

PRIMARY CARE DRUG ALERTS

For Physicians and Nurses

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EpiPen Availability

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

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

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

Essure Contraceptive Market Withdrawal

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

from the ovary. The *Essure* device has been associated with persistent pain, uterine and/or fallopian tube perforation, and coil migration into the pelvis or abdomen.

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

Lasmiditan for Migraine

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

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

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

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

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

Vila-Pueyo M: Targeted 5-HT_{1F} therapies for migraine. *Neurotherapeutics* 2018;15 (April):291–303. doi 10.1007/s13311-018-0615-6. From King's College London, U.K. **Source of funding not stated. The author declared no competing interests.**

Plazomicin for UTI

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

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

Escitalopram and Cardiac Outcomes

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

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

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

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

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

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

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

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

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

*See Reference Guide.

Statin-Associated Gynecomastia

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

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

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

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

Risk of gynecomastia in statin users and users of finasteride (active control)	
	Adjusted rate ratio*
Any statin use	1.23
Current (past 1–30 days)	1.19
Recent (31–60 days)	1.38
Past (61–365 days)	1.20
Any finasteride use	3.71

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

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

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

*See Reference Guide.

Evening-Dosed Methylphenidate Approval

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

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

Timolol Eyedrops for Migraine

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

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

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

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

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

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

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

Rate Ratio: A comparison of the rates of a disease/event in 2 groups that differ by demographic characteristics or exposure history. The rate for the group of primary interest is divided by the rate for a comparison group.

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