Pharmacy Today

An official publication of the **American Pharmacists Association**

FEBRUARY 2023

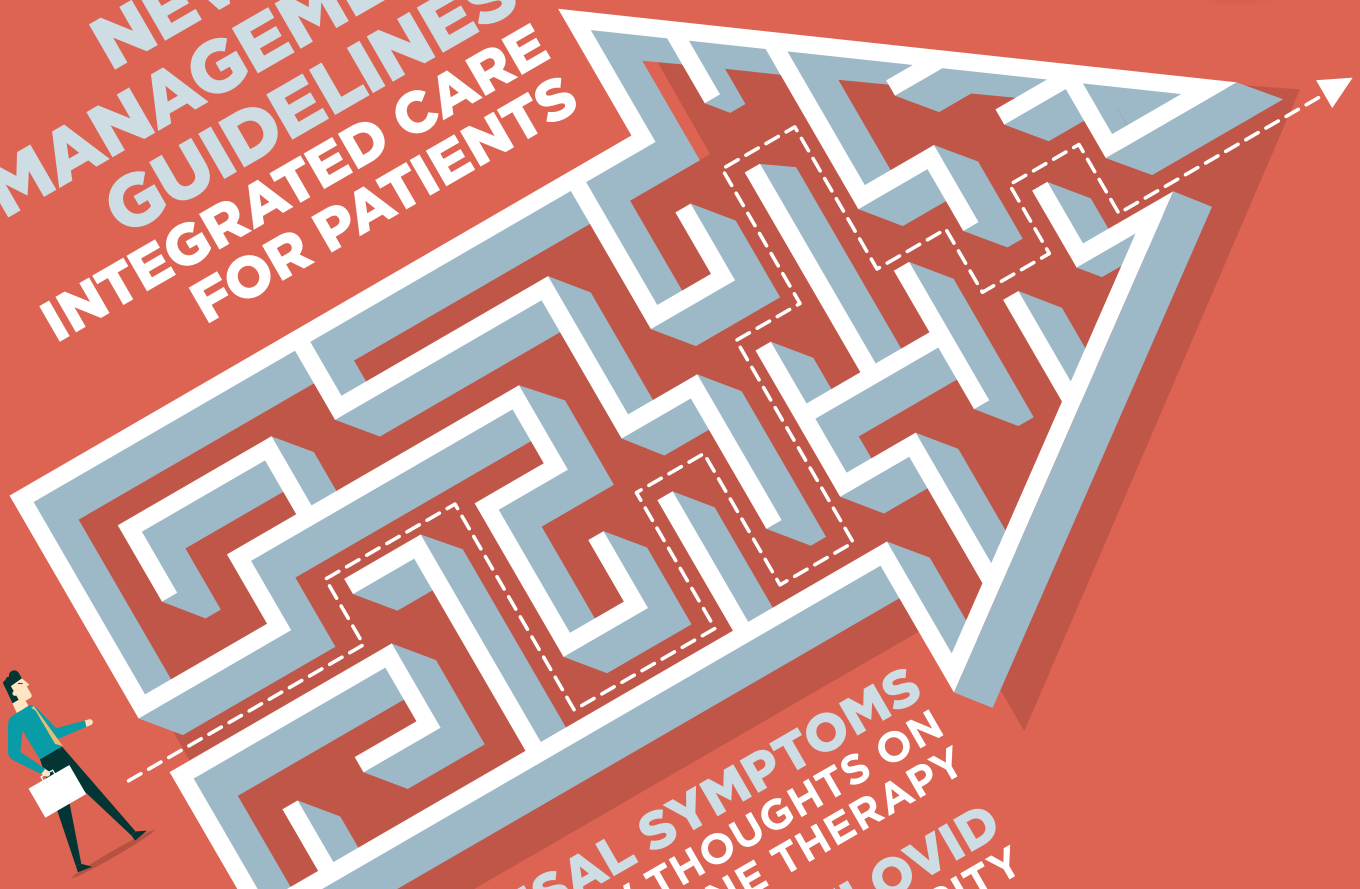
CONTINUING PHARMACY EDUCATION

CPE

UPDATES IN HEART FAILURE MANAGEMENT

NEW PAIN MANAGEMENT GUIDELINES

INTEGRATED CARE FOR PATIENTS



MENOPAUSAL SYMPTOMS

NEW THOUGHTS ON HORMONE THERAPY

PAXLOVID

PRESCRIBING AUTHORITY

RENAL FUNCTION CLEARANCE

CHALLENGING ADJUSTMENTS BASED ON RACE

APhA

BulletinToday

What's the longer-term effect of treatment for critically ill patients with COVID-19?

Researchers of a new study published December 16, 2022, in *JAMA* found that among critically ill patients with COVID-19, there was a high likelihood of improved 180-day mortality among patients treated with IL-6 receptor antagonists and antiplatelet agents.

Researchers used data from the ongoing REMAP-CAP trial to gauge the longer-term effectiveness of 6 categories of treatment used among critically ill patients with COVID-19: immune modulators, convalescent plasma, antiplatelet therapy, anticoagulation, antivirals, and corticosteroids. For the study, patients were randomized to receive one or more of these treatment interventions.

"When considered with previously reported short-term results, the findings indicate that initial in-hospital treatment effects were consistent for most therapies through 6 months," concluded the study authors.

Specifically, they were looking at longer-term mortality, disability, and health-related quality of life.

The REMAP-CAP trial included critically ill adult patients with COVID-19 enrolled between March 9, 2020, and June 24, 2021. Patients came from 14 countries.

The primary outcome was survival through day 180. Of the 4,869 randomized patients, 84.3% had known vital status and 63.1% were alive at 180 days.

According to the study, the pooled IL-6 receptor antagonists and antiplatelet treatment groups each had a high probability of benefit compared with the control groups. The probability of benefit for fixed-dose corticosteroids and shock-dependent corticosteroids compared with no corticosteroids was 61.6% and 57.1%, respectively. However, the corticosteroid domain was stopped early on the basis of external evidence.

In contrast, the likelihood of trial-defined statistical futility was high for therapeutic anticoagulation in critically ill patients, convalescent plasma, and lopinavir/ritonavir. In addition, there was a high likelihood of harm for hydroxychloroquine and its combination with lopinavir/ritonavir. ■

FDA issues guidance on homeopathic drugs

A final guidance document from FDA details the agency's efforts to prioritize enforcement and regulatory actions for homeopathic drug products marketed in the United States. There are currently no FDA-approved products labeled as homeopathic.

The agency has created a risk-based approach under which it aims to prioritize certain categories of homeopathic drug products that potentially pose a greater risk to public health, such as those intended for populations at higher risk for adverse reactions as well as ophthalmic and injectable products, as the routes of administration for these products bypass some of the body's natural defenses.

FDA noted it expects many homeopathic drug products will fall outside the types of drug products it plans to prioritize for enforcement and regulatory action. ■

Drug overdose deaths among teenagers surged during the COVID-19 pandemic

A new CDC report found that monthly drug overdose deaths nearly tripled among adolescents aged 10 to 19 years during the first 2 years of the COVID-19 pandemic. Deaths increased from 31 to 87 per month from July 2019 to May 2021 before declining to 51 per month in December 2021.

"Although deaths appear to have begun declining in late 2021, they are still alarmingly higher than in 2019," wrote the study authors in CDC's *Morbidity and Mortality Weekly Report*.

More than 2,200 adolescents fatally overdosed during the 2.5-year period, 96% of whom were teens aged 15 to 19 years. Fentanyl was implicated in 84% of the deaths, while opioid analgesics of any type were involved in 91% of deaths.

Among adolescents, fentanyl deaths more than tripled from 31 per month in July 2019 to a peak of 87 per month in May 2021, declining to 44 per month in December 2021. Approximately 70% of the fatalities were among males and 30% in females. Roughly 60% of those who died were white, 21% were Hispanic, and 13% were Black.

An estimated 25% of the adolescent overdose deaths may have involved counterfeit drugs resembling oxycodone (OxyContin—Purdue Pharma) or alprazolam (Xanax—Pfizer). Both often contain fentanyl.

"Whether adolescents intended to take legitimate pharmaceutical medications or were aware pills were counterfeit is unclear," the authors wrote.

Roughly 41% of those who overdosed had a prior history of mental health issues, with about 24% reporting prior mental health treatment; 19% diagnosed with depression; and 15% had a prior history of suicidal or self-harm behavior.

The authors stressed the importance of teaching teenagers about the risks of fentanyl and its likelihood of contaminating counterfeit drugs. ■

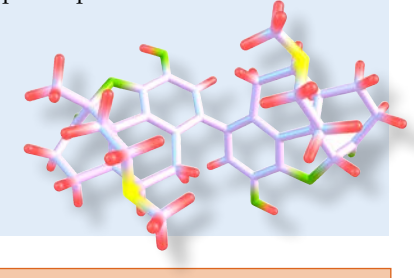
A second naloxone nasal spray gets FDA fast track for OTC clearance

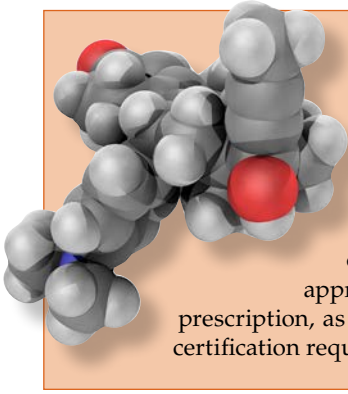
A nasal spray version of naloxone (Rivive—Harm Reduction Therapeutics) is now on the FDA fast track for OTC clearance. According to the manufacturer, FDA is aiming for April 28, 2023, as an approval date after priority review.

With cost and access in mind, Harm Reduction Therapeutics also noted that it would price the overdose antidote at about $18 per dose for sale to pharmacies, public-sector workers, and advocacy organizations. The nonprofit company will also donate one-tenth of its production, which is slated to reach 2 million doses annually.

This approval shortly follows FDA's decision in late 2022 to put an OTC version of naloxone nasal spray (Narcan—Emergent BioSolutions) on the fast track to approval. That opioid overdose antidote tentatively could receive clearance early this spring.

Another company, Pocket Naloxone Corp., has submitted its application for a nasal-swab version of naloxone that it says would be more affordable than the sprays and faster acting than prescription formulations. ■





FDA gives certified pharmacies green light to dispense mifepristone

In early January 2023, FDA announced modifications to the REMS for mifepristone (Mifeprex–Danco Labs). The revisions would allow pharmacies to become certified to dispense this FDA-approved drug to patients with a prescription, as long as they comply with the certification requirements.

Among other requirements, a certified pharmacy must ensure certain processes and procedures are in place, and dispense, including by mail-order, within a specific timeframe.

The U.S. Postal Service announced on December 23, 2022, that current law supports delivery of mifepristone and misoprostol through the mail.

Some states, however, still ban or restrict access to mifepristone following the Supreme Court's recent *Dobbs v Jackson* decision overturning *Roe v Wade*. ■

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Take the Crossword Challenge

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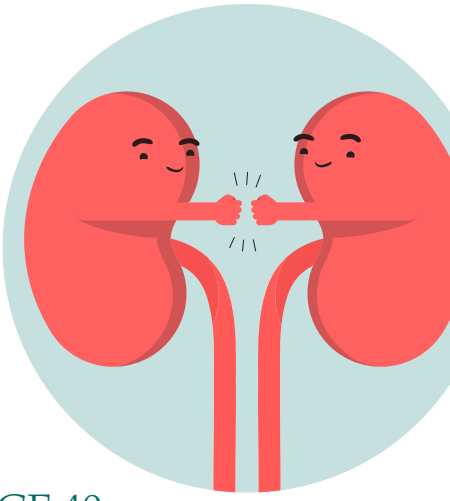
Drugs & Diseases

Practice & Trends

Health Systems



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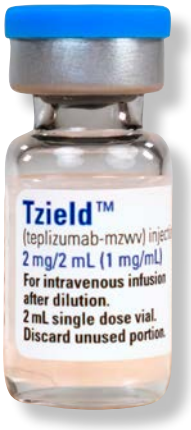

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Shared decision-making can improve pain management

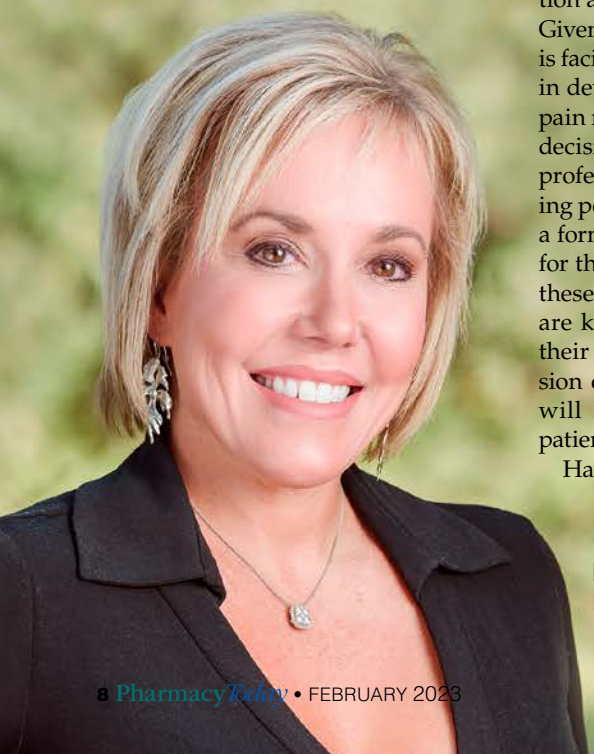
According to the Agency for Healthcare Research and Quality, shared decision-making "occurs when a health care provider and a patient work together to make a health care decision that is best for the patient." It benefits both patients and pharmacists. Patients have an improved experience of care and better adherence to treatment recommendations; pharmacists can ensure enriched quality of care and increased patient satisfaction. The concepts of both shared and person-centered decision-making are hallmarks of CDC's 2022 Clinical Practice Guideline for Prescribing Opioids for Pain.

The cover story in this issue focuses on this new guidance and teases out specific recommendations for pharmacists. Overall, many pharmacists will be happy to know that the emphasis has shifted from the previous guideline's presentation of rigid patient care choices focused on hard limits to a more flexible approach that stresses patient and provider communication, empowerment, and collaboration in pain management. In addition, "The guideline explicitly recognizes various roles for pharmacists in integrated pain management as part of care teams," said Anne Burns, RPh, former vice president of professional affairs at APhA, who served on the workgroup for the guideline. Care teams, as outlined by CDC, empower pharmacists to assist with treatment plans and tapering opioids, coprescribe naloxone, and help interpret prescription drug monitoring program data. These latest guideline opens the door for interprofessional collaboration in pain management and seeks to close the door on the strict, prescriptive approach that many institutions had adopted as policies and practices based on previous CDC guidance.

In this issue of *Today*, you'll also get an update on new drug approvals including teplizumab-mzwv for diabetes, and find guidance on recommending OTC treatments for headaches and OTC hearing aids. Learn what's included in the North American Menopause Society's updated position statement on hormone therapy for menopause and why pharmacists are still facing challenges with prescribing Paxlovid. Catch up on your CPE credit with this month's article on updates in heart failure management.

CDC's new pain management guideline follows trends that we are seeing in other areas of practice: collaboration and expanding pharmacists' roles. Given the opioid crisis that our nation is facing, this guidance will be essential in developing successful care plans for pain management patients. Sharing the decision-making process among interprofessional providers and emphasizing person-centered decision making is a formidable step in the right direction for this field. Take a moment to review these recommendations—pharmacists are key to their implementation. And their adoption, along with their inclusion of pharmacists on the care team, will lead to improved outcomes for patients with pain.

Have a great *Today!* ■



Kristin Wiisanen
PharmD, FAPhA, FCCP
***Pharmacy Today* editor in chief**

Serving underserved populations

Access and health disparities continue to impact patient care. Action is needed for patients to have ready access to critical medications to sustain their quality of life. Pharmacies are often the only health care destination available in a community, and the growth of pharmacy deserts in many underserved areas of the country is sobering. In our efforts to promote patient care and ensure equity, it's vital that community pharmacies maintain their ability to keep their doors open and serve as access points for medications and their community.

There are several avenues for supporting our pharmacies and underserved communities. One is to remedy the mischief around pharmacy payment and reimbursement, where DIR fees, clawbacks, below-cost payments, and other actions from Goliath companies threaten the financial viability of pharmacies.

Fixing this is multifaceted and we are working with Congress, the Administration, CMS, FTC, state policymakers, the commercial sector, and others to drive needed change. Policymakers across the country are ready for these conversations in 2023, and APhA will be your voice in these discussions.

APhA is proud to work with our partners in state organizations, who are making advancements in payment for pharmacists' patient care services. An increasing number of states have passed laws that require payment for pharmacists' patient care services "in parity" with other health care professionals. The types of services covered—and billing codes used—can vary, but these developments provide both a revenue stream to support pharmacists' time to provide clinical care and a new opportunity for service growth, addressing equity, and strengthening community pharmacies.

Commercial health plans are also independently seeing the benefits of pharmacists' patient care services. I'm seeing pockets around the country where arrangements are brokered so that plans pay pharmacists for patient care. I'm encouraged by the positive outcomes and efficiencies being generated from these arrangements. They will no doubt support advocacy efforts to scale this up for multifaceted coverage, such as in fee-for-service or value-based payment, across payer types.

The care and impact of pharmacy on health disparities is premised on expanding state scope of practice through legislative directives, statewide protocols, or enhancements to collaborative practice authority. There has been a lot of activity in the states to make permanent authorities for COVID-19-related services in addition to advancements for test-and-treat, HIV PrEP and PEP, hormonal contraception, nicotine cessation, furnishing naloxone, and more. State legislators and public health officials see firsthand the level of care pharmacists provide, and with this recognition we expect to see further advancement in scope authorities aligned with pharmacists' education and training. The future is bright for scope of practice expansion wins.

New tensions between federal and state authorities emerged in June 2022 with the Supreme Court decision that placed the regulation of abortion services with individual states. States have adopted a myriad of often-confusing requirements related to medications that have multiple purposes but could cause the loss of a pregnancy. The most recent rule change by FDA allows certified pharmacies to dispense medication for abortion, but pharmacists and pharmacies remain caught in the middle of this issue. It's still too early to know which pharmacies will become certified; the quest for clarity will likely continue throughout this year.

Structural and system inequities persist to this day, contributing to health disparities and inequities. As one of the most accessible health care resources for underserved communities, pharmacists stand at the forefront of patient care and advocacy. There is still a lot of work to be done, and we continue to move forward with solutions that help our patients, our communities, and our colleagues in pharmacy. We move forward together. ■

ILISA BG BERNSTEIN
PharmD, JD, FAPhA
Interim Executive Vice President and CEO
American Pharmacists Association

NEW DRUGS

ADAGRASIB
(Krazati—Mirati Therapeutics)

Drug class: Adagrasib is an inhibitor of the RAS GTPase family.

Indication: Krazati is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer, as determined by an FDA-approved test, who have received at least one prior systemic therapy. This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of a clinical benefit in a confirmatory trial.

Recommended dosage and administration: The recommended dosage is 600 mg orally twice daily. Krazati tablets should be swallowed whole with or without food.

Common adverse effects: The most common adverse reactions were nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, renal impairment, edema, dyspnea, decreased appetite, decreased lymphocytes, decreased hemoglobin, increased ALT, increased AST, hypokalemia, hyponatremia, increased lipase, decreased leukocytes, decreased neutrophils, and increased alkaline phosphatase.

Warnings and precautions: Monitor patients for diarrhea, nausea, and vomiting and provide supportive care as needed. Withhold, reduce the dose, or permanently discontinue based on severity. Avoid concomitant use of Krazati with other products with a known potential to prolong QTc intervals. Monitor ECG and electrolytes in patients at risk, and in patients taking medications known to prolong the QT interval. Withhold, reduce the dose, or permanently discontinue based on severity. Monitor liver laboratory tests prior to the start of Krazati and monthly for 3 months after and as clinically indicated. Reduce the dose, withhold, or permanently discontinue based on severity. Monitor for new or worsening respiratory symptoms. Withhold Krazati for suspected interstitial lung disease (ILD)/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified. Avoid concomitant use with strong CYP3A4 inducers. Avoid concomitant use with strong CYP3A4 substrates until Krazati concentrations have reached steady state. Avoid concomitant use with sensitive CYP3A4 substrates. Avoid concomitant use with sensitive CYP2C9 or CYP2D6 substrates or P-gp substrates where minimal concentration changes may lead to serious adverse reactions. Advise patients not to breastfeed while taking Krazati.

OLUTASIDENIB
(Rezlidhia—Rigel Pharmaceuticals)

Drug class: Olutasidenib is an isocitrate dehydrogenase-1 (IDH1) inhibitor.

Indication: Rezlidhia is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia with a susceptible IDH1 mutation as detected by an FDA-approved test.

Recommended dosage and administration: The recommended dosage is 150 mg orally twice daily, until disease progression, or unacceptable toxicity. Rezlidhia should be taken on an empty stomach at least 1 hour before or 2 hours after a meal.

Common adverse effects: The most common adverse reactions in patients taking Rezlidhia include increased AST, increased ALT, decreased potassium, decreased sodium, increased alkaline phosphatase, nausea, increased creatinine, fatigue, arthralgia, constipation, increased lymphocytes, increased bilirubin, leukocytosis, increased uric acid, dyspnea, pyrexia, rash, increased lipase, mucositis, diarrhea, and transaminitis.

Boxed warning: Differentiation syndrome, which can be fatal, can occur with Rezlidhia treatment. If differentiation syndrome is suspected, withhold Rezlidhia, and initiate corticosteroids and hemodynamic monitoring until symptom resolution.

Other warnings and precautions: Monitor liver function tests during treatment with Rezlidhia. If hepatotoxicity occurs, interrupt and reduce or discontinue Rezlidhia. Patients should be advised not to breastfeed while taking Rezlidhia. Avoid concomitant use with strong or moderate CYP3A inducers. Avoid concomitant use with sensitive CYP3A substrates and monitor if concomitant use is unavoidable.

XENON XE 129 HYPERPOLARIZED
(Xenoview—Polarean Inc.)

Drug class: Xenoview, prepared from the Xenon Xe 129 Gas Blend, is a hyperpolarized contrast agent.

Indication: Xenoview is indicated for use with magnetic resonance imaging for evaluation of lung ventilation in adults and pediatric patients aged 12 years and older.

Recommended dosage and administration: The recommended target dose of Xenoview for adult and pediatric patients aged 12 years and older is 75 mL to 100 mL dose equivalent (DE) of hyperpolarized xenon Xe 129 by oral inhalation of the entire contents of one Xenoview Dose Delivery Bag. Each bag contains at least 75 mL DE of hyperpolarized xenon Xe 129 with a recommended targe DE range of 75 mL to 100 mL measured within 5 minutes of administration, in a volume of 250 mL to 750 mL total xenon with additional nitrogen, with NF added to reach a total volume of 1,000 mL. Administer dose within 5 minutes of DE measurement and initiate imaging immediately after inhalation.

Common adverse effects: The most common adverse reactions were oropharyngeal pain, headache, and dizziness.

Warnings and precautions: Xenoview has not been evaluated for use with lung perfusion imaging.

Supplemental oxygen administered simultaneously with Xenoview inhalation can cause degradation of image quality. For patients on supplemental oxygen, withhold oxygen inhalation for 2 breaths prior to Xenoview inhalation, and resume oxygen inhalation immediately following the imaging breath hold. Inhalation of anoxic gas such as Xenoview may cause transient hypoxemia in susceptible patients. Monitor all patients for oxygen saturation and symptoms of hypoxemia and treat as clinically indicated.

UBLITUXIMAB-XIIY

(Briumvi—TG Therapeutics)

Drug class: Briumvi is a CD20-directed cytolytic antibody.

Indication: Briumvi is indicated for the treatment of relapsing forms of multiple sclerosis in adults to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.

Recommended dosage and administration: Prior to initiating therapy, Hepatitis B virus and quantitative

serum immunoglobulin screening are required. Premedicate with methylprednisolone and an antihistamine prior to each infusion. Administer Briumvi by I.V. infusion. The first infusion should be 150 mg and the second infusion, administered 2 weeks after the first, should be 450 mg. Subsequent infusions should be 450 mg 24 weeks after the first infusion and every 24 weeks thereafter. Briumvi must be diluted in 0.9% sodium chloride prior to administration. Patients should be closely monitored during and for at least 1 hour after the completion of the first 2 infusions.

Common adverse effects: The most common adverse reactions were infusion reactions and upper respiratory tract infections.

Warnings and precautions: Briumvi is contraindicated in active hepatitis B virus infection and history of life-threatening infusion reaction to Briumvi. Monitor patients for infusion reactions and permanently discontinue Briumvi if a life-threatening or disabling infusion reaction occurs. Serious, including life-threatening and fatal infections, have occurred. Delay Briumvi administration in patients with an active infection until after the infection has resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation, until B-cell repletion. Monitor the level of immunoglobulins at the beginning, during, and after discontinuation of treatment with Briumvi, until B-cell repletion, and especially when recurrent serious infections are suspected. Briumvi may cause fetal harm and patients of reproductive potential should be informed of the potential risk to a fetus and to use contraception during treatment and for at least 6 months after stopping Briumvi.

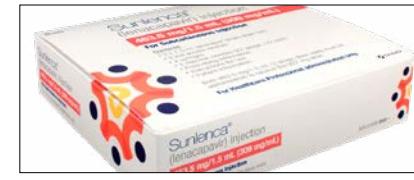
ENACAPAVIR

(Sunlenca—Gilead Sciences)

Drug class: Lenacapavir is a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor.

Indication: Sunlenca is indicated, in combination with other antiretrovirals, for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

Recommended dosage and administration: Initiation of Sunlenca should follow 1 of 2 options and then maintenance dosing once every 6 months. Tablets should be taken without regard to food. The first initiation dosing option is 927 mg S.C. injection and 600 mg orally on day 1 followed by 600 mg orally on day 2. The second initiation dosing option is 600 mg orally on days 1 and 2, 300 mg orally on day 8, and 927 mg by S.C. injection on day 15. The maintenance dose is 927 mg by S.C. injection every 6 months from the date of the last injection +/- 2 weeks. If more than 28 weeks has passed since the last injection and it is clinically appropriate to continue Sunlenca, restart initiation from day 1, using either option 1 or option 2.



Common adverse effects: The most common adverse reactions are nausea and injection site reactions.

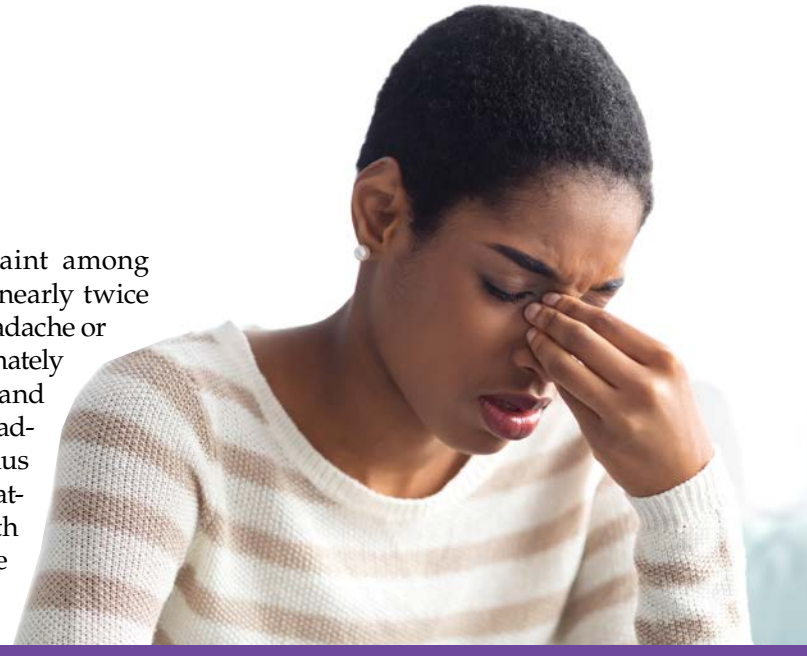
Warnings and precautions: Concomitant administration of Sunlenca with strong CYP3A inhibitors is contraindicated. If immune reconstitution syndrome occurs, further evaluation and treatment may be necessary. Residual concentrations of lenacapavir may remain in systemic circulation for up to 12 months or longer.

Counsel patients regarding the dosing schedule, as nonadherence could lead to loss of virologic response and development of resistance. Sunlenca may increase exposure and risk of adverse reactions to drugs primarily metabolized by CYP3A that are initiated within 9 months after the last Sunlenca dose. If discontinued, initiate an alternative, fully suppressive antiretroviral regimen where possible no later than 29 weeks after the final injection of Sunlenca. If virologic failure occurs, switch to an alternative regimen if possible. Injection site reactions may occur, and nodules and indurations may be persistent. Individuals infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission. ■

Also in this issue
FDA approves new drug for diabetes (page 17)

Rein in headache pain

Mary Warner



Headaches are a common complaint among patients of all ages, with women nearly twice as likely as men to have had a severe headache or migraine in the past 3 months. Approximately 90% of headaches, including episodic and chronic tension headaches, migraine headaches with and without an aura, and sinus headaches, are amenable to self-care treatment, though in some cases, patients with chronic migraine headaches may require prescription pain relievers.

Headache characteristics

Feature	Tension headache	Migraine headache	Sinus headache
Location	Bilateral	Usually unilateral	Face, forehead, or periorbital area
Nature	Diffuse ache, tightening, pressing, constricting	Throbbing, pulsating	Pressure behind eyes or face, dull and bilateral pain
Intensity	Mild–moderate	Moderate–severe	Mild–severe
Onset	Gradual	Sudden	Simultaneous with sinus symptoms
Duration	30 minutes to 7 days	4–72 hours	Days (resolves with sinus symptoms)
Aggravating factors	Stress, anxiety	Physical activity, light, sound	Nasal congestion
Nonheadache symptoms	Scalp tenderness, neck pain and muscle tension	Nausea, vomiting, aura	Nasal congestion nasal discharge

Source: APhA's *Handbook of Nonprescription Drugs.*

Most patients turn to OTC analgesics—including aspirin, acetaminophen, naproxen sodium, and ibuprofen—for relief of headache pain. Because tension headaches, migraine headaches, and sinus headaches vary in location, nature, intensity, onset, and duration, the same analgesic may not be most effective for all types of headaches.

Combination products are also commonly used for headache pain relief. Caffeine is commonly used in these products as an adjunct to analgesics for tension and migraine headaches. Clinical trials have suggested that combining caffeine with analgesics may result in better efficacy; however, caffeine itself may be a trigger for migraines, and withdrawal of caffeine may result in headache.

Combination products containing a decongestant and either acetaminophen or an NSAID are available for treatment of sinus headaches.

Investigators now believe that migraine headaches have a genetic cause.

The choice of nonprescription analgesic depends on patient preferences, the presence of contraindicating conditions, concurrent prescription medications, cost, and other factors.

Tension headaches

Tension (or stress-related) headaches are usually relatively mild, come on gradually, and are often accompanied by neck pain and muscle tension. They are considered chronic if they occur for 15 or more days per month or for at least 3 months; headaches are considered frequent if at least 10 headaches occur per month. Women suffer from tension headaches more than 3 times as often as men.

Tension headaches generally respond well to nonprescription analgesics, including acetaminophen and NSAIDs such as salicylates, especially when taken at the onset of the headache. Patients with chronic tension headaches may also benefit from relaxation exercises in addition to nonprescription (or prescription) medications.

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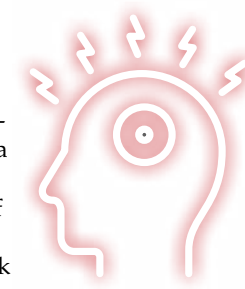
Migraine headaches

Most patients who suffer from migraines describe it as intense pulsing or throbbing pain in one area of the head, often accompanied by nausea and/or vomiting, or sensitivity to both light and sound. Migraine headaches are 3 times more common in women than in men and roughly one-third of affected individuals see an aura (visual disturbances that appear as flashing lights, zig-zag lines) or a temporary loss of vision before onset. According to NIH, migraines were once believed to be linked to the dilation and constriction of blood vessels in the head, but it is now believed that migraines have a genetic cause.

Taking an NSAID at the onset of symptoms can abort mild or moderate migraine headache.

Stress, fatigue, irregular sleep patterns, fasting or missing a meal, vasoactive substances in food, caffeine, alcohol, changes in hormones, changes in barometric pressure and altitude, bright lights, odors, neck pain, exercise, and smoking can all trigger a migraine headache. Some medications—including reserpine, nitrates, oral contraceptives, and postmenopausal hormones—may also trigger a migraine.



Taking an NSAID at the onset of symptoms can abort mild or moderate migraine headache, as analgesics work best in the early stages of a migraine. Patients with migraine who can predict the occurrence of the headache should take an analgesic before the event known to trigger the headache as well as throughout the duration of the headache. For patients with coexisting tension and migraine headaches, treatment of the initiating headache type can halt the mixed headache.

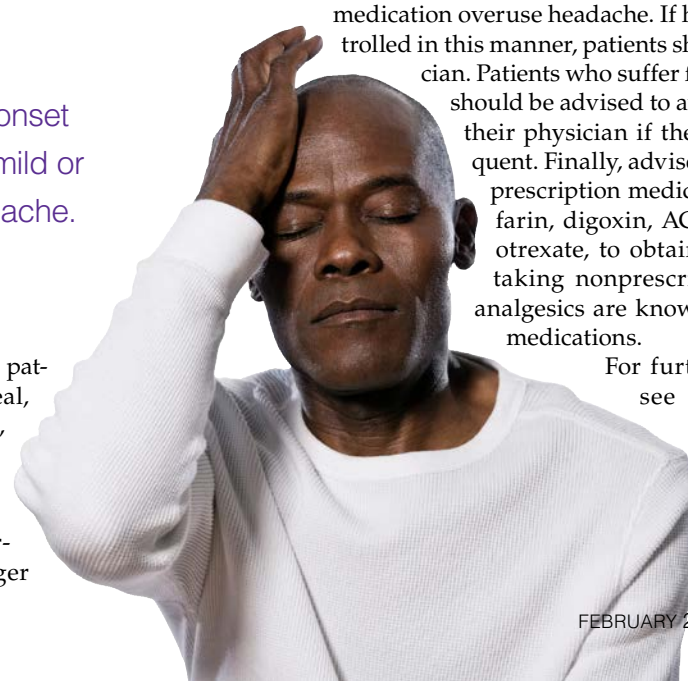
Sinus headaches

Sinus headaches occur when nasal congestion causes inflammation of the sinus walls caused by viral or bacterial infection or allergic rhinitis. Symptoms of sinus headaches include pain, pressure, and fullness in the cheeks, brow, or forehead and worsening pain when bending forward or lying down. Sinus headaches are often accompanied by fatigue and an achy feeling in the upper teeth.

Sinus headaches respond well to oral and nasal decongestants such as pseudoephedrine and oxymetazoline that reduce the congestion causing the headache. Nonprescription analgesics taken with the decongestant can relieve sinus headache pain while congestion is present. Patients with chronic congestion and sinus infections should be encouraged to consult a specialist as these symptoms may be a sign of structural abnormalities.

What to tell your patients

Advise patients that if nonprescription analgesics are used to treat chronic headache, their use should be limited to less than 3 days per week or 14 days per month to prevent medication overuse headache. If headaches cannot be controlled in this manner, patients should consult their physician. Patients who suffer from migraine headaches should be advised to avoid triggers and consult their physician if the headaches become frequent. Finally, advise patients who are taking prescription medications, particularly warfarin, digoxin, ACE inhibitors, and methotrexate, to obtain medical advice before taking nonprescription pain relievers as analgesics are known to interact with these medications.

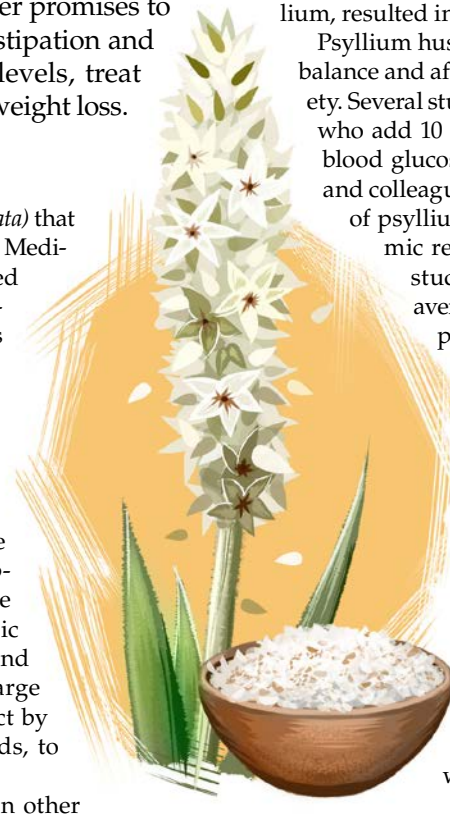


For further information, please see Chapter 5 of APhA's *Handbook of Nonprescription Drugs*, available in print via the bookstore on pharmacist.com or online through Pharmacy Library. ■

Psyllium husk

Mickie Cathers

A high intake of dietary fiber is associated with extensive health benefits including lower cholesterol and a reduced risk of heart disease. Psyllium husk is a popular dietary fiber supplement widely used as a gentle bulk-forming laxative and is probably best known as the main ingredient in Metamucil. This concentrated hit of soluble fiber promises to help lower cholesterol, relieve constipation and diarrhea, regulate blood glucose levels, treat intestinal issues, and contribute to weight loss.



Background

Psyllium is a shrub-like herb (*Plantago ovata)* that grows worldwide, most commonly in the Mediterranean and India. The name is derived from the Greek word for "flea" (psýllos) owing to thousands of small seeds on the plant. These gel-coated seeds are harvested from the herb, and the husk is removed and minimally processed to expose the soluble and insoluble fiber.

Much like other sources of fiber found in foods such as barley, beans, legumes, seeds, nuts, oat bran, and some fruits and vegetables, psyllium contributes to overall digestive health. In the small intestine, fiber drives metabolic effects such as lowering cholesterol and improving glycemic control. In the large intestine, fiber provides a laxative effect by binding with water and digestive fluids, to soften or bulk stool.

Psyllium husk boasts more fiber than other foods in similar portions. A single teaspoon of ground psyllium husk provides nearly 8 times more soluble fiber by weight compared with oat bran.

Psyllium is also a prebiotic which promotes healthy colonies of probiotics to grow in the gut, improving digestion and strengthening the immune system.

Most Americans do not consume the recommended amount of fiber. The Institute of Medicine recommends 25 g/day of dietary fiber for women and 38 g/day for men. The average intake of fiber for American adults has been reported to be only 17 g/day.

Is there a benefit?

Many well-designed studies have shown that psyllium husk relieves common GI complaints such as constipation and mild to moderate diarrhea. By soaking up water in the digestive tract, psyllium produces more bulk, which stimulates the intestines to contract and contributes to stool that is easier to pass.

Psyllium husk has also been shown to provide significant relief for abdominal pain, bloating, and distension as well as gas from those suffering from irritable bowel syndrome (IBS).

Diets high in fiber are associated with lower triglyceride levels and a lower risk of cardiovascular disease. Adding soluble fiber such as psyllium husk to the diet has been shown to lower cholesterol. A 2021 systematic review and meta-analysis of randomized controlled trials published in *Nutrition, Metabolism & Cardiovascular Diseases* by Schoeneck and Iggman found foods high in soluble fiber, including psyllium, resulted in moderate LDL cholesterol reduction.

Psyllium husk can help maintain a healthy glycemic balance and affect body weight through increased satiety. Several studies suggest people with type 2 diabetes who add 10 grams of psyllium daily saw improved blood glucose levels. A 2019 critical review by Jane and colleagues in *Nutrition* showed that the addition of psyllium improved blood lipid profiles, glycemic response, and increased satiety. Another study showed sustained weight loss of an average of 3.3 kg in the treatment group supplementing their diet with 3.5 grams psyllium husk twice a day before breakfast and dinner.

Dosage

Psyllium husk is widely available in a variety of forms, such as a capsules, tablets, or powder meant to be mixed with water. Psyllium is also found in cereal. In 1998, FDA approved Kellogg Co.'s promotion of psyllium as having positive potential health benefits.

Recommended dosages for adults suffering from constipation and IBS range from 3.5 g to 7 g mixed in 8 oz of water 1–3 times daily.

What to tell your patients

Psyllium husk is an easy way to increase daily fiber on occasion or regularly added to a healthy diet to help promote overall digestive health. Psyllium husk has laxative effects and potential adverse effects including gas, bloating, and abdominal cramps.

While proven safe to take 1–3 times a day with a full glass of water, it's preferable to start psyllium husk slowly and monitor reactions. Advise patients to follow the directions on the package and drink at least 6 to 8 glasses of water daily when taking psyllium husk. Patients with trouble swallowing, or esophageal or GI issues should not take psyllium husk and those with kidney disease should speak with their health care provider before using the supplement. Contraindications include taking antidepressants, carbamazepine, diabetes medications, cholesterol-lowering medications, digoxin, and lithium. Psyllium husk should not be combined with these drugs. ■

Teplizumab-mzwv for diabetes

Lauren Howell, PharmD

While the market for new drugs that can treat diabetes has boomed, until recently there has been little news on the prevention front. But in November 2022, FDA approved teplizumab-mzwv (Tzield–Provention Bio, Inc.), the first and only treatment indicated to delay the onset of stage 3 type 1 diabetes (T1D) in patients aged 8 and older.

Recommended dosage and how it works

Teplizumab-mzwv binds to CD3, a cell surface antigen present on T lymphocytes, to delay the onset of stage 3 T1D in patients with stage 2 T1D. The mechanism of action most likely involves partial agonistic signaling and deactivation of pancreatic beta cell autoreactive T lymphocytes. Teplizumab-mzwv leads to an increase in the proportion of regulatory T cells and of exhausted CD8+ T cells in peripheral blood.

Prior to initiating teplizumab-mzwv, a complete blood count and liver enzyme tests should be performed. It is not recommended to use teplizumab-mzwv in patients with a lymphocyte count <1,000 lymphocytes/µL, hemoglobin <10 g/dL, platelet count <150,000 platelets/µL, absolute neutrophil count <1,500 neutrophils/µL, elevated ALT or AST >2 times the upper limit of normal, bilirubin >1.5 times the upper limit of normal, laboratory or clinical evidence of acute infection with Epstein-Barr virus or cytomegalovirus, or active serious infection or chronic active infection other than localized skin infections. Teplizumab-mzwv must be diluted in 0.9% sodium chloride injection. Patients need to be premedicated with an NSAID or acetaminophen, an antihistamine, and an antiemetic before each teplizumab-mzwv dose for at least the first 5 days of the 14-day treatment course. Administration of teplizumab-mzwv should occur by I.V. infusion, over a minimum of 30 minutes, once daily for 14 consecutive days.

Prior to initiating teplizumab-mzwv, a complete blood count and liver enzyme tests should be performed.

Before treatment with teplizumab-mzwv is initiated, stage 2 T1D must be confirmed by documenting at least 2 positive pancreatic islet autoantibodies in those who have dysglycemia without overt hyperglycemia using an oral glucose tolerance test (OGTT) or alternative method if appropriate and OGTT is unavailable. In patients who meet these criteria for diagnosis of stage 2 T1D, it is important to review the patient's clinical history to ensure that they do not have type 2 diabetes.

Teplizumab-mzwv is packaged in a 2 mg/2 mL single-dose vial. The recommended dose is

- 65 mcg/m² on day 1
- 125 mcg/m² on day 2
- 250 mcg/m² on day 3
- 500 mcg/m² on day 4
- 1,030 mcg/m² on days 5–14

Two doses should not be administered on the same day.

Drug interactions

The safety of immunization with live-attenuated vaccines in patients treated with teplizumab-mzwv has not been studied. Teplizumab-mzwv may interfere with the immune response to vaccination and decrease vaccine efficacy. All age-appropriate vaccines should be administered prior to starting teplizumab-mzwv.

Inactivated or mRNA vaccinations should not be administered within the 2 weeks prior to teplizumab-mzwv treatment, during treatment, or 6 weeks after completion of treatment. Live-attenuated vaccinations should not be administered within the 8 weeks prior to teplizumab-mzwv treatment, during treatment, or up to 52 weeks after treatment.

Adverse effects and contraindications

The most common adverse reactions in patients treated with teplizumab-mzwv were lymphopenia, rash, leukopenia, and headache. Currently, there are no contraindications to teplizumab-mzwv.

Patient counseling

Patients should be informed about the signs and symptoms of cytokine release syndrome, infection, and hypersensitivity reactions. Pregnant patients and patients of reproductive potential should be advised that teplizumab-mzwv may cause fetal harm. A lactating patient may consider pumping and discarding breast milk during and for 20 days after teplizumab-mzwv administration. ■

New guidelines, new thinking, new drugs for menopause

Sonya Collins

Treatment for menopause symptoms continues to be a topic of great controversy among health care providers and menopausal patients themselves. Last year, in an attempt to quell the debate, the North American Menopause Society (NAMS) released an updated position statement on hormone therapy.

The statement takes into account recent papers that recast the findings of the seminal Women's Health Initiative (WHI) hormone therapy trials, whose original findings (and framing of them) led to the initial controversy around hormone replacement therapy. Meanwhile, drug developers are gaining ground on nonhormonal therapies for the vasomotor symptoms of menopause.

"Because of fear associated with the results of the Women's Health Initiative, a lot of patients go without treatment," said Nicole Cieri-Hutcherson, PharmD, BCPS, NCMP, a clinical assistant professor at the University at Buffalo School of Pharmacy and Pharmaceutical Sciences, who has a special focus on women's health. "But hormone therapy is the most effective thing we have right now, so completing a risk assessment and counseling patients that most women can use hormone therapy safely with proper oversight can have a significant impact on their quality of life."

She added that more nonhormonal therapies may soon be an option, too.

"Because of fear associated with the results of the Women's Health Initiative, a lot of patients go without treatment."

NAMS 2022 hormone therapy position statement

In its first updated position statement on hormone therapy since 2017, NAMS offers guidance on hormone prescribing based on literature published since the last statement.

The consensus of the advisory panel of clinicians and researchers states that hormone therapy is the most effective treatment for vasomotor and genitourinary symptoms of menopause and that it may also prevent bone loss and fracture. The benefit-risk ratio is favorable for patients under 60 or who are within 10 years of menopause onset and have no contraindications. Individual risk varies by type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used.

The statement emphasizes that for women over 60, or who start hormone therapy more than 10 years after menopause onset, the benefit-risk ratio is not as favorable due to greater absolute risk of heart disease, stroke, blood clot, and dementia.

Recent criticism of the WHI framing

NAMS' statement comes on the heels of recent papers that critique the framing of the WHI study findings. WHI was a series of NIH-sponsored clinical trials and observational studies started in 1991 that examined major causes of illness and death in postmenopausal patients. The framing of the hormone replacement therapy trial findings seemed to overshadow the benefits of hormone replacement therapy and overemphasize the risks. Among recent papers that critique the trial's conclusion are the 2021 review of the WHI and other recent hormone therapy trials by Flores and colleagues and published in *Endocrine Reviews* and a 2022 analysis of the WHI findings by Manson and colleagues published in *Menopause*.

A key criticism of the WHI trials is that the average age of study participants was 63 years old, and the largest age group was women aged 60 to 69.

"That's more than ten years out from menopause onset, so there are already higher inherent risks for heart disease, stroke, and breast cancer associated with aging, so the critique is that maybe the Women's Health Initiative overestimates those risks," Cieri-Hutcherson said.

New drug class

Though NAMS reaffirms the safety of hormone therapy for some patients, it is not right for everyone, nor is it everyone's preference. This highlights a need for nonhormonal treatments for the vasomotor symptoms of menopause. A new drug class, neurokinin-3 receptor antagonists, has garnered a great deal of attention and excitement as a way to meet this need.

These drugs block neurokinin B (NKB) binding on the kisspeptin/neurokinin/dynorphin (KNDy) neuron, which in turn moderates neuron activity in the thermoregulatory center of the brain to reduce the frequency and severity of moderate to severe hot flashes.

"Now that we know a little more about how hot flashes work," Cieri-Hutcherson said, "we are seeing therapies that fall outside of replacing estrogen."

Astellas Pharma announced last August that FDA has accepted a new drug application for its neurokin-3 receptor antagonist fezolinetant. Other drugs in this class may soon follow. ■

The complete position paper (www.menopause.org/docs/default-source/professional/nams-2022-hormone-therapy-position-statement.pdf) offers guidance on formulation, dosing, and routes of administration. ■

Challenges remain with COVID-19 vaccine labeling

Johanna Taylor Katroscik, PharmD

The first COVID-19 vaccines gained FDA EUA status in late 2020, but as new vaccines have emerged and some FDA EUAs have changed to approvals, health care personnel have had to stay up to date in an ever-changing environment.

This past fall, the Institute for Safe Medication Practices (ISMP) and CDC's Advisory Committee on Immunization Practices identified some potentially serious issues with the labeling of COVID-19 vaccines—issues they were concerned may lead to a delay in vaccine administration or even incorrect administration of the vaccines to patients.

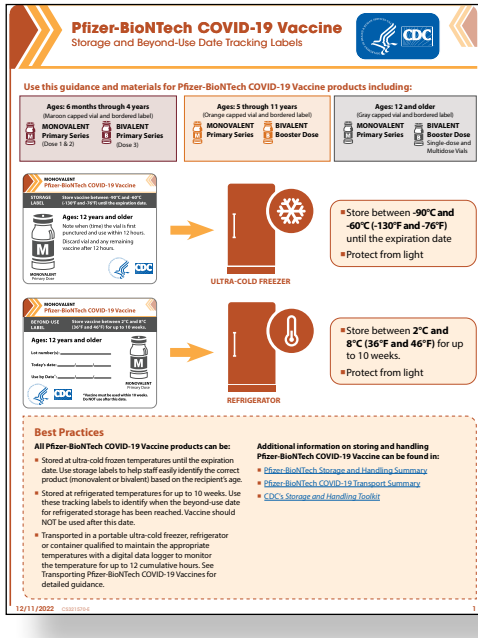
Cause for concern

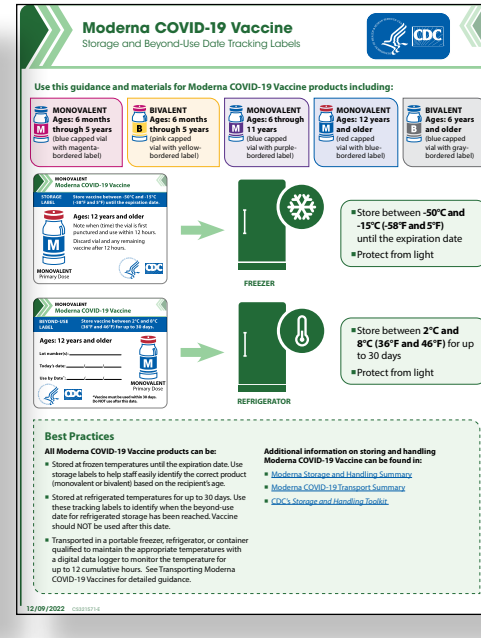
Both Pfizer–BioNTech and Moderna have gained new authorizations for their COVID-19 vaccines over the past 2 years. Unfortunately, with these new authorizations have also come steep learning curves for vaccine administrators. These COVID-19 vaccines were initially authorized only for use in patients 18 years and older and the big differences had to do with administration timelines and proper storage. However, as more age groups have received the official green light for the vaccines and as bivalent ones have become available, there is now more confusion than ever about giving the right dose to the right person at the right time.

In the fall of 2022, concerns were raised about the labeling of both Pfizer–BioNTech and Moderna vaccines—specifically that the labels of the monovalent and bivalent vaccines look very similar and could easily be confused with each other.

For the Moderna vaccines, the labels are very similar for both the monovalent vaccine and the bivalent vaccine. Both vials have light blue caps, making them more difficult to differentiate from one another, leading to potential administration errors. Another key concern with the Moderna vaccines is that the vaccines authorized for use in children aged 6–11 years have a label that reads 'for booster doses only' even though the vaccine is meant for the primary dose for this age group.

With the Pfizer–BioNTech vaccines, the main concern is that the labels for all vaccines look very similar and the caps for both monovalent and bivalent doses are the same within age groups—making it potentially easy for health care personnel preparing and giving the vaccine to administer the incorrect vaccine.





CDC resources for vaccines

Pfizer:
apha.us/CDCPfizerVaccine

Moderna:
apha.us/CDCModernaVaccine

However, CDC released several pages of helpful information regarding both the Pfizer–BioNTech and Moderna COVID-19 vaccines on their website in December 2022. The CDC pages include color-coded guides for which vaccines should be given to which age group, information about proper storage and transportation, and links for more in-depth information as well. The page also provides storage and beyond-use-date templates that can be used by pharmacies to help keep their vaccines organized.

ISMP gives key recommendations to help prevent age-related vaccine errors

ISMP offers a number of recommendations to help prevent age-related vaccine errors from occurring. Several key recommendations include utilizing appropriate technology for vaccine administration; clear and easy to understand vaccine storage that separates any potential look-alike and sound-alike vaccines from one another; proper vaccine documentation; and engaging with the patient and/or caregiver to ensure that the correct vaccine is being given to the correct patient. ■

High HDL-C levels may not be protective against CVD in Black individuals

Clarissa Chan, PharmD

A November 2022 study published in the *Journal of the American College of Cardiology* spotlights the racial disparities in current cholesterol treatment guidelines that are based on studies overrepresenting white patients.

"Our understanding of the cardiovascular risk factors stem mostly from white cohort studies like the Framingham heart study—the risk estimates or recommendations do not apply to everyone," said Nathalie Pamir, PhD, at Oregon Health and Science University's Knight Cardiovascular Institute in Portland, who was part of the study. "This is especially true for Black adults where their cardiovascular risk is underestimated."

The retrospective observational cohort study set out to investigate how high-density lipoprotein (HDL-C)—"good" cholesterol—contributes to CVD risk. Traditionally, low HDL-C levels were thought to increase CVD risk, and high HDL-C levels were thought to decrease CVD risk, but study authors found that low HDL-C levels may be associated with increased risk of coronary heart disease (CHD) in white adults, but not in Black adults. They also found that high HDL-C levels were not predictive of CHD risk in either racial group.

Study methods

The study population was based on REGARDS, a national longitudinal study of 30,239 Black and white community-dwelling adults 45 years and older.

Exclusion criteria included races other than Black or white, cognitive impairment, cancer treatment in the previous year, chronic conditions that prevent long-term study participation, inability to effectively communicate in English, and nursing home residence. Participants with prior CHD were excluded from the study, which lasted from 2003 to 2007.

Screening processes included an initial telephone interview to determine eligibility and obtain consent and later demographic information, including race (self-classified by participants) and medical history. An in-home assessment was conducted to determine baseline vital signs and labs via electrocardiogram, blood draw, and urinalysis.

The resulting cohort analysis included 23,901 participants, with 57.7% and 58.3% identifying as white and female, respectively. During the IRB-approved study by all participating institutions, follow-up phone calls were made to participants every 6 months to document CV events.

Outcomes included incident CHD defined as a definite or probable nonfatal myocardial infarction (MI) or CHD death after the baseline in-person visit or before December 31, 2017. CHD death was defined as definite or probable fatal MI within 28 days from event or death from cardiac signs or symptoms without noncoronary causes.

Results

Both racial groups had comparable mean age, lipid profiles, smoking status, and diabetes and hypertension medication use.

Roughly 1,615 CHD events occurred in a median follow-up time of 10.7 years, with 41.1% and 45.5% occurring in Black and women participants, respectively. Black women experienced a higher incidence of CHD than white women, but there was no difference between men of both racial groups. CHD fatalities were higher in Black participants of both sexes than in white participants.

Based on lipid profiles, researchers found that for every 1 SD increase in low-density lipoprotein cholesterol (LDL-C) (34 mg/dL) and triglyceride (82 mg/dL) levels there was an associated increased CHD risk. Levels increased by 1 SD (16 mg/dL) in HDL-C were associated with decreased CHD risk in both races. Following statistical adjustment for clinical and behavioral variables, there was no association found between HDL-C levels and CHD risk in both races.

Low HDL-C levels were associated with poor CHD-free survival rates in white but not in Black participants, while high HDL-C levels were correlated with positive CHD-free survival rates in white but not in Black participants.

In unadjusted race-stratified models, lower HDL-C levels were associated with increased CHD risk in white but not in Black participants, while high HDL-C levels were associated with decreased CHD risk in both races.

Following statistical adjustment for clinical and behavioral variables, there was no association found between HDL-C levels and CHD risk in both races.

However, after clinical factor adjustments, low HDL-C was associated with increased CHD risk in white but not in Black participants, and high HDL-C did not provide a protective benefit for both races.

Takeaways

"These findings might change the conversation between the doctor and a patient with high HDL-C," said Pamir. "Patients might no longer get the 'pat on the back' for having the protective effect of high HDL-C, because the doctor now might say 'you have high HDL-C, but we don't know what this means for your cardiovascular disease risk.'"

More studies are needed to focus on diverse ethnicities to assess the impact of traditional risk factors for each ethnicity. "When we build risk prediction algorithms, they need to apply to everybody," said Pamir. ■

Editor's note: This article is part of *Pharmacy Today's* ongoing coverage of structural racism.

APhA

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20378

CDC releases new pain management guidelines, advocating tailored care for patients

LOREN BONNER

CDC's updated guidelines on pain management are "a step in the right direction," said Chris Herndon, PharmD, BCACP, FASHP, FCCP. Most pain experts, like Herndon, are pleased with the new guidance, which covers acute, subacute, and chronic pain, and replaces the controversial 2016 CDC opioid guideline for chronic pain.

"Removing the 'line in the sand' doses will hopefully remove some of the misconceptions and stigma around opioids," said Herndon, who is a professor at Southern Illinois University Edwardsville School of Pharmacy.

CDC's Clinical Practice Guideline for Prescribing Opioids for Pain throws out the rigid numbers and hard thresholds for pain medication doses and duration that were emphasized in the recommendations from the 2016 version. The 2016 CDC guidelines—which were simply intended to "guide" therapy—turned into policies and practices that, for example, encouraged hard limits and in some cases, resulted in abrupt tapering of opioid drug doses. Insurance companies, for instance, put coverage restrictions in place for opioid prescriptions above a certain morphine milligram equivalent per day. Turning back these laws and policies is difficult, however, and the new guidelines will take time to reverse the hard limits that insurance companies and others have enacted.

In the 2022 guidance, CDC promotes tailored care for patients through shared decision-making between patients and their care teams, which includes pharmacists.

"The guideline explicitly recognizes various roles for pharmacists in integrated pain management as part of care teams," said Anne Burns, RPh, former vice president of professional affairs at APhA. Burns was part of a workgroup for the guideline. "The new recommendations and user-friendly format should help pharmacists in providing individualized pain care to their patients," she said.

On these care teams, pharmacists can, for example, help with tapering services, coprescribing of naloxone, monitoring prescription drug monitoring programs (PDMPs), and be involved when opioids are coprescribed with other central nervous system depressants.

"Patients with pain should receive compassionate, safe, and effective pain care."

In a press statement, CDC said the updated guideline is a clinical tool to improve communication between clinicians and their patients and empower them to make informed decisions about safe and effective pain care. The recommendations are voluntary and provide flexibility to clinicians and patients to

Intended use of CDC's 2022 Clinical Practice Guideline for Prescribing Opioids for Pain

This clinical practice guideline is

- A clinical tool to improve communication between clinicians and patients and empower them to make informed, person-centered decisions related to pain care together.
- Intended for primary care clinicians and other clinicians providing pain care for outpatients aged ≥18 years with
  - Acute pain (duration of <1 month),
  - Subacute pain (duration of 1–3 months), or
  - Chronic pain (duration of >3 months)
- Intended to be flexible to enable person-centered decision-making, taking into account a patient's expected health outcomes and well-being.

This clinical practice guideline is not

- A replacement for clinical judgment or individualized, person-centered care.
- Intended to be applied as inflexible standards of care across patients or patient populations by health care professionals, health systems, pharmacies, third-party payers, or governmental jurisdictions or to lead to the rapid tapering or abrupt discontinuation of opioids for patients.
- A law, regulation, or policy that dictates clinical practice or as a substitute for FDA–approved labeling.
- Applicable to
  - Management of pain related to sickle cell disease,
  - Management of cancer-related pain, or
  - Palliative care or end-of-life care; or
- Focused on opioids prescribed for opioid use disorder.

Adapted from Dowell et al. *MMWR Recomm Rep.* 2022;71:1–795. doi: http://dx.doi.org/10.15585/mmwr.rr7103a1

support individualized, patient-centered care. According to CDC, the guidelines should not be used as an inflexible, one-size-fits-all policy nor should they replace clinical judgment about personalized treatment.

"Patients with pain should receive compassionate, safe, and effective pain care," said Christopher Jones, PharmD, MPH, acting director of CDC's National Center for Injury Prevention and Control, in the press statement. "We want clinicians and patients to have the information they need to weigh the benefits of different approaches to pain care, with the goal of helping people reduce their pain and improve their quality of life."

The new clinical practice guideline is intended for clinicians who are treating outpatients aged 18 years and older with acute (duration of less than 1 month), subacute (duration of 1–3 months), or chronic (duration of more than 3 months) pain, and excludes pain management related to sickle cell disease, cancer-related pain treatment, palliative care, and end-of-life care.

Specifics

The new CDC guidance addresses 4 key areas for pain management: 1) determining whether to initiate opioids for pain, 2) selecting opioids and determining opioid dosages, 3) deciding duration of initial opioid prescription and conducting follow up, and 4) assessing risk and addressing potential harms of opioid use.

With 12 recommendation statements in total, each is followed by considerations for implementation and a rationale for the recommendation.

In general, the recommendations state that clinicians should not consider opioids as first-line or routine therapy for many types of acute, subacute, or chronic pain. Nonopioid therapies, like prescription gabapentin and OTC nonsteroidal anti-inflammatory medication, are often preferable for several types of acute pain, CDC pointed out. In the subacute timeframe of patients receiving opioids for 1 to 3 months, CDC recommends that clinicians carefully reassess treatment goals, benefits, and risks before continuing any opioid treatment.

The new guideline reinforces the 2016 guideline's recommendation for judicious use of opioids for chronic pain.

In a commentary about the new guideline published in *NEJM*, authors noted that clinicians should maximize use of nonopioid therapies for chronic pain and consider initiating opioid therapy only if the expected benefits for pain and function are anticipated to outweigh the risks.

In the commentary, guideline coauthor Debbie Dowell, MD, MPH, chief clinical research officer for CDC's Division of Overdose Prevention, and colleagues wrote, "when opioids are needed [for chronic pain], clinicians should initiate therapy at the lowest effective dosage, carefully evaluate individual benefits and risks when considering increasing dosages and avoid increasing the dosage above levels likely to yield diminishing returns in benefits relative to risks.

"These principles do not imply that nonpharmacologic and nonopioid pharmacologic therapies must all be tried unsuccessfully in every patient before opioid therapy is offered. Rather, expected benefits specific to the clinical context should be weighed against risks before therapy is initiated."

Like the 2016 guideline, the 2022 guideline says that when opioids are needed for acute pain, they should be prescribed at the lowest effective dose and for no longer than the expected duration of pain severe enough to warrant opioids. Tapering is recommended when opioid treatment is discontinued after being used continuously for more than a few days, according to the *NEJM* commentary.

unexpectedly persists to gain timely access to re-evaluation in order to promote more equitable access and reduce barriers to high-quality care.

The guideline also cautions clinicians about potential bias in interpreting data from PDMPs and toxicology tests.

Five new guiding principles have been added to help clinicians put the recommendations into practice and support appropriate, individualized care.

> "We want clinicians and patients to have the information they need to weigh the benefits of different approaches to pain care, with the goal of helping people reduce their pain and improve their quality of life."

Equitable access

According to CDC, the new recommendations should "result in greater and more equitable access to the full range of evidence-based treatments for pain, more judicious initial use of opioids, and more careful consideration and management of benefits and risks associated with continuing, tapering, or discontinuing opioids in patients who are already receiving them long term."

Herndon said the guidelines do a good job of ensuring proper interpretation and use of the recommendations as well as the patient population to which they pertain.

"It's important to remember that any opioid exposure is associated with some increased risk and that the risk is dose-dependent," he said. "However, to assume that 48 mg of MME daily has less risk than 51 mg of MME daily, especially without considering patient-specific factors, creates barriers to access that have proven to be detrimental to patients."

Writing in the *NEJM* commentary, Dowell and colleagues suggest finding ways to allow patients whose pain

They include

- Acute, subacute, and chronic pain needs must be appropriately assessed and treated independently of whether opioids are part of a treatment regimen.
- Recommendations are voluntary and are intended to support, not supplant, individualized, person-centered care. Flexibility to meet the care needs and the clinical circumstance of a specific patient is paramount.
- A multimodal and multidisciplinary approach to pain management attending to the physical health, behavioral health, long-term services and supports, and expected health outcomes and well-being of each person is critical.
- Special attention should be given to avoid misapplying this clinical practice guideline beyond its intended use or implementing policies purportedly derived from it that might lead to unintended and potentially harmful consequences for patients.
- Clinicians, practices, health systems, and payers should vigilantly attend to health inequities; provide culturally and linguistically appropriate communication, including communication that is accessible to persons with disabilities; and ensure access to an appropriate, affordable, diversified, coordinated, and effective nonpharmacologic and pharmacologic pain management regimen for all persons.

Best available evidence

According to the CDC press statement, the agency followed a rigorous scientific process using the best available evidence and expert consultation to develop the 2022 Clinical Practice Guideline.

An independent federal advisory committee, peer reviewers, and members of the public reviewed the draft updated guideline, and CDC revised it in response to this feedback, they noted. An opioid workgroup reviewed the guideline and provided recommendations.

CDC also engaged with patients with pain, caregivers, and clinicians to gain insights and gather feedback from people directly affected by the guideline.

"The science on pain care has advanced over the past 6 years," said Dowell, in the CDC press statement. "During this time, CDC has also learned more from people living with pain, their caregivers, and their clinicians. We've been able to improve and expand our recommendations by incorporating new data with a better understanding of people's lived experiences and the challenges they face when managing pain and pain care."

The recommendations in the 2016 CDC Opioid Prescribing Guideline were based on a systematic review of the best available evidence at the time, along with input from experts and the public.

The 2022 guideline also supports the primary prevention pillar of the HHS Overdose Prevention Strategy—supporting the development and promotion of evidence-based treatments to effectively manage pain.

For example, the new guidance suggests that clinicians work with patients to incorporate plans to mitigate risks, including offering naloxone. ■

Pharmacists continue to face challenges with Paxlovid prescribing authority

Lauren Howell, PharmD

Since July 2022, pharmacists have been able to prescribe Paxlovid (Pfizer) with certain limitations. They are able to order and prescribe the oral antiviral, under certain conditions, for eligible patients who test positive for COVID-19.

FDA revised Paxlovid's EUA in July 2022 to include pharmacists among other health care professionals permitted to prescribe this therapeutic medication, recognizing pharmacists' expertise and the accessibility of pharmacies to provide a test-to-treat model, especially in underserved areas. This authority provides a significant opportunity for pharmacists to demonstrate an enhanced level of service delivery and take advantage of the current scope of practice, while advocating for the scope to be broadened.

While this authority is a step in the right direction for pharmacists, few pharmacists and pharmacies have successfully incorporated prescribing of Paxlovid into their practice.

APhA survey data from August 2022 show that payment and access to laboratory data are the biggest barriers that prevent pharmacists from prescribing Paxlovid. Most pharmacists in pharmacies don't have access to information from physician practices or hospital systems to receive the data needed to properly assess hepatic and renal function, despite pharmacists having the education and expertise needed to do so.

Payment pathways

While pharmacists receive reimbursement for dispensing of medications, including Paxlovid, there are very few pathways in place for payment for the pharmacist's clinical assessment to determine if the patient is a candidate for Paxlovid.

Most clinical assessments for Paxlovid take 15–30 minutes or longer, and coverage for the pharmacist's time is critical for creating a sustainable financial model to provide this service. It's important that the pharmacist's time for the clinical assessment is covered, regardless of whether the assessment results in a prescription or not. This approach is consistent with the way that other health care providers are paid for performing clinical assessments. However, the lack of incentive and reimbursement is leading many pharmacists to decide not to take advantage of the opportunity to offer this service. To solve the reimbursement issue for these services and to increase patient access to Paxlovid, several states have implemented pathways to payment for clinical assessments performed by pharmacists.

Additionally, the federal employee benefit health program has issued a directive to care plans in their network to cover pharmacists' provision of this service. Some large community and independent pharmacies have begun implementing a cash pay program for Paxlovid clinical assessments to provide needed access to the service and cover their costs.

APhA has created several resources to help pharmacists implement these services and assess patients for treatment with Paxlovid. Access apha.us/Paxlovid and apha.us/TreatmentPrescribingConsiderations for pharmacist decision-making support tools, training resources, information on APhA advocacy surrounding the topic, and information from FDA.

Paxlovid prescribing in Canada

While the United States has seen limited uptake of pharmacists prescribing Paxlovid, a different narrative is playing out in Canada. In Quebec, 65% of prescriptions for Paxlovid have been written by pharmacists to date. More robust mechanisms are in place for Canadian pharmacists to access the kidney and liver function laboratory data that are needed for prescribing. There is also a payment mechanism in place for pharmacists to receive payment for performing a clinical assessment regardless of whether it results in a prescription.

The president of Association québécoise des pharmaciens propriétaires, Benoit Morin, said "With the ability to adjust medication dosage and to order and interpret lab results, as well as an existing compensation framework for the assessment and prescribing for minor ailments such as antivirals for influenza, pharmacists in Quebec have been able to contribute quickly and are now prescribers for approximately two-thirds of Paxlovid prescriptions dispensed in Quebec. With their great accessibility as frontline practitioners, Quebec pharmacists are thus contributing to public health efforts to protect patients at risk of complications of COVID-19." ■

Paxlovid EUA specifics

To prescribe Paxlovid, a pharmacist must have

- Access to patient's medical records that are less than 12 months old for hepatic and renal function assessment.
- Access to a comprehensive list of the patients' current medications to assess for potential drug interactions.

A pharmacist must refer patients if there is

- Lack of pharmacist access to the required information to assess renal and hepatic function or potential drug interactions.
- A need for modification of medications due to drug interactions.

If the pharmacists' assessment results in a prescription, the patient has the option to get the prescription filled at that pharmacy or the pharmacy of their choice.

OTC hearing aids bring opportunities for professional collaboration

Sonya Collins

After FDA approval of OTC hearing aids last summer, pharmacies may already be stocking these items. A recent paper published in *JAPhA* described the arrival of OTC hearing aids as an opportunity for collaboration between pharmacists and audiologists.

"We want to educate pharmacists so that they can help get those patients who are not going to benefit from an OTC hearing aid to an audiologist," said Elaine Mormer, PhD, CCC-A, an audiologist and director of audiology clinical education in the Department of Communication Science and Disorders at University of Pittsburgh School of Health and Rehabilitation Sciences. Mormer coauthored the *JAPhA* paper.

OTC hearing aids: A role for pharmacists

OTC hearing aids are approved for adults ages 18 and older who perceive their hearing loss to be mild to moderate. These are self-care devices that do not require intervention or assistance from any health care professional.

When pharmacists have the opportunity to interact with a patient seeking an OTC hearing aid, they can help ensure that the device is the right fit for their patient. Besides age and perceived hearing loss, there may be other factors that could mean a patient would not benefit from an OTC device and should see an audiologist to determine the underlying cause of the problem and identify appropriate next steps.

"Pharmacists can ask the patient questions to ensure that using an OTC hearing aid won't deter them from seeking further care when the hearing loss is caused by a treatable medical condition that should be solved first," said Lucas Berenbrok, PharmD, an associate professor in the School of Pharmacy at University of Pittsburgh, and lead author of the *JAPhA* paper.

The American Speech-Language-Hearing Association (ASHA) has created a checklist of questions for pharmacists to ask patients who are interested in OTC hearing aids. Pharmacists can visit www.asha.org/siteassets/audiology/patient-hearing-checklist.pdf to access the complete tool.

The checklist includes the following risk factors that might suggest a patient needs follow-up care with an audiologist before trying an OTC device:

- Hearing that is much better in one ear than the other
- Recent, sudden hearing loss
- Ringing, roaring, or beeping in one or both ears
- A history of head and neck chemotherapy or radiation, or medications that may include hearing loss as an adverse effect
- Recent, active drainage from one or both ears
- Constant pain or discomfort in one or both ears
- Dizziness

Pharmacists may educate themselves on the features of OTC hearing aids and help patients choose the most suitable one that meets their needs and is a match for their level of technical literacy.

"We can help patients compare devices. For example, how does it control volume—is it a button on the device or is a smartphone app required? Does the device use rechargeable batteries? Will Bluetooth connection be necessary?" said Berenbrok.

He also stressed the importance of follow up. Aside from a toll-free number on the box, pharmacists may be the only professional available to answer patient questions about these new hearing aids. When the patient returns to the pharmacy, the pharmacist should ask how they are doing with the device and gauge the need for an audiologist referral.

Aside from a toll-free number on the box, pharmacists may be the only professional available to answer patient questions about these new hearing aids.

Potential for collaboration

Berenbrok and Mormer recommend that pharmacists be prepared to refer patients to an audiologist as needed. ASHA has created a tool to help pharmacists find a hearing professional in their area (see QR code).

Many people will benefit from OTC hearing aids and not everyone who seeks out the device needs a referral to an audiologist but, Mormer said, pharmacists should communicate to patients that "You don't know how much hearing loss you have until you've had a hearing test." ■

Resources

Pharmacists can learn more about counseling patients on OTC hearing aids and collaborating with audiologists through resources available at apha.us/ASHAHearingAidToolkit.

Berenbrok and Mormer have also designed an online course for pharmacists. More information can be found at apha.us/ASHALearningCourse. ■

Epinephrine autoinjector myths still common

Clarissa Chan, PharmD

A November 2022 survey published in the *Annals of Allergy, Asthma & Immunology* of more than 1,000 adults with food allergies has helped shed light on the challenges patients face with epinephrine autoinjectors (EAIs).

According to Erin Malawer, senior author of the EAI Utilization and Access survey, and Wes Sublett, MD, MPH, an allergist in Louisville, KY, who was not part of the study, dangerous EAI myths can keep patients with food allergies from obtaining and using EAIs.

Why it is important to use EAIs

"[EAIs] should be administered as soon as anaphylaxis is recognized to prevent life-threatening symptoms in both children and adults," said Sublett. "Delayed use of epinephrine in the treatment of anaphylaxis has been associated with fatalities and hospitalizations."

Why some patients don't obtain EAIs

"[We were surprised] that 'my doctor did not indicate it was needed' was the top reason patients didn't obtain EAIs," said Malawer, who is also executive director of AllergyStrong and cofounder of Food Allergy Collaborative. Another concern may be the price tag of most EAIs. "[Cost] might be the biggest barrier to access," said Malawer. EAIs cost an average of $476.

Although follow-up questions on why some people believe that EAIs are unsafe were not asked in the survey, "it was disheartening to see that 36% of people surveyed believed that epinephrine causes life-threatening adverse effects," said Malawer.

Reasons patients didn't fill their EAI prescription included issues related to obtaining a prescription, access and availability of epinephrine at the pharmacy, insurance reimbursement, fear of both needles and adverse effects, and poor communication with health care providers.

Why EAIs are underprescribed

Despite published guidelines, research supporting the importance of epinephrine in anaphylaxis, and an emphasis on EAI training, the use and access of epinephrine is suboptimal.

"Many patients who experience anaphylaxis never receive an EAI or allergist referral," he said. "Referral to a board-certified allergist-immunologist is critical to evaluate potential triggers of anaphylaxis."

Some myths about food allergies

Misconceptions about food allergies spill over into a person's belief about whether they need epinephrine. "Some mistakenly believe that because they've only experienced mild reactions, they will never need epinephrine," said Malawer. "Reactions can vary; a previous reaction does not predict a future one."

Some believe that because they aren't allergic to nuts or shellfish, for example, they do not need epinephrine. "Any allergen can cause a serious reaction; it's not just peanuts," said Malawer.

Others believe that antihistamines—particularly first-generation antihistamines—are effective at stopping a severe reaction, because antihistamines are affordable, accessible, and commonly used for seasonal allergies. Patients who have not had a severe reaction in recent years may feel they don't need epinephrine because they have antihistamines available. "Antihistamines can mask symptoms, but do not stop anaphylaxis; epinephrine is the only medication that will stop an anaphylactic reaction," said Malawer.

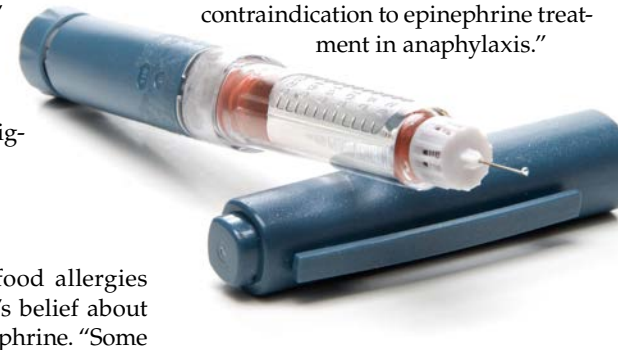
Financial assistance for patients who cannot afford EAIs

Generic EAIs are typically more affordable. Pharmacists can collaborate with patients and providers to see which EAIs are most appropriate and affordable.

"Speak with your insurance company about which autoinjectors they cover and at what rates, so there are no surprises," said Malawer.

How can pharmacists help?

Reassure patients that EAIs are safe and effective. "Epi First, Epi Fast," said Sublett. "Emphasize that epinephrine is the first-line and only FDA-approved treatment for anaphylaxis in both children and adults. There is no absolute contraindication to epinephrine treatment in anaphylaxis."



"Any allergen can cause a serious reaction; it's not just peanuts."

Encourage patients to ask questions and be prepared to dispel myths. Arming patients with accurate information about epinephrine will help them use EAIs in emergency situations. Acknowledge patients' needle phobias and reassure them that autoinjectors help make administration easier for them, said Malawer. Utilizing EAI trainers to demonstrate and allowing patients to practice using a device ensures that they are educated and feel empowered to correctly use device-specific autoinjectors when faced with anaphylaxis, said Sublett. ■

Cough, cold, and allergy

While there may not be a known cure for colds, we can at least reduce bothersome symptoms, improve our sense of well-being, and receive some relief.

Cough, cold, and allergy

Adult allergic reaction treatment (n = 554)

Benadryl	67%
Zyrtec	6%
Claritin	2%
Cortizone 10	1%
Walgreens	1%

Nasal decongestant spray (n = 555)

Afrin	43%
Flonase	21%
Vicks Sinex	2%
Sudafed	2%
Ocean	1%

Adult cough suppressant — Topical treatments (n = 590)

Vicks VapoRub	32%
Delsym	11%
Robitussin	9%
Chloraseptic	4%
Halls	4%

Sinus rinse (n = 645)

NeilMed	33%
Neti Pot kit	13%
Ocean	8%
Navage	2%
Ayr	1%

Cough lozenges (n = 509)

Halls	38%
Cepacol	18%
Ricola	15%
Ludens	3%
Fisherman's Friend	2%

Liquid cough suppressant (dry cough) (n = 587)

Delsym	43%
Robitussin	24%
Mucinex	6%
Vicks Dayquil Nyquil	2%

Cold medication (n = 510)

Vicks Dayquil Nyquil	25%
Tylenol	11%
Mucinex	9%
Robitussin	8%
Sudafed	5%

Cough, cold, and flu medication (n = 587)

Vicks Dayquil Nyquil	27%
Mucinex	15%
Robitussin	12%
Tylenol	8%
Sudafed	5%

Adult seasonal allergy relief (n = 635)

Zyrtec	34%
Claritin	27%
Allegra	13%
XYZAL	3%
Flonase	3%

Cough medication (n = 598)

Robitussin	30%
Delsym	30%
Vicks Dayquil Nyquil	4%
MucinexDM	2%
CVS Health	1%

Flu medication (n = 598)

Theraflu	19%
Vicks Dayquil Nyquil	14%
Tylenol	11%
Mucinex	4%
Alka-Seltzer Plus	2%

Liquid cough expectorant (n = 561)

Robitussin	37%
Mucinex	31%
Delsym	8%
Vicks Dayquil Nyquil	1%
Equate	1%

Sore throat lozenges (n = 655)

Cepacol	34%
Halls	21%
Chloraseptic	8%
Ricola	8%
Sucrets	3%

Self-care survey redux

This section of *Pharmacy Today*'s Self-Care Product Survey is reprinted from the full survey results published in the January 2023 issue of the magazine and available online at pharmacytoday.org.

The current survey was conducted using scientifically valid methodology and determines those nonprescription products most often recommended by pharmacists in the United States to consumers.

The winners were selected based on a survey of 1,682 pharmacists practicing in the United States who gave their unaided write-in opinions on which brands they'd recommend to patients in 86 categories. The highest share of citations as Most Trusted in the category determined the winner. If the margin of citation share between the leading brands did not exceed the estimate of sampling error at 90% statistical confidence, a tie was declared.

The n value given for each category represents the total number of responding pharmacists' recommendations.

Please also see APhAs *Handbook of Nonprescription Drugs*, the definitive source of professional information about OTC products. The Handbook is available online at PharmacyLibrary.com or in print in the bookstore at www.pharmacist.com.

When cutting costs doesn't pay

David B. Brushwood, BSPharm, JD

Rising health care costs are a concern for every health care institution. Residential assisted living facilities (RALFs) are among the health care institutions constantly looking for ways to promote efficiency and reduce costs. A recent legal case from the Supreme Court of Idaho ruled that a policy denying residents the right to choose their pharmacy or pharmacist is not justifiable as a way for a RALF to reduce its costs.

Background

The plaintiff in the case was a RALF that had adopted an integrated management software system to "manage all aspects of its facility's operations, including the tracking and delivery of residents' prescription medications."

The license fee for the system was $11.00 per resident per month. After requesting proposals from various pharmacies, the RALF selected one pharmacy to be its "preferred pharmacy" because the pharmacy offered unit dose packaging and delivery services at no extra cost. The selected pharmacy also offered to help offset the monthly software license fee if the majority of the RALF residents opted to use that pharmacy.

After selecting this preferred pharmacy, the RALF increased the monthly rent by $10.00 for those residents who opted not to use the preferred pharmacy.

A state administrative agency determined that this added fee was in violation of a state Pharmacy Choice Rule that says, "Each resident shall have the right to control his receipt of health-related services, including the right to select the pharmacy or pharmacist of their choice so long as it meets the statutes and rules governing residential care or assisted living and the policies and procedures of the residential care or assisted living facility."

The RALF argued that "its proposed fee would not inhibit residents from selecting the pharmacy of their choice." The RALF appealed the administrative agency's determination.

Rationale

On appeal, the Supreme Court of Idaho concluded that, "The Pharmacy Choice Rule unambiguously protects the right to both control one's health care services, and to select the pharmacist or pharmacy of one's choice, so long as the pharmacy meets statutory norms. [The RALF's] attempt to impose a $10.00 surcharge on residents who do not use [the preferred pharmacy] violates both of these rights. Requiring residents to pay this fee implicitly impels residents to choose [the preferred pharmacy]; otherwise, those residents subsidize the computer licensing fees for the facility in an amount greater than residents who choose [the preferred pharmacy]. This policy would place undue financial pressure on those residents to switch to [the preferred pharmacy]. While the amount is minimal month-by-month, for individuals living in these facilities, typically on fixed incomes, such pressure could make a difference. This tension limits residents' capacity to control and select pharmaceutical providers free from outside influence."

The court upheld the determination by the state administrative agency. The RALF's policy was held to be in violation of the state Pharmacy Choice Rule applicable to RALFs. The court concluded that the state administrative agency was "obliged to restrict facilities from decisions that impede resident rights for the sake of business."

"Each resident shall have the right to control his receipt of health-related services, including the right to select the pharmacy or pharmacist of their choice."

Takeaways

Patients choose a pharmacy for a variety of reasons, including personal interactions, convenience, quality, service, and cost. Many residents of an assisted living facility have an established relationship with a pharmacy of their choice, and many of these residents choose to continue that relationship when they transition from independent to assisted living. The relationship between a patient and a pharmacist or pharmacy is of value to the patient. Many states have enacted laws recognizing the value of that relationship through the establishment of pharmacy choice laws.

Although health care institutions, such as RALFs must adopt policies of economic efficiency so that they can stay open and continue to provide their valuable services, the value of a patient–pharmacist relationship must be respected under the law. The value of institutional cost-saving measures don't necessarily outweigh the value of patient choice. Patients have the right to make their own choices. ■

Using Vigiv for mpox? The concentration is not as it may seem

Institute for Safe Medication Practices, Horsham, PA

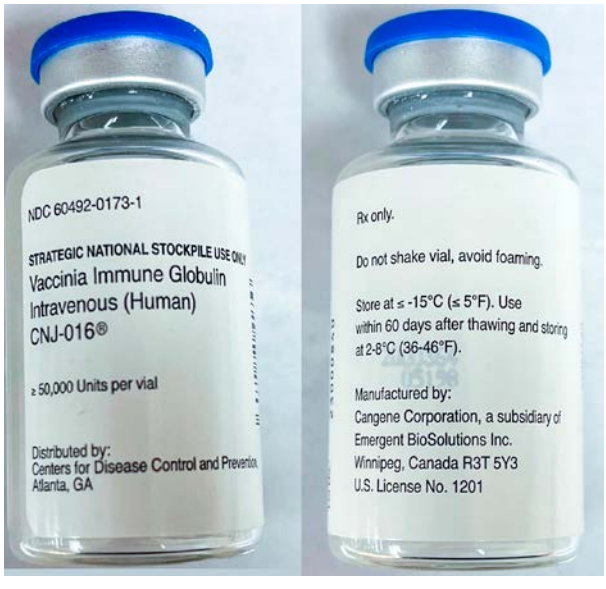
A prescriber ordered vaccinia immune globulin intravenous, human (Vigiv–Cangene Corporation) 6,000 units/kg for a hospitalized 3.49 kg neonate (total dose of 20,940 units) with mpox-like symptoms. A single-dose vial arrived from the national stockpile in an unlabeled carton without a package insert.

The vial label displayed, "greater than or equal to 50,000 units per vial," without listing a corresponding volume or concentration. When trying to determine how to prepare this product, a pharmacist found the package insert on DailyMed on the NIH website, which states that Vigiv is provided in a 20-mL single-dose vial containing antibodies to vaccinia virus at greater than or equal to 50,000 units per vial. The package insert states to remove the entire contents of the vial to obtain the labeled dosage of Vigiv. Practitioners might assume the vial contains a total volume of 20 mL equaling 50,000 units, but 20 mL is the size of the glass vial. The actual volume in each vial is variable.

The pharmacist consulted with CDC and was instructed to withdraw the total volume in the vial, then divide 50,000 units by the volume to determine the final concentration. The total volume was determined to be 11.5 mL and resulted in a concentration of 4,348 units/mL. Therefore, the patient-specific dose (20,940 units) was calculated to be 4.82 mL. If the CDC specialist had not been available, the pharmacist might have incorrectly determined the concentration to be 50,000 units/20 mL (2,500 units/mL), which would have resulted in a final dose of 36,436 units/8.38 mL, almost double the intended dose.

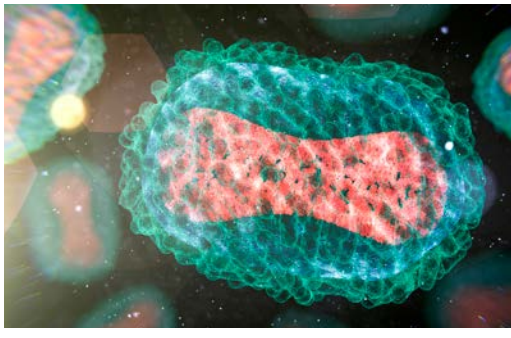
Before the pharmacist could verify the order in the electronic health record and generate a patient-specific label, which requires the volume and concentration, the technician had to first draw up the volume of the vial to determine the concentration. This is another opportunity for error because the technician will not have a printed label for the syringe.

ISMP has confirmed this unusual situation with CDC. The vials are filled from pooled plasma with a minimum of 50,000 units per vial, thus the volume and concentration per vial vary. When this medication is requested and approved to treat mpox, CDC emails an investigational new drug (IND) protocol to the prescriber in advance, and this should be distributed to pharmacy staff for reference in dose preparation and titration instructions.



The vaccinia immune globulin intravenous (human) CNJ-016 vial label displays greater than or equal to 50,000 units per vial, without a corresponding volume or concentration.

The vials are filled from pooled plasma with a minimum of 50,000 units per vial, thus the volume and concentration per vial vary.



In addition to the container label issue, the "administration" section of the package insert states that Vigiv should be given intravenously at an infusion rate no greater than 2 mL/minute. For patients weighing less than 50 kg, it should be administered at a rate no greater than 0.04 mL/kg/minute (133.3 units per kg/minute). However, when the pharmacist consulted with CDC, they learned about the IND protocol which indicated that for certain patients, Vigiv administration should be initiated at an infusion rate of 0.01–0.02 mL/kg/minute for the first 30 minutes and then it can be increased by 0.01–0.02 mL/kg/minute from the initial infusion rate for the next 30 minutes. After that time, the remaining infusion may be administered at a rate of 2 mL/minute.

If a patient requires the use of Vigiv, obtain the current IND protocol from the prescriber or CDC, consider creating a worksheet to calculate the concentration in the vial in hand, and include a label to use when drawing up the vial contents. Include complete titration instructions for the nurse so that Vigiv is administered at the correct rate. ■

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Empirical antimicrobial therapy for BSIs may decrease in-hospital mortality

Bloodstream infections (BSIs) can result in short-term mortality rates of 10% to 30%, making early antimicrobial treatment critical for patients with BSIs. However, the time needed to identify the cause of the infection as well as increasing antimicrobial resistance can make determining an appropriate antibiotic difficult.

According to the authors of a recent paper in *JAMA Network Open,* a delicate balance exists between overuse of broad-spectrum antibiotics and undertreatment of infections. The authors of the study, published online on January 4, 2023, investigated whether the use of initial empirical antimicrobial therapy resulted in lower in-hospital mortality in patients with BSIs.

The retrospective cross-sectional study used data from the Premier Healthcare database from 2016 to 2020 and included more than 32,000 adult patients from 183 U.S. hospitals who received at least one new systemic antimicrobial agent within 2 days after blood samples were collected during hospitalization. Patients with polymicrobial infections were excluded from the analysis. Appropriate empirical therapy was defined as initiation of at least one new empirical antimicrobial agent to which the pathogen isolated from blood culture was susceptible either on the day of or the day after the blood sample was collected.

Multilevel logistic regression models were used to estimate the association between receipt of appropriate initial empirical antimicrobial therapy and in-hospital mortality for patients infected with gram-negative rods, gram-positive cocci, and *Candida* species.

The findings indicated that the crude proportions of appropriate empirical therapy use were 94.4% for gram-negative rods, 97.0% for gram-positive cocci, and 65.1% for *Candida* species, with lower proportions for resistant pathogens, and resulted in lower in-hospital mortality for patients infected with these three pathogen groups.

The researchers concluded that it is important for clinicians to carefully choose empirical antimicrobial agents to improve outcomes in patients with BSIs. ■

Shorter treatment for rifampin-resistant tuberculosis shows promise

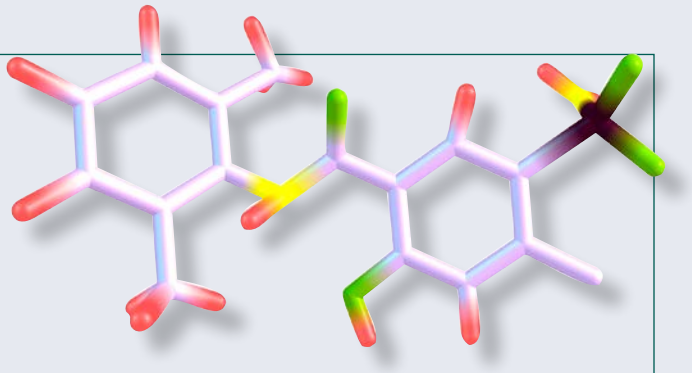
Current guidelines for treatment of rifampin-resistant tuberculosis (TB) involves up to 20 tablets per day for 9 to 20 months; unfavorable outcomes are common, making effective, shorter treatment options critical to controlling TB. A paper in the December 22, 2022, issue of *NEJM* described the TB-PRACTECAL Study, which evaluated the efficacy and safety of three 24-week, all-oral regimens for the treatment of rifampin-resistant TB.

The researchers conducted an open-label, phase 2–3, multicenter, randomized, controlled, noninferiority trial involving patients in Belarus, South Africa, and Uzbekistan who were 15 years or older and had rifampin-resistant pulmonary TB.

In stage 2 of the trial, a 24-week regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) was compared with a 9- to 20-month standard-care regimen. The primary outcome was an unfavorable status (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of TB) at 72 weeks after randomization.

Among patients who had received at least one dose of trial medication and were diagnosed with microbiologically proven rifampin-resistant TB, 11% had an unfavorable outcome, compared with 48% of patients in the standard treatment group.

In addition, the incidence of serious adverse events was lower in the BPaLM group than in the standard-care group (19% vs. 59%). The authors concluded that the 24-week, all-oral regimen was noninferior to and had a better safety profile than the accepted standard-care treatment. ■



Preventing cardiovascular events in patients with hypertension

Thiazide diuretics are a common first-line treatment for hypertension. Although guidelines have preferentially recommended chlorthalidone, hydrochlorothiazide is also widely used.

A recent study by researchers at several VA hospitals, published in *NEJM* on December 29, 2022, sought to determine if chlorthalidone is superior to hydrochlorothiazide for preventing major adverse cardiovascular events in patients with hypertension.

The researchers randomly assigned more than 13,500 patients in the Department of Veterans Affairs health system who were 65 years or older and had been receiving hydrochlorothiazide at a daily dose of 25 mg or 50 mg to continue therapy with hydrochlorothiazide or to switch to chlorthalidone at a daily dose of 12.5 mg or 25 mg. The primary outcome was a composite of nonfatal myocardial infarction, stroke, heart failure resulting in hospitalization, urgent coronary revascularization for unstable angina, and noncancer-related death.

At baseline, the mean baseline systolic blood pressure in each group was 139 mm Hg. At a median follow-up of 2.4 years, there was little difference in the occurrence of primary-outcome events between the chlorthalidone group (10.4%) and the hydrochlorothiazide group (10.0%). There were no between-group differences in the occurrence of any of the components of the primary outcome, though the incidence of hypokalemia was higher in the chlorthalidone group than in the hydrochlorothiazide group (6.0% vs. 4.4%).

The authors concluded that at doses commonly used in practice, patients who received chlorthalidone did not have a lower occurrence of major cardiovascular outcome events or noncancer-related deaths than patients who received hydrochlorothiazide. ■

VTE chemoprophylaxis may not improve outcomes

Current recommendations for prevention of VTE in surgical patients include prophylactic medications based on an evaluation of preoperative risk. But a recent retrospective cohort study, published in the December 2022 issue of *Annals of Surgery* indicated that while postoperative thromboprophylaxis was broadly applied, it was associated with no decrease in VTE.

Researchers at the University of Michigan hypothesized that a high rate of prescription of VTE chemoprophylaxis would be associated with decreased VTE incidence and mortality. Their study analyzed VTE incidence, morbidity, and mortality among postsurgical patients with and without VTE chemoprophylaxis between April 2013 and September 2017 from 63 hospitals within the Michigan Surgical Quality Collaborative. Most practitioners reported performing formal VTE risk assessment.

Among 32,856 operations, there were 480 (1.46%) cases of postoperative VTE and an overall mortality of 609 (1.85%) patients. Using a propensity matched cohort, the authors found that rates of VTE were similar in those receiving unfractionated heparin or low molecular weight heparin compared to those not receiving chemoprophylaxis.

Surprisingly, even the highest risk patients did not have an associated lower VTE rate. In addition, postoperative transfusion (8.28% vs. 7.50%) and mortality (2.00% vs. 1.62%) rates were similar among those receiving and those not receiving chemoprophylaxis.

The authors concluded that despite wide adoption of VTE risk assessment, VTE remains a significant occurrence and that prophylactic medications don't appear to improve outcomes. ■

Health care–associated infections persisted in 2021

Olivia C. Welter, PharmD

Released in late 2022, CDC's most recent National and State Healthcare-Associated Infections (HAI) Progress Report examined the prevalence of 6 common infections across 3 health care settings: acute care hospitals (ACHs), inpatient rehabilitation facilities, and long-term acute care hospitals. However, the main takeaways from the report are focused on ACHs.

The 6 common infections include central-line associated bloodstream infections (CLABIs), ventilator-associated events (VAEs), methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, catheter-associated urinary tract infections (CAUTIs), *Clostridioides difficile infections*, and surgical site infections (SSIs). CDC's HAI Progress Report, released annually, compiles institutional data reported to the National Healthcare Safety Network (NHSN). This report intends to inform health care professionals of trends in HAIs and examines potential contributing factors to changes in the data trends.

The numbers outlined in the NHSN report are for 2021 and are compared to findings from 2020. Due to delays in reporting, data shown in this iteration of the report were collected through June 2022.

Impact of COVID-19

The COVID-19 pandemic affected all aspects of health care, including factors associated with HAIs. At the beginning of the pandemic, most facilities opted to delay elective surgical procedures and non-urgent operations were put on hold indefinitely for many patients. Patients may also have refrained from going to hospitals or other types of facilities during the COVID-19 pandemic if they didn't feel the visit was necessary. Because of this, there may have been fewer surgical procedures to report on as compared to before patients and institutions adhered to these precautions.

Data collected by NHSN and reported out by CDC showed that 4 of the 6 common infections were more prevalent among ACHs nationwide in 2021 as compared to 2020.

However, patients with severe COVID-19 infection overwhelmed health systems and kept beds full. In addition, the health care system suffered extreme staffing and supply shortages, some of which are not fully resolved.

NHSN had also implemented a reporting exemption in 2020, meaning not all institutions were submitting data for analysis. The exemption ended mid-2020.

Increased prevalence of infection

Data collected by NHSN and reported out by CDC showed that 4 of the 6 common infections were more prevalent among ACHs nationwide in 2021 as compared to 2020.

CLABSIs increased 7%, and the difference from 2020 was greater among intensive care units (ICUs), which experienced an overall increase of 10% in CLABSIs.

VAEs increased by 12% across ICUs, but by 16% in non-ICU areas of ACHs.

CDC reported that CAUTIs increased by 5% at ACHs, but ICUs were affected more overall with a 9% increase in infection prevalence.

MRSA bacteremia increased by 14% overall with no distinctions made between which areas of care saw the greatest rate of increase.

Health care providers should note that, although there were increases from 2020 in prevalence of these various infections, they are far lower increases than what was reported from 2019 to 2020. For example, CLABIs had increased 47% in 2020, but only 7% in 2021.

Decreased prevalence of infection

C. diff. infections saw a significant decrease in prevalence in ACHs, with 3% less infections being reported. ACHs had only 1 of the 6 infection categories reported as being lower in 2021 than in 2020. This is a continued trend—*C. diff.* was also a category which saw a decrease in 2020 compared to 2019 data.

No significant change in prevalence of infection

NHSN tracks 10 select procedures performed in ACHs—part of the Surgical Care Improvement Project—for SSI data. Data analysis for SSI revealed that there was not a significant increase or decrease in infections associated with surgery. However, the report specifies that there was an 11% increase in infection from abdominal hysterectomies between 2020 and 2021, and there was not a significant change in infection prevalence associated with colon surgery from the same timeframe. ■

Race and BSA may be arbitrary consideration in renal prediction

Corey Diamond, PharmD

A study published in *Pharmacotherapy* on November 19, 2022, challenges the long-held notion that renal function should be adjusted based on race.

After running a pharmacokinetic population analysis on a large group of patients, researchers found "race" (more specifically, those self-identified as African American) was an insignificant covariate in determining the clearance of both gentamicin and tobramycin.

Additionally, a secondary finding by Pai and colleagues suggests that indexation of renal clearance estimates to a body surface area (BSA) of 1.73 m^2—such as is often done in estimated glomerular filtration rate (eGFR) calculations—may make eGFR equations less accurate.

Pharmacokinetic analysis design

Manjunath and colleagues conducted a retrospective cohort analysis using pharmacokinetic data from DATADIRECT, a clinical database maintained by the University of Michigan. Their analysis included data from over 2,900 adult patients from 2009 to 2022 who received gentamicin or tobramycin.

The authors derived a highly accurate base pharmacokinetic model for aminoglycoside clearance using their patient data. They then attempted to fit that model to several different renal function clearance equations—including the Cockcroft-Gault equation (eCLcr), the 2009 CKD-EPI eGFRcr equation, and the 2021 CKD-EPI eGFRcr equation—in order to determine how well these equations correlated with the aminoglycoside clearances of the patients in the study. Additionally, as a secondary investigation, the authors modified the 2009 and 2021 CKD-EPI renal function estimate equations to include or exclude BSA—indexing to 1.73 m^2—to see if it strengthened or weakened correlation with their model.

Ultimately, the authors attempted to fit 5 different equations to their base model: the Cockcroft-Gault equation, the 2009 CKD-EPI equation with BSA, the 2009 CKD-EPI equation without BSA, the 2021 CKD-EPI equation with BSA, and the 2021 CKD-EPI equation without BSA. The Akaike information criterion—a mathematical method for evaluating how well a model fits the data—was used to measure which renal function equation fit the aminoglycoside clearance model the best.

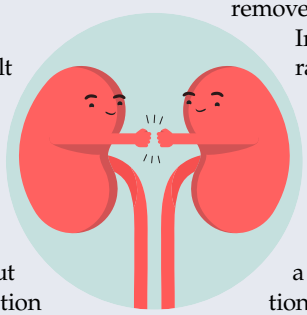
Overall, the analyses demonstrated that renal clearance equations that included race as a covariate (such as the 2009 CKD-EPI equation) fit almost identically to the pharmacokinetic population model compared to renal clearance equations that did not incorporate race (Cockcroft-Gault and the 2021 CKD-EPI equation).

Additionally, the modified CKD-EPI eGFR equations, that deindexed BSA, fit the aminoglycoside clearance model more strongly than the equations that used BSA as a covariate.

Why the change?

Adjusting eGFR based on certain racial ancestry has been, until recently, a standard of practice in the United States. This was, in part, due to previous studies showing an increased average serum creatinine value of 10% to 20% in self-identified African Americans patients compared with American Caucasian patients. Thus, the 2009 CKD-EPI eGFR equation included a 1.159 correction factor to prevent underestimating eGFR in the African American population.

However, the 2009 CKD-EPI eGFR equation has received increasing scrutiny over the past decade due to concern over race being a social construct rather than a biological one. Ultimately, unease in the medical field over ignoring diversity and contributing to systemic racism culminated in 2020, resulting in the American Society of Nephrology and the National Kidney Foundation helping to publish a new CKD-EPI eGFR equation in 2021 that removed race as a covariate.



In addition to the use of race, another issue with CKD-EPI eGFR is its indexing of BSA to 1.73 m^2. Historically, 1.73 m^2 was considered normal BSA for humans and has been used to index a variety of medical equations as a means of normalizing several physiological variables. However, this too, has recently been scrutinized. Due to the obesity epidemic, normal BSA in Americans is currently about 2 m^2 and the arbitrary role of BSA in eGFR calculations may be contributing to unnecessary errors in renal predictions.

"Our study does not support race as a relevant covariate either alone or in equations that estimate GFR for determining aminoglycoside CL."

Results and rationale

"Our study does not support race as a relevant covariate either alone or in equations that estimate GFR for determining aminoglycoside CL," concluded the authors in their article. They wrote that the 2021 CKD-EPI eGFR equation offers similar precision to the 2009 CKD-EPI eGFR equation for the estimation of gentamicin and tobramycin clearance.

"The 2021 CKD-EPI eGFR equation without race and BSA indexation should be evaluated as a potential standard model for drug dosing across kidney function in drug development," wrote the study authors. ■

Editor's note: This article is part of *Pharmacy Today's* ongoing coverage of structural racism.

ASHP releases drug diversion prevention measures for health systems

Ariel Clark, PharmD

On October 26, 2017, the opioid crisis was officially declared a public health emergency in the United States. Since then, opioid overdoses have failed to decline—CDC's 2020 data on opioid overdoses demonstrated a 31% increase over 2019.

While multifactorial, drug diversion remains a major contributor to the public health crisis, leading to increased misuse, addiction, and death.

In their 2022 update to the Guidelines on Preventing Diversion of Controlled Substances, the American Society of Health-System Pharmacists (ASHP) aimed to close some of the gaps from previous guideline editions and add in recommendations from the ASHP Opioid Task Force. These guidelines give providers recommendations on how to build an effective diversion program, including administrative elements, system-level controls, and individual-level controls.

Investigation and reporting

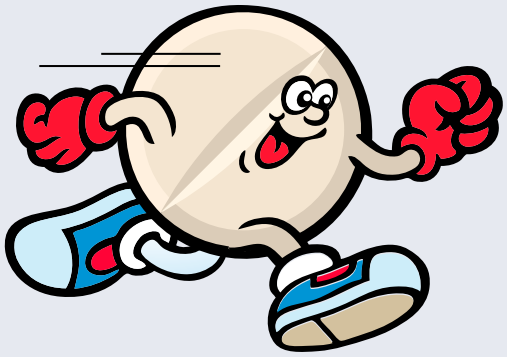
In cases of suspected diversion, ASHP noted that a "detailed and thorough approach" to the investigation is imperative. Health systems should have a predetermined process in place for any "unresolvable discrepancy" that includes coordination within the system, with outside affiliates—in cases where it is necessary—and which results in a root cause analysis by the drug diversion team.

Tracking, storage, security

Within system tracking of controlled substances is a critical protection against diversion, which also aids a health system in identifying when and where a diversion has occurred. ASHP recommends that tracking parameters be maintained throughout the entirety of the "chain-of-custody," between departments and individuals.

Another key element in maintaining autonomy over controlled substances is the mechanism of storage and the security of those storage centers, ASHP said. Limiting access, maintaining an electronic record, and ensuring all contents remain under lock-and-key, unless under "the direct physical control of an authorized individual," will all aid health care practitioners in the prevention of diversion cases.

In cases of suspected diversion, ASHP noted that a "detailed and thorough approach" to the investigation is imperative.



Technology

Automation technology in pharmacy has been increasingly used over the last several decades. Reducing drug diversion using technology can include the use of automated dispensing cabinets, management of inventory, and prepackaging of drugs that are at risk for diversion. ASHP said that automation can also include electronic surveillance and monitoring—both electronic and manual—through audits and reviews to ensure the health system continues to "meet legal, regulatory, and functionality requirements."

Pharmacy procurement and dispensing

Drug diversion within the confines of the pharmacy department can occur, and steps should be taken to mitigate these risks. ASHP suggests a variety of methods to reduce this risk, such as limiting access and rotating the health care workers assigned to handle controlled substances, for example. These key principles outlined by the ASHP guideline can help minimize drug diversion within the pharmacy department.

Prescribing, administrating, and wasting

With a shift in technology, prescribers have the opportunity to "write" orders electronically, lowering the risk of potential diversion through prescription pads, which can more easily be falsified. In the updated diversion guidelines, ASHP recommends using order sets whenever possible, as long as they "are supported by clinical evidence." ASHP also noted that methods to reduce controlled substance diversion "should not delay patient treatment or compromise patient needs," helping to ensure that providers are still fully able to care for patients to the best of their ability.

Drugs that are set to be or are in the process of being wasted are highly susceptible to diversion. ASHP recommends designing systems to attempt to reduce waste whenever possible by using unit-dose packaging and avoiding multidose vials. When waste must occur, practitioners should follow guideline recommendations by incorporating witnessing and extensive documentation procedures as defined by federal and state laws.

As pharmacy professionals play their part in helping to end the opioid epidemic, they must also take an active role in preventing drug diversion in their workplace. Using these updated guidelines can set up health care organizations to build their own procedures, improve awareness, and reduce controlled substance diversion. ■

A minute with ...

Olunife Akinmolayan, APhA–ASP National Member-at-large, and 2023 PharmD candidate, University of Findlay, Findlay, OH

Pharmacy intern, Walgreens, Aurora, IL

Member since 2019

"When I first joined APhA in 2019, I quickly learned that APhA serves as a foundational building block upon which all members of the profession can stand. Through my personal engagement, I have discovered that my APhA membership is an investment both in my future and the future of pharmacy, an investment that afforded me the opportunity to serve the profession on local, national, and international levels. Through my membership, I have been blessed with friends with whom I can share visions and build relationships to make those visions a reality."

How has APhA helped you establish meaningful connections?

Through APhA–ASP, I've been given the opportunity to cultivate relationships across the country and the world. Developing connections such as these has been paramount to increasing my confidence and engagement on important conversations in the practice of pharmacy. APhA provides experiences and environments that bring members together to share ideas and hopes for what the profession can become. Through these experiences, I have created relationships with student pharmacists, pharmacists, and community leaders that will be cherished beyond my pharmaceutical career.

How has APhA helped prepare you for your career as a pharmacist?

Serving in the International Pharmaceutical Students Federation National Project Coordinator role gave me increased courage and confidence, and it affirmed what I can offer to the profession following graduation. It's my belief that the next generation of pharmacists' success lies within our ability to forge connections and utilize resources that have been provided by those who came before us. APhA's granted me the opportunity to advocate on Capitol Hill, promote the growth of our local chapters, and reflect on the patient's experience through pharmacy services. Opportunities such as these are preparing me for success as a future pharmacist.

What excites you about the profession of pharmacy?

As a final-year student pharmacist, my inspiration stems from the ability to both witness and play an active part in the advancement of the profession of pharmacy. What excites me most about our profession is changing perceptions of what pharmacy has to offer. The general public is learning how pharmacists play a pivotal role in the full activation of the health care system. It gives me hope to know that pharmacy services are being expanded to relieve burdens and recuperate cost for the health care system.

Can you share a meaningful story about a time you interacted with a patient? Perhaps a time you felt like you really made a difference for them?

As an intern, I met a young family of 3 who came in to receive immunizations. In the ever-changing pace that is community pharmacy, it's easy to forget that many patients present with hesitation before accepting any type of treatment, especially when it involves children. It's also easy to forget that taking the time to establish a personal connection can go a long way in harboring their trust.

Increasing the representation of minorities in our profession will aid efforts to provide informed quality care in diverse patient populations like that of my Walgreens in Aurora, IL.

By taking the time to share my story as an African American student pharmacist with an African American mother raising 2 children on her own and making medical decisions on their behalf, I saw how I made an impact in helping this patient make an informed decision to vaccinate her 6- and 12-year-old children against COVID-19 and the flu. ■

Get involved

The purpose and mission of the APhA Medication Management Special Interest Group is to create an online community in which pharmacists from different areas of practice have the opportunity to communicate professional interests, concerns, and prospective goals for MTM services. This community will serve as a conduit for APhA to address the needs of practicing pharmacists in order to continuously and actively shape the provision of pharmacist-led MTM services into financially viable models of practice that produce improved patient outcomes.

APhA's new Marketing MTM Services resource helps pharmacists communicate the value of their patient care services to patients, providers, and payers. The comprehensive guide explores the differences between digital and traditional marketing, provides considerations for marketing strategies and messaging, and lists marketing resources and tools. Developing relationships with prescribers can greatly enhance MTM services in community pharmacies—benefiting the pharmacist, prescriber, and the patients they care for. The Medication Management SIG's Toolkit for Marketing MTM to Prescribers includes 10 resources that help to guide pharmacists through the general approach and conversation components that will fuel budding collaborations between pharmacists and prescribers in MTM service delivery.

Visit apha.us/MedManagement to learn more. ■

Preceptor guides

Preceptors take on many roles, that of teacher, coach, practitioner, provider, and faculty member. Just as you may have had great preceptors who made an impact on your personal and professional development, you can make a lasting impact for future pharmacists.

While it may seem intimidating getting ready for a rotation with a learner, with a bit of preparation and organization, you'll be able to ensure a great learning experience for your learner, your pharmacy team, and yourself.

Check out APhA's full guide at apha.us/PreceptorToolkit for tips and ideas for new preceptors and helpful reminders for seasoned preceptors. Much of this material is applicable for different types of learners, including both student pharmacists and pharmacy residents, but focuses on student pharmacist learners.

APhA also offers advanced preceptor training for those seeking the knowledge and confidence of a successful preceptor. If you currently serve as a preceptor, this program will give you access to peer-developed content which will provide you with additional knowledge and tools to enhance the experiential education process for you and your student pharmacists and residents. For new preceptors, the APhA Advanced Preceptor Training available at apha.us/PreceptorTraining will provide you with a strong foundation to get started in your new role. ■

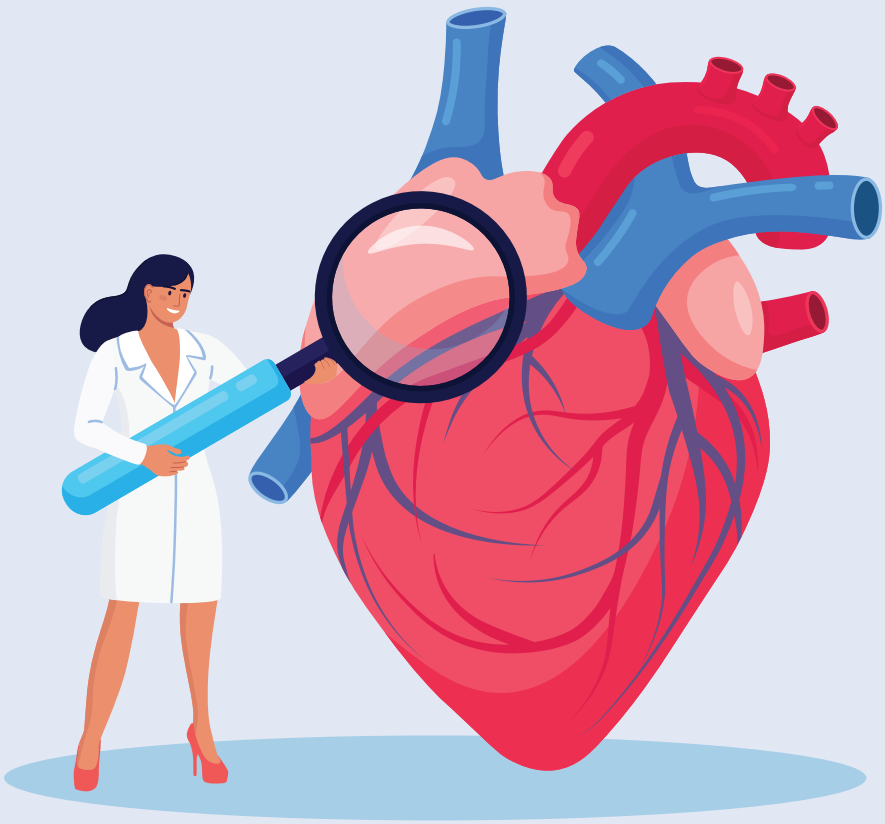
Did you know?

APhA's 2023 Annual Meeting & Exhibition is only a few months away!

We know it's been tough, but we are reaching a pivotal point where we can make real change. As a theme of APhA2023, we will focus on how we'll work to address the challenges that we face. Together, we'll RISE!

Make sure to register for the conference, and we'll see you in **Phoenix March 24–27, 2023!**

APhA2023



Updates in heart failure management

Jason S. Haney, PharmD, BCPS, BCCCP, Associate Professor and Clinical Pharmacy Specialist, Medical University of South Carolina, College of Pharmacy, Charleston, SC.

Approximately 6 million Americans have heart failure (HF), and the prevalence of HF is projected to increase by 46% by 2030 with an estimated 3% of the population affected.[1] The incidence of 5-year mortality in patients with HF is estimated to be 24.4% for patients 60 years old and 54.4% for patients 80 years old.[1] As some of the most accessible and knowledgeable members of the interdisciplinary health team, pharmacists play a key role in the management of patients with HF by helping to ensure optimization of medication regimens to reduce morbidity and mortality by knowing the most recent HF guidelines,[2] including updated classifications and stages of HF, and new guidance for initiating and titrating guideline-directed medical therapy (GDMT) as well as the ways pharmacists can maximize availability of GDMT as part of their practice.

Defining HF

The universal definition of HF was recently updated by an international writing committee to provide a concise but comprehensive, applicable, and standardized definition that includes symptoms or signs as well as objective evidence of volume overload.[3] HF is a clinical syndrome with current or prior symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels or objective evidence of cardiogenic pulmonary or systemic congestion at rest or with exercise (Table 1).[3]

Structural and functional cardiac abnormalities of HF include

- Left ventricular ejection fraction (LVEF) of >50%
- Abnormal cardiac chamber enlargement
- Elevated left ventricular filling pressure demonstrated by an elevated echocardiographic index (E/e' ratio) >15
- Moderate-to-severe ventricular hypertrophy
- Moderate-to-severe valvular obstruction or regurgitation

Thresholds for elevated natriuretic peptide levels supporting the definition of HF vary by clinical severity and can be found in Table 2.[3] Cardiogenic pulmonary or systemic congestion may be evidenced by imaging (e.g., chest radiograph or elevated filling pressures on echocardiography) or hemodynamic measurement (e.g., right heart catheterization, pulmonary artery catheter).

It is important to note that "congestive" is not part of the term "heart failure" to emphasize a patient's signs and symptoms may range from absent to severe once diagnosed. Even if patients are asymptomatic, the diagnosis remains and treatment adherence should be emphasized.

Stages and functional classification of HF

The American College of Cardiology (ACC)/American Heart Association (AHA) describe stages of HF that recognize the development and progression of disease, which ranges from patients with structural and subclinical heart disease who are at risk for developing HF to those with advanced disease (Table 3).[2,3] In the absence of intervention, many at-risk patients will develop structural and/or functional cardiac abnormalities and ultimately become symptomatic. The therapeutic goal is thus to prevent disease progression by modifying risk factors and implementing evidence-based therapies which decrease symptoms, morbidity, and mortality.

Learning objectives

At the conclusion of this knowledge-based activity, pharmacists will be able to

- Compare and contrast the classifications and stages of heart failure
- Discuss recent updates to the American Heart Association/American College of Cardiology/Heart Failure Society of America heart failure guidelines, including initiation and titration of guideline-directed medical therapies (GDMT)
- Describe when and how additional medical therapies beyond the core 4 GDMT should be integrated into the management of heart failure with reduced ejection fraction (HFrEF)
- Explain practical strategies to mitigate potential barriers to GDMT initiation

Preassessment questions

Before participating in this activity, test your knowledge by answering the following questions. These questions will also be part of the CPE assessment.

1. A 78-year-old woman presents with history of heart failure has routine echocardiograms to follow her left ventricular ejection fraction (LVEF). Her 4 most recent echocardiograms were each taken 12 months apart. Her LVEF was reported as 58%, 31%, 33%, and 44% (in chronological order). How should this patient's heart failure be classified?

a. Heart failure with reduced ejection fraction (HFrEF)
b. Heart failure with mildly reduced ejection fraction (HFmrEF)
c. Heart failure with preserved ejection fraction (HFpEF)
d. Heart failure with improved ejection fraction (HFimpEF)

2. A 59-year-old man with heart failure with reduced ejection fraction (HFrEF) has experienced dyspnea on exertion for the past 2 weeks. He gets short of breath walking up 2 flights of stairs while carrying his groceries. He also gets fatigued while doing laundry. In which New York Heart Association functional class is his heart failure classified?

a. I
b. II
c. III
d. IV

3. Which of the following medications has not been shown to improve mortality in a patient with HFrEF?

a. Furosemide
b. Eplerenone
c. Carvedilol
d. Sacubitril-valsartan

The New York Heart Association (NYHA) classification system is used to characterize symptoms and functional capacity of patients with symptomatic (stage C) and advanced (stage D) HF (Table 4).[3] This classification system is a subjective assessment ranging from no limitation of physical activity (class I) to severe limitation and discomfort with any physical activity and having symptoms while at rest (class IV).

A functional assessment should be completed at baseline after the initial diagnosis and at each clinical encounter, as symptoms may fluctuate over time and will impact therapeutic decisions. The goal is for optimally treated patients to become functional class I. Because worsening NYHA functional class is an independent predictor of mortality, GDMT should be optimized for any symptomatic patient with functional class II through IV symptoms.

Classification of HF and trajectories based on LVEF

Departing from the historical dichotomy of systolic and diastolic HF, the guidelines categorize patients into groups across the spectrum of LVEF.[2,3] This method was chosen due to differences in prognosis and treatment response as well as practicality, since LVEF is an inclusion criterion in most clinical trials. The guidelines include 4 main classifications, as seen in Table 5.[2,3] Other cardiac structural and functional information such as chamber volumes are complementary to help guide therapeutic management.

Understanding the differences in these classifications is important as treatment differs between groups. Heart failure with mildly reduced ejection fraction (HFmrEF) and HF with improved ejection fraction (HFimpEF) are newly coined and clinically meaningful classifications. In previous guidelines, these groups were categorized as subsets of HF with preserved ejection fraction (HFpEF).[4]

Patients in the mildly reduced range (LVEF 41–49%) are often in a dynamic trajectory of improvement or deterioration. As with other patients, longitudinal surveillance is indicated as a significant decrease in LVEF indicates a poor prognosis and should trigger intensification of therapy. Likewise, treatment for patients with improvement from a previously reduced LVEF is distinct from those presenting with an LVEF in the preserved range.

Although LVEF may be improved, structural and functional abnormalities mostly persist, and discontinuation of GDMT in these patients leads to poor outcomes. The HFimpEF classification is a reminder to celebrate success with our patients but to also avoid terminology such as "stable" or "recovered," as these terms lead to therapeutic inertia.

Focus on prevention for stages A and B

Primary prevention for patients at risk for HF (stage A) focuses on lifestyle modifications and management of underlying disease states that lead to cardiac structural changes and higher risk of HF.[2]

Increasing physical activity and cardiorespiratory fitness is associated with decreased incidence of HF.[5] Typical goals for aerobic exercise include at least 150 minutes per week of moderate-intensity physical activities, such as brisk walking or raking the yard, or other activities that require 50–60% of

Table 1. Symptoms and signs of HF

Symptoms		Signs	
Typical	**Less typical**	**More specific**	**Less specific**
Breathlessness	Noctural cough	Elevated jugular venous pressure	Peripheral edema (ankle, sacral, scrotal)
Orthopnea	Wheezing	Third heart sound (S3)	Pulmonary rales
Paroxysmal nocturnal dyspnea	Abdominal bloating	Third and fourth heart sound (S3 and S4) gallop	Unintentional weight gain (>5 lb/week)
Reduced exercise tolerance	Postprandial satiety	Cardiomegaly	Weight loss with muscle wasting and cachexia
Fatigue	Loss of appetite	Hepatojugular reflux	Cardiac murmur
Swelling of ankles or other body parts	Decreased cognition or confusion	Cheyne-Stokes respirtation	Tachycardia
Bendopnea	Depression	—	Tachypnea
—	Dizziness or syncope	—	Hepatomegaly or ascites
—	—	—	Cold extremites
—	—	—	Oliguria
—	—	—	Narrow pulse pressure

Source: Adapted from Reference 1.

Table 2. Natriuretic peptide levels supporting definition of HF

Peptide	Ambulatory	Hospitalized/decompensated
BNP	≥35 pg/mL	≥100 pg/mL
NT-proBNP	≥125 pg/mL	≥300 pg/mL

Abbreviations used: BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

a person's maximal capacity.[6,7] Alternatively, a goal of 75 minutes of vigorous physical activity such as running or jogging may be used by patients who are able to sustain higher-intensity exercise.[5] Resistance or muscle-strengthening activities that involve all major muscle groups are also recommended 2 or more days per week.[6] If chronic conditions or disabilities prevent achieving these goals, then regular physical activities that are within the patient's abilities should be encouraged. Exercise training can be continued even for patients with HF, as it improves functional capacity in HFpEF and HFrEF and increases survival in HFrEF.[5]

Maintaining a normal weight, eating healthily, and avoiding smoking all help lower the lifetime risk of developing HF.[2] Dietary patterns such as plant-based, Mediterranean, or Dietary Approaches to Stop Hypertension (DASH) diets—all of which increase fruit, nut, vegetable, legume, and lean protein consumption—should be encouraged.[7] Patients with atherosclerotic cardiovascular disease (ASCVD) and/or hypertension should be managed in accordance with guideline recommendations.[2,7] Blood pressure (BP) should be lowered to less than 130/80 mm Hg in patients with an ASCVD risk of 10% or higher.[7]

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are the only mentioned class of medications within the guideline recommendations for patients at risk for HF (i.e., stage A). This class of oral antidiabetic medications inhibits glucose reabsorption and increases glucose excretion in the kidney, modestly lowering plasma glucose levels, but they are no longer viewed as simply diabetes medications. Several CV outcomes trials compared various SGLT-2 inhibitors to placebo in patients with type 2 diabetes mellitus (T2DM). Although other outcomes varied between trials, a consistently significant benefit of decreased HF hospitalization was seen for these agents in patients with and without HF and appeared independent of the glucose-lowering effects.[8–10] These findings led to the recommendation that SGLT-2 inhibitors should be used for patients with T2DM and either established ASCVD or high CV risk to prevent hospitalizations for HF.[2]

Screening tools and coordinated multidisciplinary care can help identify and manage patients at higher risk of HF. Natriuretic peptide biomarker–based screening along with team-based care may be useful to prevent the development of left ventricular (LV) dysfunction or new-onset HF in patients with hypertension, diabetes, or vascular diseases.[2] Multidisciplinary care is recommended for patients with exposure to or being considered for cardiotoxic agents such as anthracycline-based chemotherapy.[2]

Table 3. Stages of HF

Stages	Definition and criteria
A: At risk for HF	At risk for HF but without current or prior symptoms or signs of HF, structural heart disease, or elevated cardiac biomarkers of stretch or injury. Patients with hypertension, atherosclerotic cardiovascular disease, diabetes, obesity, exposure to cardiac toxins, or genetic cardiomyopathy are in this category.
B: Pre-HF	No current or prior symptoms or signs of HF and evidence of one of the following: • Structural heart disease (reduced left or right ventricular systolic function, cardiac chamber enlargement, ventricular hypertrophy, wall motion abnormalities, or valvular heart disease) • Evidence for increased filling pressures (by invasive [right heart catheterization] or noninvasive [echocardiography] hemodynamic measurements) • Elevated natriuretic peptide levels (Table 2) or persistently elevated cardiac troponin (greater than 99th percentile), especially in the setting of exposure to cardiotoxins and in the absence of competing diagnoses resulting in such biomarker elevations (e.g., acute coronary syndrome, chronic kidney disease, pulmonary embolus)
C: Symptomatic HF	Structural and/or functional cardiac abnormalities with current or prior symptoms of HF
D: Advanced HF	Severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite guideline-directed medical therapy (GDMT), refractory or intolerant to GDMT, or requiring advanced therapies (e.g., consideration for transplantation, mechanical circulatory support, or palliative care)

Abbreviations used: HF, heart failure.

Table 4. New York Heart Association funcitonal classification

Functional class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause symptoms.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity causes symptoms.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms.
IV	Severe limitation and discomfort with any physical activity. Symptoms occur even at rest.

Source: Adapted from Reference 3.

In the general population, incorporating multivariable risk scoring into clinical practice using tools such as Pooled Cohort Equations to Prevent HF (PCP-HF) or Framingham HF Risk Score can lead to improved patient outcomes.[2]

Genetic screening and consultation with a trained counselor are recommended by the HF guidelines for individuals whose first-degree relatives have genetic or inherited cardiomyopathies.[2] Screening these at-risk individuals affords earlier detection of cardiac disease and initiation of treatments to decrease progression to HF or sudden death. Similarly, genetic counseling and testing are reasonable for patients with pre-HF (stage B) who are diagnosed with nonischemic cardiomyopathies to help guide care for those patients and immediate family members.[2]

Other recommendations for stage B pre-HF include specific therapies to prevent or delay the transition to symptomatic HF in patients with reduced LVEF. ACE inhibitors and evidence-based beta blockers (BBs) with mortality benefit in HF should be used in patients with LVEF of ≤40%.[2] Several randomized controlled trials in patients with asymptomatic LV systolic dysfunction, including patients after acute myocardial infarction (MI) as well as those without ischemic heart disease, have shown that ACE inhibitors reduce HF hospitalizations and mortality.[11–16] Although data are limited on the use of BBs in asymptomatic patients with reduced LVEF without a history of MI, BBs are recommended for all patients with a LVEF of ≤40% to prevent symptomatic HF and reduce the risk of death.[2,17–21]

Unlike ACE inhibitors, the benefits of BBs are not class-wide. Bisoprolol, metoprolol succinate, and carvedilol are the only BBs with evidence of reduced mortality in patients with HFrEF.[22–24] Generally, the choice of BB is driven by the receptor selectivity since this leads to the major differences in adverse effects. Bisoprolol and metoprolol succinate are cardioselective, meaning they selectively inhibit beta-1 adrenoreceptors.[25] However, bisoprolol has greater selectivity and is the safest option for patients with restrictive airway disease. Metoprolol loses selectivity as doses escalate above 100 mg/day.[26] Therefore, patients may develop more bronchopulmonary symptoms as doses approach target. Carvedilol nonselectively binds to beta-1 and beta-2 receptors, making it the least desirable option for patients with pulmonary symptoms.[25]

Table 5. Classification of HF by LVEF

Classification	Criteria
HF with reduced EF (HFrEF)	LVEF ≤40%
HF with improved EF (HFimpEF)	Previous LVEF ≤40% and a follow-up measurement >40% with a ≥10% increase
HF with mildly reduced EF (HFmrEF)	LVEF 41–49% with evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HF with preserved EF (HFpEF)	LVEF ≥50% with evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

Abbreviations used: EF, ejection fraction; HF, heart failure; LV left ventricular; LVEF, left ventricular ejection fraction.

Additionally, carvedilol blocks alpha-adrenergic receptors which may lead to more hypotension and/or added benefit in patients with hypertension.[25]

In patients with a history of MI or acute coronary syndrome, high-intensity hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) are recommended by multiple guidelines due to reduced rates of recurrent MI, mortality, need for myocardial revascularization, and stroke.[27–29] Statins are also recommended by the HF guidelines in these patients due to additional benefits of preventing symptomatic HF and adverse CV events.[2] The guidelines also recommend angiotensin receptor blockers (ARBs) be used to prevent symptomatic HF and reduce mortality in patients with LVEF of ≤40% and history of MI who are intolerant to ACE inhibitors.[2] This recommendation is based on 2 trials that showed comparable benefits for ARBs versus ACE inhibitors in this population.[30,31] Although there are no data evaluating the effects of ARBs versus ACE inhibitors in asymptomatic patients with LV dysfunction without a previous MI, it is reasonable to use ARB in this patient population if ACE inhibitors are not tolerated.[2]

Diuretics to relieve volume overload

Patients who develop symptoms of congestion or fluid retention should receive diuretics, regardless of their HF classification.[2] The goal of diuretic treatment is to achieve euvolemia using the lowest possible dose. Initially, diuretics may be given as needed or for short courses. However, most patients require maintenance doses to maintain euvolemia and clinical stability.

Diuretics are a cornerstone of HF treatment that improve patient symptoms, functional capacity, and quality of life, but they do not alter disease progression or prolong survival for any HF classifications. Consequently, diuretics should always be used as adjunctive therapy to GDMT that reduces hospitalizations and mortality.

Although chlorthalidone or hydrochlorothiazide may be appropriate for patients with relatively normal kidney function (estimated glomerular filtration rate [eGFR] >50 mL/min/1.73 m^2), hypertension, and mild congestion, loop diuretics are preferred for most patients due to their greater diuretic efficacy. Furosemide, bumetanide, and torsemide are most frequently utilized and are equally effective if given in equipotent doses. Table 6 reviews some common pharmacologic characteristics of these agents.[2,32] Notably, the bioavailability of furosemide is highly variable (average 50%) which impacts dose conversion and potentially therapeutic efficacy.[32] Furosemide's bioavailability is impacted by its absorption from the GI tract, which is slower than its elimination half-life.[32]

Additionally, food intake, abdominal edema, and poor gastric perfusion can further decrease absorption.[32] Switching to another loop diuretic may be beneficial in patients with an unpredictable or poor response to furosemide.

Diuretics elicit a response once concentrations exceed the diuretic threshold after which the dose-response curve steeply increases and rapidly plateaus beyond a ceiling dose.[32] A measurable increase in urine output should be expected within 2 hours of giving a loop diuretic. Subsequent doses should be doubled until a response is noted or the maximum dose is reached. Twice daily doses are commonly needed for furosemide and bumetanide due to their shorter duration of action, whereas torsemide is typically dosed once daily.

Optimization of GDMT may allow and necessitate a diuretic dose reduction to avoid hypotension and volume depletion.[32] Conversely, diuretic response may wane over time due to numerous prerenal and intrarenal mechanisms of diuretic resistance.[32] In the outpatient setting, increasing the dose or switching loop diuretics are common strategies to overcome resistance. Sequential nephron blockade with combination thiazide (or thiazide-like) and loop diuretics may also be used, particularly for patients with refractory edema and resistance to loop monotherapy.[32] Metolazone is usually given as a one-time dose of 2.5 mg or 5 mg, optimally at least 30 minutes before the first daily dose of loop diuretic.[2,32] Some patients may require thrice-weekly dosing or greater of metolazone, but the risk of severe electrolyte abnormalities (e.g., hypokalemia, hyponatremia), over-diuresis, and worsening kidney function is high with this approach.[2,32]

Optimize the Core 4 for stage C HFrEF

In addition to diuretics and treatment recommendations for stages A and B, the latest guidelines recommend quadruple therapy for patients with HFrEF who have developed symptoms of HF.

These 4 foundational pillars of GDMT have distinct pathophysiological mechanisms that help mitigate HF progression, improve symptoms and functionality, and reduce mortality.[33] Benefits may be achieved as early as

Table 6. Oral diuretics for chronic heart failure

Characteristic	Bumetanide	Furosemide	Torsemide
Usual initial outpatient dose	0.5–1 mg daily or twice daily	20–40 mg daily or twice daily	5–10 mg daily
Usual maintenance outpatient oral dose	1–5 mg	40–240 mg	10–20 mg
Maximum total daily dose	10 mg	600 mg	200 mg
Duration of action	4–6 hours	6–8 hours	12–16 hours
Affected by food	Yes	Yes	No
Bioavailability	80–100%	10–100% (average 50%)	80–100%
Relative oral potency	1 mg	80 mg	20 mg

2–3 weeks with many of these therapies.[33]

If possible, all 4 may be started simultaneously at initial low doses. Table 7 provides dosing information for commonly prescribed GDMT for HFrEF.

If necessary, quadruple therapy may be started sequentially in a personalized sequence based on patient phenotype and etiology, not by the order in which they were studied. It is important to note, though, that all 4 therapies should be started as soon as possible since the incremental progressive benefits of quadruple therapy are greater than what can be achieved by up-titrating existing therapy.

Renin-angiotensin system inhibitors

The first pillar of quadruple therapy is an angiotensin receptor-neprilysin inhibitor (ARNi), ACE inhibitor, or ARB. Angiotensin receptor-neprilysin inhibitors are the newest class of inhibitors of the renin-angiotensin system with a unique mechanism of action. This class of medications inhibits angiotensin II from binding to angiotensin receptors as well as blocking neprilysin from breaking down endogenous vasoactive peptides such as natriuretic peptides, bradykinin, and adrenomedullin. When neprilysin is inhibited, increased concentrations of these substances offset the neurohormonal activation that leads to vasoconstriction, sodium retention, and cardiac remodeling. Sacubitril-valsartan is currently the only available ARNi.

In the PARADIGM-HF (Prospective Comparison of ARNi with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in HF) randomized controlled trial, sacubitril-valsartan significantly reduced the composite endpoint of HF hospitalization or CV death by 20% versus enalapril in symptomatic patients with HFrEF tolerating an adequate dose of either ACE inhibitor or ARB over a mean follow up of 27 months.[34]

PARADIGM-HF was terminated early due to an interim analysis suggesting superiority of sacubitril-valsartan. Although early termination can overestimate treatment effects, overestimation of the benefits in PARADIGM-HF is likely small due to the large sample size and number of outcomes events. An absolute 4.7% reduction in the primary outcome was seen with sacubitril-valsartan (21.8% vs. 26.5%), equating to a number needed to treat (NNT) of 21 patients over 27 months to prevent one composite endpoint.[34] This benefit was consistent across prespecified subgroups. The findings of improved morbidity and mortality compared to the standard of care for afterload reduction were compelling results for sacubitril-valsartan in the treatment of HFrEF.

Because of the higher risk of hypotension and angioedema with ARNis, PARADIGM-HF was designed with a run-in period of ACE inhibitor or ARB therapy to ensure patient tolerance prior to starting sacubitril-valsartan. More recent trials have included patients with de novo HF as well as patients who are naïve to ACE inhibitor and ARB therapy.[35–38] The outcomes of these trials suggest similar efficacy and safety outcomes for sacubitril-valsartan in HFrEF, even though data are limited by sample size and surrogate markers of efficacy such as reduced natriuretic peptide levels.

The most recent guidelines recommend ARNis over ACE inhibitors or ARBs to reduce morbidity and mortality in patients with HFrEF and NYHA class II to III symptoms, including patients with de novo HF or who are treatment naïve.[2] It is also recommended to transition patients to an ARNi if they have chronic symptomatic HFrEF and NYHA class II or III symptoms while receiving an ACE inhibitor or ARB.[2] A minimum of 36-hour washout period is necessary when switching from an ACE inhibitor to an ARNi or vice versa to minimize the risk of angioedema.[2]

Sacubitril-valsartan should be initiated at the lowest dose (24–26 mg twice daily) in most patients (Table 7). Patients should only be started on the 49–51 mg dose if they were already tolerating high-dose ACE inhibitors or ARBs (equivalent of >10 mg enalapril or 160 mg valsartan total daily dose) or if they are markedly hypertensive. Even if the patient is tolerating high-dose ACE inhibitors or ARBs, low-dose sacubitril-valsartan should be chosen in patients with severe kidney impairment (eGFR <30 mL/min/1.73 m^2), with moderate hepatic impairment (i.e., Child Pugh class B), age ≥75 years, or with a systolic BP (SBP) of <110 mm Hg.

Decreasing the maintenance loop diuretic dose should be considered if the patient is euvolemic when starting sacubitril-valsartan to mitigate the risk of hypotension or volume depletion.

Up-titration of sacubitril-valsartan doses are generally done at 2-week intervals or longer.

Several scenarios exist in which an ACE inhibitor or ARB is preferred. Because patients with severe symptoms were not well-represented in the PARADIGM-HF trial (60 of 8,399 patients), ACE inhibitors or ARBs are recommended in patients with NYHA class IV symptoms.[2] Patients who cannot tolerate an ARNi should receive an ACE inhibitor unless the intolerance is due to angioedema.[2] ARBs are recommended by the HF guidelines for patients with an intolerable cough due to ACE inhibitors or as an alternative to ACE inhibitors and ARNis in patients with a history of angioedema.[2] Anecdotally, more clinicians are choosing an ARB when an ARNi is unable to be initiated (e.g., due to marginal BP or financial constraints) because of the eventual easier transition without a necessary washout period.

SGLT-2 inhibitors

The latest addition and the second pillar of HF GDMT are the SGLT-2 inhibitors. Unlike recommendations for earlier stages, SGLT-2 inhibitors are recommended for patients with or without T2DM who have symptomatic chronic HFrEF to reduce HF hospitalization and CV mortality.[2] Numerous mechanisms which lead to these benefits—including preload and afterload reduction, improved cardiac energy metabolism, reduced inflammation and oxidative stress, improved kidney function, and reduced stress on the kidney—are still being elucidated.[39]

The Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) trial evaluated the efficacy and safety of dapagliflozin in patients with HFrEF, regardless of the presence of T2DM.[40] In 4,744 randomized patients, dapagliflozin reduced the combined outcome of CV mortality, HF hospitalization, or urgent HF visit by 26% when compared with placebo over a mean follow up of 18 months.[40] A subgroup analysis indicated the benefit was seen independent of glycemic status. Significant benefits were also demonstrated for prespecified secondary endpoints, including CV death and death from any cause.[40] A post hoc analysis indicated these benefits were independent of background therapies, which included well-optimized rates of the other 3 pillars of GDMT.[40]

In the Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure (EMPEROR-Reduced) trial, 3,730 patients with HFrEF were randomized to empagliflozin or placebo and followed over a median duration of 16 months.[41] Notably, this trial enrolled patients with more severe HF (i.e., higher median natriuretic peptide levels and lower mean LVEF) who were at increased risk for a serious event compared to the DAPA-HF trial. In this study, the incidence of the composite primary outcome of CV mortality or HF hospitalization was significantly lower with empagliflozin versus placebo regardless of the presence of T2DM.[41] Unlike DAPA-HF, though, the difference in primary outcome in this study was driven by HF hospitalization, as rates of CV mortality were similar between groups.[41] This difference may have been due to the sicker patient population, lack of power, or simply chance. However, a meta-analysis of DAPA-HF and EMPEROR-Reduced showed SGLT-2 inhibitor use was associated with a reduction in all-cause mortality and CV death.[42]

There are little data on kidney-related endpoints for patients with eGFR <25 mL/min/1.73 m^2 who are receiving SGLT-2 inhibitors. The efficacy of SGLT-2 inhibitors is reduced with more severe kidney dysfunction, but their safety does not appear to differ for chronic kidney disease (CKD) stages 2–4.[43,44]

When initiating SGLT-2 inhibitors in patients with HF, however, it is important to note that empagliflozin and dapagliflozin are contraindicated in patients with eGFR less than 20 and 30 mL/min/1.73 m^2, respectively.

Changes in intraglomerular pressures result in an acute transient reduction in eGFR upon initiation of SGLT-2 inhibitors.[44] A dip in eGFR of up to 5 mL/min/1.73 m^2 is expected during the first few weeks of therapy, after which SGLT-2 inhibitors slow the progression of CKD compared to placebo.[44] The initial dip in eGFR should be largely tolerated and SGLT-2 inhibitors should be discontinued only if eGFR decreases by ≥30%.[44]

Unlike other pillars of HF GDMT, no titration is required for SGLT-2 inhibitors. Dapagliflozin and empagliflozin are currently the only 2 SGLT-2 inhibitors that are approved by FDA for HFrEF. Both agents are started at their target dose of 10 mg daily for HF (Table 7).[2] However, concomitant therapies (i.e., loop diuretics, antihypertensives, diabetic therapies) may need to be adjusted when initiating SGLT-2 inhibitors.

The osmotic diuresis and natriuresis produced by SGLT-2 inhibitors are additive to loop diuretics.[44] This is beneficial in patients who are acutely or chronically volume overloaded, but larger dips in eGFR are possible in patients who are more volume depleted. Additive fluid losses of 1–2 kg can be seen within the first couple of weeks of treatment that subsequently stabilizes. Initiation of SGLT-2 inhibitors should be delayed in patients who are hypovolemic. A reduction in maintenance diuretic dosage should be considered when initiating SGLT-2 inhibitors in patients who are not volume overloaded on clinical examination.

Overall, SGLT-2 inhibitors modestly reduce SBP/diastolic BP by an average of 2–4/1–2 mm Hg. However, greater BP reductions may be seen when simultaneously initiating other GDMT or when patients are volume depleted. Caution should be used when SBP is <95–100 mm Hg, as these patients were excluded from DAPA-HF and EMPEROR-Reduced trials.[40,41]

SGLT-2 inhibitors typically have a modest glucose-lowering effect with decreases in A1C of 0.6–1.0% in patients with preserved kidney function and lesser effect in those with kidney dysfunction.[44,45] The risk of hypoglycemia is low when SGLT-2 inhibitors are used as monotherapy because of their insulin-dependent mechanism of action.[40,41,45] However, the risk is higher when SGLT-2 inhibitors are combined with insulin or insulin secretagogues such as sulfonylureas.[45]

Table 7. Dosing of commonly prescribed medication therapies for HFrEF

Drug	Initial daily dose(s)	Target dose(s)	Mean total daily dose achieve in clinical trials
ARNi			
Sacubitril-vasartan	24/26 mg twice daily	97/103 mg twice daily	182/193 mg twice daily
ACE inhibitor			
Enalapril	2.5 mg twice daily	10–20 mg twice daily	16.6 mg
Lisinopril	2.5–5 mg daily	20–40 mg daily	32.5–35 mg
Ramipril	1.25–2.5 mg daily	10 mg daily	N/A
ARB			
Candesartan	4–8 mg daily	32 mg daily	24 mg
Losartan	25–50 mg daily	50–150 mg daily	129 mg
Valsartan	20–40 mg daily	160 mg twice daily	254 mg
SGLT-2 inhibitor			
Dapagliflozin	10 mg daily	10 mg daily	9.8 mg
Empagliflozin	10 mg daily	10 mg daily	N/R
BB			
Bisoprolol	1.25 mg daily	10 mg daily	8.6 mg
Carvedilol	3.125 mg twice daily with meals	25 mg twice daily with meals, 30 mg twice daily with meals if patient weighs ≥85 kg	37 mg
Metoprolol succinate	12.5–25 mg daily	200 mg daily	159 mg
MRA			
Eplerenone	25 mg daily, 25 mg every other day if eGFR is 30–49	50 mg daily, 25 mg daily if eGFR is 30–49	42.6 mg
Spironolactone	12.5–25 mg, 12.5 mg daily to every other day if eGFR is 30–49	25–50 mg daily, 12.5–25 mg daily if eGFr is 30–49	26 mg
Additional therapies			
Isosorbide dinitrate and hydralazine	20/30.5 mg 3 times daily	10/75 mg 3 times daily	90/175 mg
Ivabradine	5 mg twice daily with meals, 2.5 mg twice daily with meals if age ≥75 years	7.5 mg twice daily with meals	12.8 mg
Vericuguat	2.5 mg daily	10 mg daily	9.2 mg

Abbreviations used: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; eGFR, estimated glomerular filtration rate (mL/min/1.73 m2); GDMT, guideline directed medical therapy; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; N/A, not applicable; NR, not reported; SGLT-2, sodium-glucose cotransporter 2.

When combined with SGLT-2 inhibitors in patients with preserved kidney function, the dose of insulin should be reduced by 10–20% and the dose of sulfonylureas should be reduced or potentially discontinued in patients who are near their glycemic target.[45]

Patients with type 1 diabetes should not receive SGLT-2 inhibitors due to an increased risk of serious adverse events, including euglycemic diabetic ketoacidosis (DKA), as well as lack of inclusion in HF clinical trials.[40,41,45] Other patients at risk for DKA include those with acute illness or dehydration,

undergoing major surgery, following a restricted carbohydrate diet, or abusing alcohol.[45] These patients should hold SGLT-2 inhibitors for 2–3 days before surgery or in the presence of other risk factors.[45] Usually, therapy may be resumed within 24–48 hours following recovery, resumption of normal diet, and/or euvolemia.

The risk of genital mycotic infections is up to fourfold higher with SGLT-2 inhibitors because of the increased urinary excretion of glucose.[44] Women and those with prior infections are at increased risk.[44] Patients should be counseled to keep the genital region dry and hygienic. Uncomplicated infections may be treated orally while maintaining SGLT-2 inhibitor treatment. Temporary or permanent discontinuation of SGLT-2 inhibitor therapy may be required for severe or recurrent infections.

BBs

Evidence-based BBs with proven mortality benefit are the third pillar of HFrEF GDMT. Initiation of one of these three BBs (as previously discussed with stage B) is recommended to reduce mortality and hospitalizations in patients with HFrEF with current or previous symptoms.[2] BBs should be initiated at a low dose and only when patients are euvolemic and in stable condition (Table 7).

As with renin-angiotensin inhibitors, up-titration is usually at 2-week intervals or longer and doses are typically doubled. If necessary, the dose of BBs should be reduced instead of discontinued, as abrupt withdrawal can lead to clinical deterioration and should be avoided if possible.

Mineralocorticoid receptor antagonists

The benefits of mineralocorticoid receptor antagonists (MRAs) are well-established as agents that counteract aldosterone's effects of cardiac fibrosis and remodeling as well as block the renin-angiotensin system. In the RALES (Randomized Aldactone Evaluation Study), EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in HF), and EPHESUS (Eplerenone Post-Acute MI HF Efficacy and Survival Study) trials, spironolactone and eplerenone demonstrated consistent improvements in symptoms, HF hospitalizations, and all-cause mortality in patients with HFrEF and NYHA class II to IV symptoms.[46–48] Consequently, MRAs constitute the fourth pillar of quadruple therapy for HFrEF.[2]

Aldosterone antagonists block potassium excretion in the distal tubule and collecting ducts of the kidney. To decrease the risk of hyperkalemia, MRAs should only be initiated in patients with eGFR >30 mL/min/1.73 m^2 and serum potassium <5 mEq/L. Lower doses are recommended for patients with eGFR 30–49 mL/min/1.73 m^2 (Table 7).[2,4] Newer HF treatments, such as ARNis and SGLT-2 inhibitors, have been shown to facilitate initiation of MRA due to a reduction in the decline in eGFR and a decreased risk of hyperkalemia.[49,50]

During therapy, serum potassium and kidney function should be monitored. Concomitant nephrotoxic medications, potassium supplements, and other potassium-sparing agents should be avoided. In patients who are taking MRAs, the dose of MRAs should be halved if potassium approaches 5.5 mEq/L and discontinued if levels approach 6 mEq/L or there is worsening kidney function. Additional therapies that affect potassium and kidney function (i.e., renin-angiotensin inhibitors, diuretics) may need to be adjusted.

Potassium binders (i.e., patiromer, sodium zirconium cyclosilicate) are a reasonable addition to maintain acceptable potassium levels and facilitate continuation of MRA therapy; however, the benefit of this practice is uncertain, and these potassium binders are typically costly.[2]

Consider additional therapies in HFrEF

Hydralazine and isosorbide dinitrate

Several additional medications should be considered for patients who are symptomatic despite quadruple therapy.

The combination of hydralazine and isosorbide dinitrate is recommended in patients self-identified as African American with HFrEF and NYHA class III to IV symptoms despite optimal quadruple therapy to improve symptoms and reduce morbidity and mortality.[2] This recommendation is based on the African-American HF Trial, which was terminated early due to a significant mortality benefit seen with the addition of fixed dose isosorbide dinitrate plus hydralazine to background ACE inhibitor/ARB and BB therapy.[51]

Hydralazine and isosorbide dinitrate may also be considered for patients who cannot tolerate ARNis, ACE inhibitors, or ARBs because of drug intolerance or kidney insufficiency.[2] Adherence to this combination therapy is a major issue due to pill burden of 1 to 2 tablets taken thrice daily, as well as drug-related adverse effects including headache, dizziness, and gastrointestinal complaints.

Ivabradine

Heart rate is a strong predictor of CV outcomes in patients with HF.[2] Some patients may not tolerate or achieve sufficiently low heart rates with BB therapy. Ivabradine blocks the hyperpolarization-activated cyclic nucleotide-gated channel responsible for the cardiac pacemaker I_f current of the sinoatrial node which decreases heart rate without significantly lowering BP. Ivabradine can be beneficial for patients with stable chronic HFrEF and LVEF ≤35% with NYHA class II to III symptoms despite optimal GDMT (including a BB at maximal tolerated dose) and who are in sinus rhythm with a heart rate of ≥70 bpm at rest.[2] Paroxysmal atrial fibrillation (AF) or flutter is not a contraindication for ivabradine, but patients should be in sinus rhythm at least 40% of the time.[52]

Ivabradine is dosed twice daily with food, and the dose is titrated to target a heart rate of 50–60 bpm at rest.[2]

Ivabradine reduced the composite of HF hospitalization and CV mortality in the SHIFT (Systolic HF treatment with the I_f inhibitor ivabadine

Trial) study, but the benefit was driven by reduction in HF hospitalization.[52] Benefits were greater for patients with contraindications to BBs, those on lower BB doses (i.e., ≤50% of target), and those with resting heart rate of ≥77 bpm.[52] Notably, only 26% of patients in the SHIFT study were on target doses of BB.[52] Given the mortality benefits associated with BBs, ivabradine should only be considered after optimization of BB therapy.

Vericiguat

Oral soluble guanylyl cyclase (sGC) stimulators are a novel class of therapeutic agents that may be considered in high-risk patients with recent or recurrent HF hospitalizations despite GDMT.[2] Vericiguat, the only currently available agent, stimulates and sensitizes sGC to nitric oxide, resulting in improved diastolic relaxation, vasodilation, and microvascular function.

In the VICTORIA (Vericiguat Global Study in Subjects with HF with Reduced Ejection Fraction) trial, 5,050 patients with LVEF <45%, NYHA class II–IV symptoms, elevated natriuretic peptide levels, and recently worsening HF were randomized to vericiguat or placebo.[53] Compared to the trials with ARNis and SGLT-2 inhibitors, patients in VICTORIA were overall a more vulnerable population as they were older, more symptomatic, and had higher natriuretic peptide levels.[53] Over a median follow-up of 10.8 months, patients receiving vericiguat had a significantly lower incidence of the composite primary outcomes of first HF hospitalization or CV death, which was driven by reduced hospitalizations.[53]

Symptomatic hypotension and syncope occur more often with vericiguat versus placebo.[53] Otherwise, it has a favorable adverse effect profile. Consequently, vericiguat may be an attractive therapeutic option for the highest-risk, recently hospitalized patients who remain symptomatic despite optimal quadruple therapy, if SBP is >100 mm Hg and eGFR is ≥15 mL/min/1.73 m^2.

Treatment for HFpEF

HFpEF is characterized by increased filling pressures due to ventricular diastolic dysfunction. Numerous comorbidities contribute to the development of HFpEF, making it a highly prevalent and heterogeneous disorder. HFpEF accounts for approximately half of all patients with HF.[1,54]

However, since hypertension is a major cause and often undiagnosed, the prevalence of HFpEF is potentially higher. Management of HFpEF includes management of comorbidities, treatment of specific causes, diuretics to reduce congestion and improve symptoms, and mostly the same foundational therapies used for HFrEF.[2]

Managing hypertension

All recommendations from the HF guidelines for stage A patients at risk for HF apply to patients with HFpEF. BP should be controlled to <130/80 mm Hg using individualized treatments based on comorbidities. Renin-angiotensin inhibitors and MRAs provide BP lowering effects in addition to improving morbidity with HFpEF.

There is no evidence for benefit of BBs in patients with HFpEF, but they should be used for compelling comorbidities such as history of MI, symptomatic coronary artery disease, or AF with rapid ventricular response. BBs must be used cautiously in these patients due to the potential contribution of chronotropic incompetence to activity and exercise intolerance.[55]

Controlling AF

LV filling in HFpEF is more dependent on atrial contraction due to improper ventricular relaxation. Coordinated atrial contraction is lost during AF. This coupled with reduced ventricular filling during periods of rapid ventricular rate can lead to worsening symptoms.

A review of AF is beyond the scope of this review, but individualized management of AF through rate or rhythm control can be useful to improve patient symptoms.[2] Rate control is usually accomplished with BBs or nondihydropyridine calcium channel blockers. Choices for rhythm control are typically limited to amiodarone and dofetilide in patients with HF.

Medication recommendations for HFpEF

Diuretics should be used to relieve symptoms related to volume overload. Although the lowest possible diuretic dose should be used in all patients with HF, patients with HFpEF have a steep LV pressure-volume curve which necessitates cautious dosing and patient monitoring. A small change in intravascular volume can cause a large decrease in cardiac output and BP.

In contrast to HFrEF where more robust data informed class 1 recommendations for the 4 foundational pillars, weaker recommendations are made in the HF guidelines for medication therapies in HFpEF.[2] SGLT-2 inhibitors carry the strongest recommendation of the foundational therapies in HFpEF.[2] ARNi, MRA, and ARB may be reasonable therapeutic options with notable emphasis placed on patients with LVEF on the lower end of the spectrum of HFpEF.[2]

In the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic HF with Preserved Ejection Fraction) trial, 5,988 patients with NYHA class II to IV symptoms, LVEF > 40%, and elevated natriuretic peptides were randomized to empagliflozin or placebo and followed over a median duration of 26.2 months.[56] In the study, empagliflozin reduced the composite endpoint of CV death or HF hospitalization by 21%, regardless of the presence of T2DM.[56] EMPEROR-Preserved was the first HFpEF trial to meet its primary endpoint; however, outcome differences were driven by the magnitude of the effect on HF hospitalizations.[56] In the study, empagliflozin did not improve CV death or all-cause mortality.[56] Benefits were attenuated among those with LVEF >62.5%.[57] This trial led to the guideline recommendation that in patients with HFpEF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and CV mortality.[2]

The DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction HF) trial was published since the guidelines were released and supports the clinical benefit of SGLT-2 inhibitors in HFpEF.[58] Inclusion criteria in this large,

international, multicenter trial were similar to EMPEROR-Preserved and included patients with LVEF >40% with NYHA class II to IV symptoms and elevated natriuretic peptides. In 6,263 patients randomized to dapagliflozin or placebo, dapagliflozin reduced the combined outcome of CV mortality, HF hospitalization, or urgent HF visit by 18% when compared with placebo over a median of 2.3 years.[58] In the study, total events and symptom burden were lower with dapagliflozin.[58] Unlike, EMPEROR-Preserved, DELIVER included patients with HFimpEF (18%) and benefits were similar among patients with LVEF above 60%.[58]

In the PARAGON-HF (Prospective Comparison of ARNi with ARB Global Outcomes in HF with Preserved LVEF) trial, 4,822 patients with LVEF of 45% or above, NYHA class II to IV symptoms, and elevated natriuretic peptides or HF admission within 6 months were randomized to sacubitril-valsartan or valsartan.[59] After a median of 35 months, the primary endpoint of CV death or HF hospitalization was reduced by 13%, but the difference was not significant.[59]

If urgent HF visits were incorporated into the primary composite outcome, as with other contemporary HFpEF trials, the PARAGON-HF trial would have achieved its primary endpoint. Secondary analyses are only hypothesis-generating when trials do not achieve their primary endpoint. However, in the subgroup analyses there was a significant benefit for sacubitril-valsartan in patients with LVEF of ≤57% and in women.[59] Based on this trial, ARNis may be considered to decrease hospitalizations in patients with HFpEF, particularly among patients with LVEF on the lower end of this spectrum.[2]

In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[2] This recommendation is based on the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, in which 3,445 patients were randomized to spironolactone or placebo and followed over a mean of 3.3 years.[60] A small but nonsignificant reduction was seen in the composite primary outcome of CV mortality, aborted cardiac arrest, and HF.[60] Hospitalization for HF was reduced with spironolactone while also seeing increased rates of hyperkalemia and serum creatinine, as expected.[60]

An exploratory, but curious, geographical subgroup analysis of the TOPCAT trial that detailed regional differences in almost every important baseline variable between the Americas and Russia/Georgia was later published.[61] According to that post hoc analysis, hospitalization rates for HF in the Americas were in the range of 20.8% to 24.5% for spironolactone and placebo, respectively, as expected with HFpEF; however, these rates were only 2.6% and 3.4% in Russia/Georgia for the equivalent groups.[61] Additionally, a sample of the patients in Russia/Georgia had nondetectable levels of a spironolactone metabolite as well as a lack of increase in potassium and creatinine.[61] Ongoing clinical trials will hopefully provide more useful data on the use of MRAs in this patient population.

Although ACE inhibitors may be used to control hypertension, they are not recommended specifically for the management of HFpEF.[2] Instead, the use of ARBs may be considered in selected patients with HFpEF to decrease hospitalizations, particularly among those with LVEF on the lower end of this spectrum.[2] This recommendation is based on the CHARM (Candesartan in HF: Assessment of Reduction in Mortality and morbidity)-Preserved trial, in which 3,023 patients with LVEF >40% were randomized to candesartan or placebo.[62] The primary endpoint of CV death or HF hospitalization was not significantly different between groups, but the number of patients admitted to the hospital was reduced with candesartan.[62] However, when these effects were examined in a meta-analysis of randomized controlled trials, no reproducible benefit was seen as there was little to no effect on CV or all-cause death or on HF hospitalizations.[63]

HFmrEF and HFimpEF

HFmrEF is a new classification with no prospective, randomized controlled trials of patients specifically within the LVEF range of 41–49%. There are no class 1 recommendations in the HF guidelines for the foundational pillar therapies in HFmrEF because all data for the treatment of this class are derived from post hoc or subsets of previous HF trials.[2] Patients within this classification are generally on a dynamic trajectory of improvement or deterioration. Although the strength of recommendations is weaker, treatment of patients with HFmrEF generally mirrors HFrEF treatment.

In a subgroup of 1,983 patients with LVEF 41–49% in the EMPEROR-Preserved study, findings were equivalent to the overall study population as

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empagliflozin reduced the risk of the primary composite endpoint.[56,64] Based on these data and because this was the only available large-scale randomized trial, the guidelines state that SGLT-2 inhibitors can be beneficial in patients with HFmrEF to decrease HF hospitalizations and CV mortality.[2] Similar benefits were seen in the DELIVER trial among all LVEF subgroups, including the 33.8% of patients who were classified as HFmrEF, which support this recommendation.[58] Note that although no recommendation was specifically made for the use of SGLT-2 inhibitors in patients with HFimpEF because of the timing of publication, these patients also derived the same benefits seen with other LVEF classifications in the DELIVER trial.[2,58]

Other foundational therapies (e.g., ACE inhibitors, ARBs, ARNis, MRAs, and evidence-based BBs) may be considered among patients with stage C HFmrEF to reduce the risk of HF hospitalization and CV mortality, particularly among patients with LVEF on the lower end of this spectrum.[2] This recommendation is based on post hoc analyses of trials with MRAs, ARBs, and ARNis as well as a meta-analysis of 11 HF trials with BB therapy that included patients with HFmrEF.[57,59,65–69]

Many patients ask their providers when they can discontinue some of their HF medications, particularly once they are feeling better and note improvements in LVEF. It is important to reinforce the need to continue therapy in patients with HFimpEF because LV function and structural abnormalities do not fully normalize in many patients.[2]

In the TRED-HF (Withdrawal of Pharmacological Treatment for HF in Patients with Recovered Dilated Cardiomyopathy) trial, 51 patients with a prior LVEF <40% and subsequent LVEF >50% and NYHA class I were randomized to withdrawal or continuation of HF medications.[70] In the study, relapse of HF symptoms was more common in the medication withdrawal group, with 44% relapsing by 6 months compared to none in the medication continuation group.[70] This trial reinforces the recommendation to continue GDMT to prevent relapse of HF and LV dysfunction, even in patients who become asymptomatic.[2]

Mitigating barriers to GDMT implementation

Therapeutic inertia is the problem of delaying initiation of therapy and achieving target doses. Contemporary U.S. registry data have shown most eligible outpatients with HFrEF who are mainly managed in primary care settings do not receive target doses of medical therapy and few patients have GDMT up-titrated at any point during a 12-month follow-up.[71,72] More recent international data suggest similar struggles with initiating GDMT and increasing to target doses, but also an alarming proportion of patients who have GDMT discontinued within one year of HF hospitalization.[73] Clinicians should mindfully approach each patient encounter as an opportunity to optimize GDMT.

Barriers to optimization of GDMT can be categorized as health care system–, clinician-, and patient-related challenges. Team-based patient care by 2 or more providers from different disciplines collaboratively working with each patient can help overcome many of these barriers. Improving communication between providers and patients, employing academic detailing, and implementing technology such as clinical reminders, patient dashboards, and virtual patient visits are methods to help decrease therapeutic inertia.

Pharmacists are keenly aware of the financial toxicity of medications and routinely asked to find ways to help patients afford their medication. Although many newer therapies can improve outcomes for patients with HF, 2 of the 4 foundational therapies are only available as brand name formulations. The cash price of these medications can exceed $600 a month. Obtaining these medications can be challenging even for insured patients. Many insurance companies require prior authorizations or limit coverage for these medications. Others have unaffordable deductibles or out-of-pocket maximums. Manufacturers of ARNis and SGLT-2 inhibitors sometimes offer copay cards to supplement commercial insurance. These offers can possibly reduce the monthly copay to $10 per month or less.

However, patients with Medicare drug coverage (Part D) or other government-based insurance are not eligible to use these cards. Many of these patients cannot afford their medications once they reach their coverage gap or "donut hole." Patients with true financial hardship may apply for assistance through manufacturer medication assistance programs. The manufacturers offer a free trial ranging from 14- to 30-day supply which can help bridge the patient until they are approved for assistance. Pharmacists should be good stewards of these trials as they are only available once per patient.

Conclusion

The latest guidelines adopted an updated definition of HF that includes symptoms or signs of HF as well as objective evidence of volume overload in addition to structural and/or functional myocardial changes. Heart failure classifications have expanded to include HFrEF, HFpEF, HFmrEF, and HFimpEF. Novel therapeutic options, including ARNi and SGLT-2 inhibitors, are now incorporated as foundational therapies of the different HF classifications with the strongest evidence in the HFrEF population. Pharmacists should work with insurance companies and manufacturers to help patients afford these new medications. Each patient encounter is an opportunity to optimize GDMT and impact patient outcomes.

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CPE assessment

This assessment must be taken online; please see "CPE information" in the sidebar on the following page for further instructions. The online system will present these questions in random order to help reinforce the learning opportunity. There is only one correct answer to each question.

1. **A 78-year-old woman presents with history of heart failure has routine echocardiograms to follow her left ventricular ejection fraction (LVEF). Her 4 most recent echocardiograms were each taken 12 months apart. Her LVEF was reported as 58%, 31%, 33%, and 44% (in chronological order). How should this patient's heart failure be classified?**
   a. Heart failure with reduced ejection fraction (HFrEF)
   b. Heart failure with mildly reduced ejection fraction (HFmrEF)
   c. Heart failure with preserved ejection fraction (HFpEF)
   d. Heart failure with improved ejection fraction (HFimpEF)

2. **A 59-year-old man with heart failure with reduced ejection fraction (HFrEF) has experienced dyspnea on exertion for the past 2 weeks. He gets short of breath walking up 2 flights of stairs while carrying his groceries. He also gets fatigued while doing laundry. In which New York Heart Association functional class is his heart failure classified?**
   a. I
   b. II
   c. III
   d. IV

3. **Which of the following medications has not been shown to improve mortality in a patient with HFrEF?**
   a. Furosemide
   b. Eplerenone
   c. Carvedilol
   d. Sacubitril-valsartan

4. **Which of the following candidates is an appropriate candidate for sodium-glucose cotransporter 2 (SGLT-2) inhibitor therapy for heart failure?**
   a. 34-year-old man with HFrEF and type 1 diabetes who is taking metoprolol succinate, sacubitril-valsartan, furosemide, and insulin
   b. 54-year-old woman with HFmrEF and chronic kidney disease stage 4 (baseline estimated glomerular filtration rate 15 mL/min/1.73 m^2) who is taking bisoprolol and hydralazine/isosorbide dinitrate
   c. 58-year-old woman with HFpEF, type 2 diabetes, and recurrent urinary tract infections who is taking carvedilol, losartan, eplerenone, and bumetanide
   d. 62-year-old man with HFrEF, hypertension, and dyslipidemia who is taking metoprolol succinate, lisinopril, spironolactone, torsemide, and atorvastatin

5. **A 34-year-old man with type 2 diabetes, hypertension, and depression presents for an annual checkup. The primary care provider ordered a routine echocardiogram which revealed a left ventricular ejection fraction (LVEF) of 38% and moderate mitral regurgitation. His home medications include lisinopril, metformin, and sertraline. His blood pressure today is 146/90 mm Hg. He denies any chest pain, dyspnea, or symptoms of heart failure. Which of the following is the most appropriate adjustment to his medication regimen?**
   a. Switch lisinopril to losartan
   b. Add amlodipine
   c. Add carvedilol
   d. Add spironolactone

6. **Which of the following is correct regarding beta blocker therapy in HFpEF?**
   a. All patients with HFpEF should be on beta blocker therapy in order to reduce mortality
   b. Beta blocker therapy has not been shown to decrease mortality but can be used to treat comorbidities
   c. Beta blocker therapy and sodium-glucose cotransporter 2 inhibitors decrease mortality in HFpEF only if used together
   d. Beta blocker therapy is contraindicated in patients with HFpEF

7. **A 42-year-old woman returns to clinic for management of HFrEF. Her current medications include furosemide, lisinopril, metoprolol succinate, pravastatin, dapagliflozin, spironolactone, and citalopram. She denies symptoms of congestion, but when asked about recent illness she reports a dry, nonproductive cough that has been present for over a month. Which of the following recommendations is most appropriate for this patient?**
   a. Decrease the dose of spironolactone and lisinopril
   b. Discontinue spironolactone and decrease the dose of metoprolol succinate
   c. Discontinue metoprolol succinate and initiate carvedilol
   d. Discontinue lisinopril and initiate valsartan

8. **A 63-year-old man presents to clinic for routine follow-up. He describes NYHA class II–III symptoms over the last few weeks. Current medications are metoprolol succinate 100 mg daily, lisinopril 40 mg daily, dapagliflozin 10 mg daily, eplerenone 50 mg daily, rosuvastatin 10 mg daily, and aspirin 81 mg daily. He took all medications this morning at 7:00 am before coming to the clinic. You plan to transition him from lisinopril to sacubitril-valsartan. Which of the following is the most appropriate recommendation?**
   a. Stop lisinopril and initiate sacubitril-valsartan 49/51 mg twice daily, with the first dose tomorrow morning at 7:00 am.
   b. Initiate sacubitril-valsartan 49/51 mg twice daily starting this evening at 7:00 pm and stop lisinopril after 36 hours of overlap with sacubitril-valsartan.
   c. Stop lisinopril and initiate sacubitril-valsartan 24/26 mg twice daily, starting the first fose tomorrow morning at 7:00 am.
   d. Stop lisinopril and initiate sacubitril-valsartan 49/51 mg twice daily, starting tomorrow evening after 7:00 pm.

9. **A 65-year-old woman with non-ischemic cardiomyopathy presents for heart failure follow-up after hospital discharge. He was admitted with shortness of breath and hypoxic respiratory failure. He was diuresed and euvolemic at discharfge. His most recent echocardiogram shows LVEF 35%. He is currently NYHA functional class III. Current medications are sacubitril-valsartan, bisoprolol, dapagliflozin, spironolactone, and furosemide. Current vitals include blood pressure 110/68 mm Hg, heart rate 65 bpm, and normal sinus rhythm. Labs on basic metabolic panel are normal except for SCr 2.4 mg/dL and an estimated glomerular filtration rate of 28 mL/min/1.73 m^2. Current NT-proBNP is 2340 pg/mL, which is elevated. Which of the following additional therapies is most appropriate for this patient?**
   a. Ivabradine
   b. Digoxin
   c. Vericiguat
   d. Patiromer

10. **A 73-year-old woman with HFimpEF is currently euvolemic, normotensive, and reports no recent symptoms. Her current medications are sacubitril-valsartan, metoprolol succinate, spironolactone, empagliflozin, torsemide, atorvastatin, and aspirin. She really doesn't like taking medications and asks you to recommend which medications can be stopped since she is feeling better and her heart function has improved. Which of the following is the most appropriate response?**
   a. We can discontinue spironolactone and empagliflozin, but we need to continue sacubitril-valsartan and metoprolol indefinitely. There is a greater chance of relapse of symptoms and heart dysfunction if those two are stopped.
   b. We need to continue your current heart failure medications for now. We can stop your medications if your ejection fraction is still within normal range after 2 consecutive years.
   c. We can discontinue your medications as long as we continue to check an echocardiogram annually. If your ejection fraction drops below 50% in the future, then we should restart therapy.
   d. We need to continue your current heart failure medications indefinitely. There is a greater chance of relapse of symptoms and heart dysfunction if therapy is stopped.

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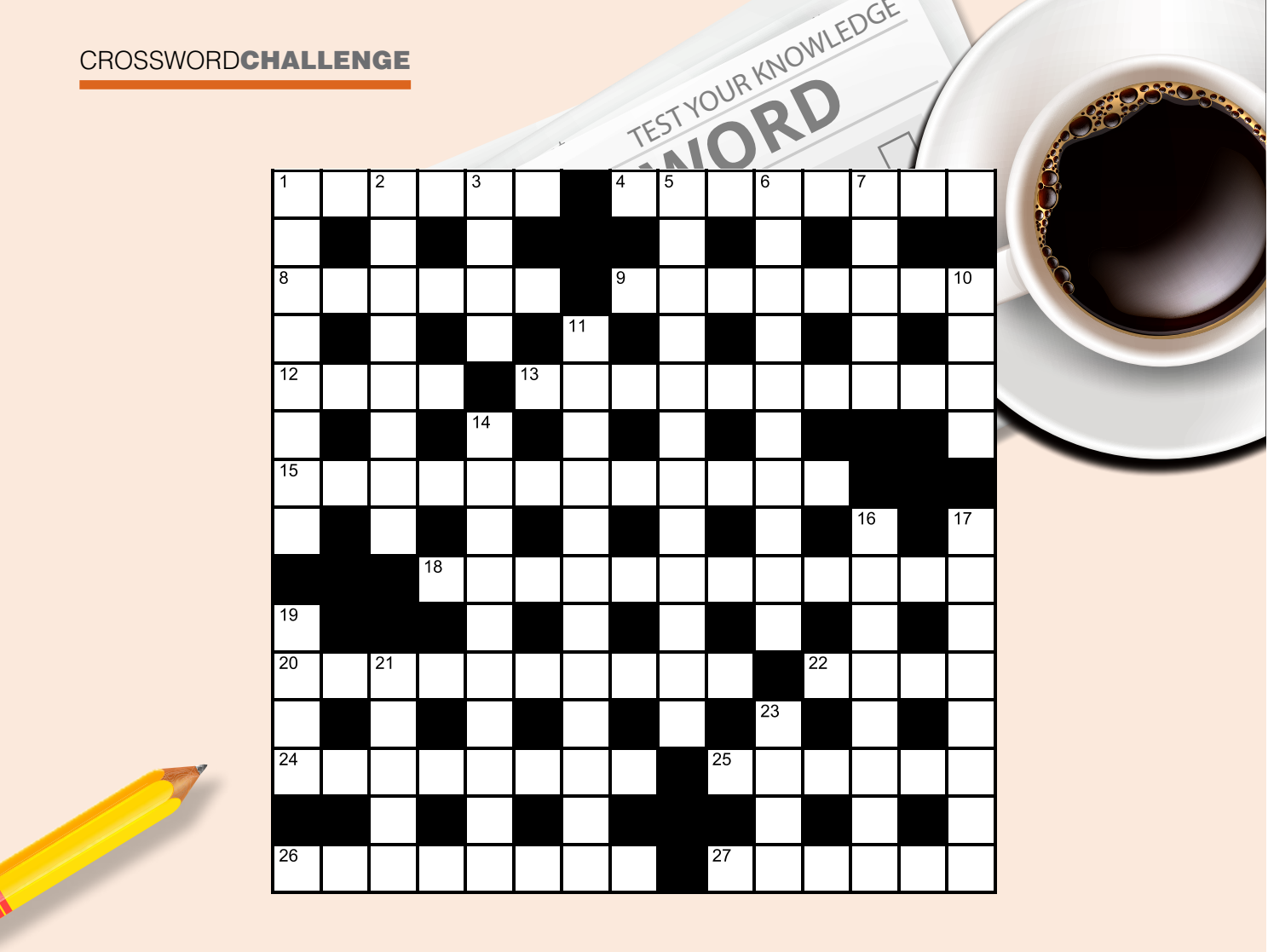

Across

1 When this persists for the long term, drug therapy may be needed
4 Oxidative enzyme
8 The "A" in AFib
9 Enterprise, for example
12 Prefix with dextrous
13 OTC treatments can help with these symptoms
15 Condition that occurs when insufficient blood is pumped—and the topic of this month's cover story
18 Normal serum levels of TSH and T4
20 Plant-based diet
22 Digital photo format
24 Blood–brain barrier, for example
25 Transparent front part of the eye
26 Move an Rx from one pharmacy to another
27 Et _____

Down

1 Analgesic target
2 Brainy
3 Council that selects official generic drug names, in short
5 Chloroquine, for example
6 Resembling epinephrine
7 Often leads to gesundheit
10 Prefix for treatments related to the feet
11 Pharmacists can improve this using patient-centered strategies and communication
14 Memorization targets in medicinal chemistry for pharmacists
16 Pharmacists do so much more than this
17 Part of the brain that processes emotions
19 Egg
21 Beta follower
23 Target of an osteoporosis treatment

Solution is available online at pharmacytoday.org.

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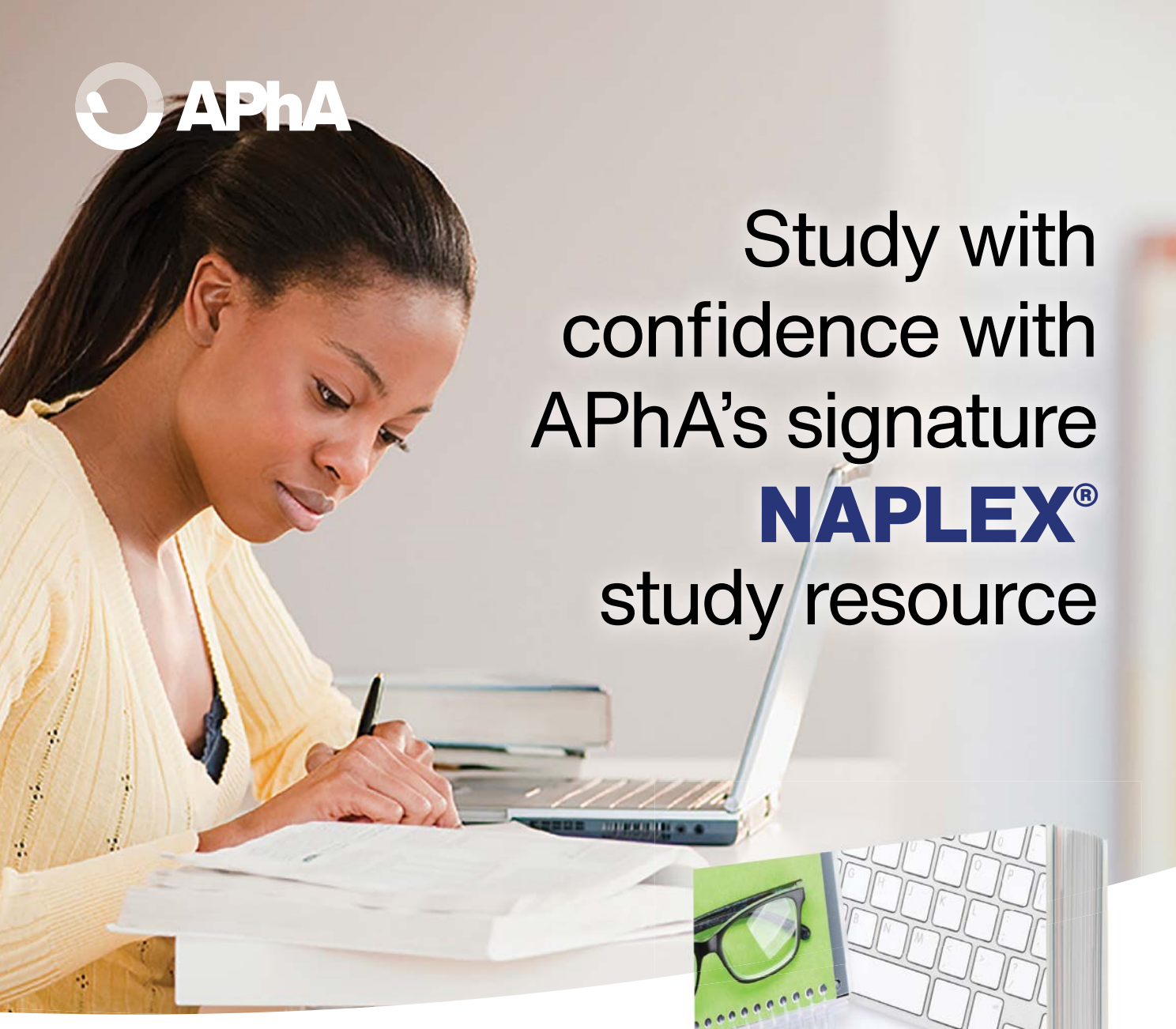

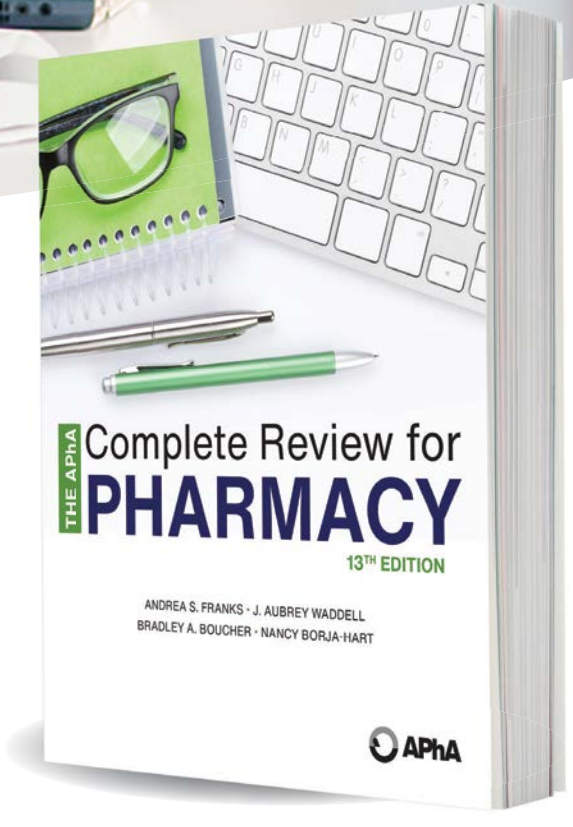

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