 Carey Avenue Ste 111, Butler, N.J. 07405. 8. Complete Mailing Address of Headquarters or General Business Office of Publisher: 45 Carey Avenue Ste 111 Butler, N.J. 07405. 9. Publisher: Trish Elliott, 45 Carey Avenue Ste 111 Butler, N.J. 07405; Editor: Trish Elliott, 45 Carey Avenue Ste 111 Butler, N.J. 07405; Managing Editor: Tara Hausmann, 45 Carey Avenue Ste 111 Butler, N.J. 07405. 10. Owner: M.J. Powers & Co. Publishers, Inc.; Trish Elliott, Tara Hausmann 45 Carey Avenue Ste 111 Butler, N.J. 07405. 11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities: None. 12. The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes: has not changed in the preceding 12 months. 13. Publication Name: Primary Care Drug Alerts. 14. Issue Date for Circulation Data Below: 08/15. 15. Extent and Nature of Circulation (Average No. Copies Each Issue During Preceding 12 Months/Actual No. Copies of Single Issue Published Nearest to Filing Date): A. Total No. Copies (269/250). B. Paid Circulation: 1. Mailed Outside-County (159/151). 2. Mailed In-County (1/None). 3. Paid Distribution Outside the Mails Including Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and other Paid Distribution Outside USPS (None/None). 4. Paid Distribution by Other Classes of Mail Through the USPS (9/9). C. Total Paid Circulation (169/160). D. Free or Nominal Rate Distribution by Mail and Outside the Mail: 1. Free or Nominal Rate Outside-County Copies (15/15). 2. Free or Nominal Rate In-County Copies (1/1). 3. Free or Nominal Rate Copies Mailed at Other Classes Through the USPS (None/None). 4. Free or Nominal Rate Distribution Outside the Mail (None/None). E. Total Free Distribution (16/16). F. Total Distribution (185/176). G. Copies Not Distributed (84/74). H. Total (269/250). I. Percent Paid (91%/91%).

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For Physicians and Nurses

Volume XXXVI / December 2015 / Number 12 www.alertpubs.com

Chewable Methylphenidate ER

The FDA has granted approval for the first chewable formulation of extended-release methylphenidate (*QuilliChew ER*). In a clinical trial of children aged 6–12 years with ADHD, *QuilliChew* improved both attention and behavior beginning 45 minutes after ingestion and lasting through an 8-hour laboratory classroom challenge. The new formulation, for use in patients aged ≥6 years, will be available in 20-, 30-, and 40-mg tablets that can be taken with or without food and is expected to be in pharmacies in the first quarter of 2016. The recommended starting dosage is 20 mg/day; dosages >60 mg/day are not recommended. As with other stimulants, patients should be evaluated for cardiac disease before starting treatment with *QuilliChew*, and use is contraindicated with concurrent or recent MAOI use. *QuilliChew* contains phenylalanine, which can be harmful to patients with phenylketonuria. Adverse effects appear to be similar to other methylphenidate formulations.

Pfizer receives U.S. FDA approval of new QuilliChew ER (methylphenidate hydrochloride) extended-release chewable tablets CII [press release]. New York, NY: Pfizer; December 7, 2015. Http://on.pfizer.com/1HQNOeg.

Sildenafil in Prediabetes

In a randomized trial, 3 months of treatment with sildenafil (*Viagra*) improved insulin sensitivity in patients with prediabetes.

Background: Increasing cyclic guanosine monophosphate (cGMP) signaling has the potential to decrease diabetes onset in high-risk patients by increasing insulin sensitivity in muscle. Phosphodiesterase 5 inhibitors such as sildenafil are one strategy to increase cGMP.

Methods: Study participants (n=51; mean age, 51 years) were adults with a body mass index (BMI) of ≥25 and a diagnosis of prediabetes, defined as impaired fasting glucose, impaired glucose tolerance, or Hb_{A1C} of 5.7%–6.4%. Patients were randomly assigned to receive 25 mg sildenafil t.i.d. or placebo for 3 months. Patients underwent a hyperglycemic clamp test at baseline and study endpoint that measured the insulin sensitivity index (ISI), glucose-stimulated insulin secretion (GSIS), and the disposition index (DI, a measure of insulin secretion and sensitivity).

Results: The ISI was significantly greater in the sildenafil group than the placebo group (p=0.049) after adjusting for baseline ISI and BMI. The DI was higher in the sildenafil group, although the difference was not statistically significant. Treatment had no effect on first-phase or late-phase GSIS or on weight, resting energy expenditure, or free fat mass. Sildenafil did not affect blood pressure.

Two patients in the placebo group and 4 in the sildenafil group had microalbuminuria at baseline. In these patients, sildenafil also decreased the average urine albumin-to-creatinine ratio. At study end, 4 patients in the placebo group and none in the sildenafil group had microalbuminuria. Sildenafil decreased levels of plasminogen activator inhibitor-1 but did not decrease tissue plasminogen activator.

Primary Care Drug Alerts® (ISSN 1061-0359) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: kasey@alertpubs.com. Periodical-class postage is paid at Butler, NJ, and at additional mailing offices. POSTMASTER: Send address changes to Primary Care Drug Alerts, 45 Carey Avenue, Ste 111, Butler, NJ 07405. Subscription $99.00 a year in the U.S.; $107.50 Canada; $117.50 elsewhere; $151 institutional. Back issues and single copies, $10.00 each; prepaid. Institutional multicopy discounts are available.

Discussion: The present study suggests that sildenafil not only increases insulin sensitivity, but also improves the fibrinolytic balance and decreases urinary albumin secretion. Larger studies with clinical endpoints are needed to determine whether sildenafil and similar drugs can prevent the onset of diabetes in high-risk persons.

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

Ramirez C, et al: Treatment with sildenafil improves insulin sensitivity in prediabetes: a randomized, controlled trial. *Journal of Clinical Endocrinology and Metabolism* 2015; doi 10.1210/jc.2015-3415. From Vanderbilt University School of Medicine, Nashville, TN. **Funded by the NIH. The authors declared no competing interests.**

***See Reference Guide.**

Nutraceuticals in Alzheimer's Disease

Current treatments for Alzheimer's disease focus on enhancing cholinergic neurotransmission, and there are no disease-modifying drugs available for the condition. Neuroinflammation and oxidative stress are secondary phenomena in Alzheimer's disease that arise in response to tissue injury due to beta-amyloid plaque formation. Neuroinflammation begins in patients with mild cognitive impairment and contributes to disease pathology when it becomes chronic. Recent studies have evaluated large-scale nutritional approaches such as the Mediterranean diet. The present review focuses on 6 individual nutrients, all with excellent tolerability and no safety concerns, that have some evidence of efficacy in patients with Alzheimer's disease.

Alpha-lipoic acid (ALA) is a chemically synthesized but naturally occurring precursor for mitochondrial enzymes. It has several mechanisms relevant to Alzheimer's disease, including increasing acetylcholine production, reducing oxidative stress, and protecting neurons from beta-amyloid-induced damage. In open-label studies in patients with Alzheimer's disease, ALA was associated with reduced cognitive decline. In a double-blind, placebo-controlled trial, ALA was associated with slower declines in cognitive function.

Docosahexaenoic acid (DHA) is a component of fish oil that has antiinflammatory effects and protects neurons from the cytotoxic effects of beta-amyloid. In a placebo-controlled pilot study, supplementation with a combination of DHA and ALA reduced cognitive and functional decline. In another, larger randomized trial, omega-3 fatty acids were associated with a slowed cognitive decline in patients with mild cognitive dysfunction.

The polyphenol epigallocatechin-3-gallate (EGCG) is a powerful antioxidant found in fresh, unfermented tea (green or white). It has been shown to reduce production of proinflammatory cytokines that are toxic to cultured neurons and, in animals, to reduce beta-amyloid plaque formation in the brain. ECGC has had positive effects on brain function in several studies in healthy volunteers. In a longitudinal study, the incidence of dementia over 4–5 years was lower in those who consumed green tea every day, compared with those who did not consume green tea at all.

Curcumin, resveratrol, and apigenin have received less attention, with few or no clinical studies, but also have potential mechanisms of action that could be beneficial in patients with Alzheimer's disease. In a cohort of healthy elderly people, a high-bioavailability curcumin formulation (*Longvida*) was associated with improved working memory and mood, compared with placebo, after 4 weeks of treatment. Resveratrol has shown very preliminary positive effects on cerebral blood flow or memory in experimental subjects but has not been studied in Alzheimer's disease. Apigenin, a flavonoid found in chamomile and other plants, has well established antioxidant and anti-inflammatory effects. In animal studies, apigenin has been found to improve memory and learning deficits and to reduce amyloid deposits. However, cognitive and neuroinflammatory effects have not been studied in humans.

Venigalla M, et al: Novel promising therapeutics against chronic neuroinflammation and neurodegeneration in Alzheimer's Disease. *Neurochemistry International* 2015; doi 10.1016/j.neuint.2015.10.011. From Western Sydney University, Campbelltown; and the University of Tasmania, Australia. **Funded by the National Health and Medical Research Council of Australia. The authors did not include disclosure of potential conflicts of interest.**

Cholinesterase Inhibitor Adverse Events

According to a large, international pharmacovigilance study, neuropsychiatric problems are the most frequent type of cholinesterase inhibitor-related adverse drug reaction (ADR). The global pattern of reported adverse events differs from the

package labeling, which lists gastrointestinal (GI) problems as the most frequent ADR.

Methods: The World Health Organization's ADR database, VigiBase, contains >8 million case reports from >100 countries. Suspected ADRs are spontaneously reported by health professionals, patients, and drug manufacturers. Data for the present analysis were extracted from all reports to VigiBase in 1998–2013 that involved the 3 cholinesterase inhibitors available for treatment of dementia: donepezil, rivastigmine, and galantamine.

Results: Nearly 44,000 cholinesterase inhibitor-related ADRs were the subject of about 19,000 reports (each consisting of a single patient with, possibly, multiple events). Nearly 90% of reports were from Europe, the U.S., and Canada. The mean patient age was 77 years, and 40% of the events occurred in men. Donepezil and rivastigmine each accounted for about 41% of reports and galantamine for 17%.

Contrary to the adverse event data from clinical trials that showed GI effects to be most common, nearly one-third of all reported ADRs in this study were neuropsychiatric events. Among the more frequent were disturbances in consciousness; syncope and related symptoms; neurological signs and symptoms; confusion and disorientation; hallucinations; anxiety symptoms; and behavioral and social disturbance. GI events accounted for 15% of all reports, general events (e.g., fever and administration site reactions) accounted for 12%, and cardiovascular disorders for 12%.

Information on severity of ADRs was available in VigiBase only after 2005. About 70% of the reported ADRs between 2006 and 2013 were serious, resulting in death, hospitalization, disability, or other important negative outcomes; 2% of the ADRs were fatal. Neuropsychiatric disturbances accounted for 34% of serious ADRs, general disorders 14%, and cardiovascular disorders 12%. Expected cholinergic adverse effects were frequently reported as serious, including nausea and vomiting, confusion, and diarrhea. More than 900 reports (5.5% of the total) described serious events related to excitatory reactions of the central nervous system, such as seizures, anxiety, aggression, and insomnia. About 2% of the serious incidents were linked with medication error or maladministration.

Discussion: The global occurrence of cholinesterase inhibitor-related adverse events is consistent with the global market for these agents, which are mainly used in affluent countries. The high proportion of reports related to donepezil and rivastigmine is consistent with these agents' position as market leaders. Cholinesterase inhibitors may not be the cause of some proportion of reported neuropsychiatric and cardiovascular adverse events, given the high background incidence in this patient population. However, there is a pharmacological rationale for some types of neuropsychiatric events: increased acetylcholine levels in the brain, possibly leading to an increase in neuronal excitation. In clinical practice, the possibility that a neuropsychiatric disturbance is cholinesterase inhibitor-related should be considered before treating the disturbance with specific drugs.

Kroger E, et al: Adverse drug reactions reported with cholinesterase inhibitors: an analysis of 16 years of individual case safety reports from VigiBase. *Annals of Pharmacotherapy* 2015;49 (November):1197–1206. From the Centre Hospitalier Universitaire de Quebec, Canada; and other institutions. **Funded by the Canadian Institutes for Health Research; and other sources. The authors declared no competing interests.**

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

Rosiglitazone REMS Lifted

In 2010, the FDA warned of increased risk for cardiovascular events (e.g., heart attack, stroke) in patients taking rosiglitazone (*Avandia*) and combination products containing rosiglitazone.[1] Based on those findings, they mandated that a risk evaluation and mitigation strategy (REMS) and a restricted access program be developed. In 2013, the dispensing and prescribing restrictions were lifted and the FDA concluded that the drugs did not confer increased risk for MI relative to standard diabetes drugs.[2] After further investigation, the FDA has determined that the REMS is no longer necessary to determine whether the benefits of the medication outweigh the risks.[3]

[1]Avandia (rosiglitazone): REMS – risk of cardiovascular events. FDAMedWatch Alert: available at www.fda.gov/Safety/MedWatch. See *Primary Care Drug Alerts* 2011; 32 (February):7.

[2]FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines. Available at http://www.fda.gov/downloads/drugs/drugsafety/ucm381108.pdf.

[3]FDA News Release (December 16, 2015): Rosiglitazone-containing diabetes medicines: drug safety communication – FDA eliminates the Risk Evaluation and Mitigation Strategy (REMS). Available at http://www.fda.gov/Drugs/DrugSafety/ucm476466.htm.

New Option for Diabetic Retinopathy

In patients with proliferative diabetic retinopathy, intravitreous injection of ranibizumab (*Lucentis*), an anti-vascular endothelial growth factor (VEGF) agent, produced visual acuity changes similar to those seen with standard treatment.[1]

Background: Panretinal photocoagulation (PRP), the standard treatment for proliferative diabetic retinopathy for nearly 4 decades, can cause permanent peripheral visual field loss, decrease night vision, and worsen diabetic macular edema (DME). Intravitreous anti-VEGF agents reduce the risk of worsening retinopathy in patients with DME and may be a viable option for diabetic retinopathy.

Methods: Study subjects were adults (n=305; 394 eyes) with proliferative diabetic retinopathy, with or without macular edema. Participants were randomly assigned to PRP or intravitreous ranibizumab, the latter injected at 4-week intervals. The primary study outcome was visual acuity, measured after 2 years.

Results: At follow-up, patients in both treatment groups showed similar and slightly improved visual acuity, indicating ranibizumab is noninferior to the standard treatment. Secondary outcomes favored ranibizumab, likely because of its effects on macular edema. PRP was associated with more peripheral visual field loss and a higher rate of subsequent vitrectomies than ranibizumab.

Editorial.[2] Intravitreous anti-VEGF therapy is an important alternative for short-term management of PDR, but it is not known whether it will obviate the need for further treatment after 2 years. Possibly patients will continue to need frequent visits and intravitreous injections for a lifetime, a concern given the often poor follow-up of patients with diabetes.

[1]Gross J, et al: Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA* 2015; doi 10.1001/jama.2015.15217. From the Carolina Retina Center PA, Columbia, SC; and other institutions. **Funded by the NIH. Ten of the 19 study authors declared financial relationships with commercial sources.**

[2]Olsen T: Anti-VEGF pharmacotherapy as an alternative to panretinal laser photocoagulation for proliferative diabetic retinopathy [editorial]. *JAMA* 2015; doi:10.1001/jama.2015.15409. From Emory University, Atlanta, GA. **Funded by Research to Prevent Blindness, New York, NY. The author declared no financial relationships with commercial sources.**

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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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