Getting Rid of a Lingering Cough
Publisher’s Note

Thank You, Pharmacy Professionals

MICHELE F. SHERMAN Post-Pandemic<br>PHARMACY PROFESSIONALS CERTAINLY PROVED THEIR value in 2021, with the pandemic showing that there has never been more of a need for the unique role that pharmacists, pharmacy technicians, and pharmacy interns play in enhancing and protecting public health.

As 2021 ends, pharmacy professionals stand at the forefront of the effort to fight COVID-19 through testing and vaccinations. They met the challenge and served their communities diligently.

Winter’s advent is a good reminder that in addition to making sure that patients get their COVID-19 vaccinations and boosters, influenza shots are also extremely important, perhaps this year more than ever.

New results of a study conducted by the University of Miami Leonard M. Miller School of Medicine in Florida show that the influenza vaccine has the potential to provide vital protection against severe effects of COVID-19.

The study, which analyzed 37,377 patient records on a global scale, strongly suggests that getting the annual influenza vaccine reduces the risks of deep vein thrombosis, sepsis, and stroke in patients with COVID-19.

Individuals with COVID-19 who have been vaccinated against influenza were also significantly less likely to visit the emergency department and be admitted to the intensive care unit, according to the study results.

In this issue, we focus on influenza, as well as cough and cold, the trifecta of misery for many patients from December through March. Our Cover Feature looks at the many potential causes behind a cough that lingers for weeks after a cold and how to advise patients to self-treat or use OTC products, unless the situation is serious enough to warrant medical attention. This issue’s OTC Cases also focuses on nasal congestion.

Elsewhere in our pages this month, pharmacy professionals can find information on gestational diabetes, identifying chest pain, and the varicella vaccination.

As we close the book on another year of educating and empowering pharmacists and look ahead to 2022, we want to thank you for your support and for all that you do to improve patient health. No matter what obstacles and opportunities await pharmacy professionals, Pharmacy Times is committed to providing them with the resources they need to continue delivering outstanding care in their communities.

From our family to yours, have a happy holiday season and a healthy and safe New Year!

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At the completion of this activity, the participant will be able to:
• Determine the pathophysiology, epidemiology, risk factors, and clinical presentation associated with vulvovaginal candidiasis (VVC)
• Compare the mechanisms of action, dosing, administration, potential adverse effects, and challenges associated with standard -azole therapies including available over-the-counter and prescription agents for VVC
• Examine the newly approved and emerging antifungals for VVC including mechanisms of action, dosing, administration, efficacy and safety data, and clinical benefits
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93 Addressing the Challenges of Managing CAD/PAD and Associated Comorbidities: The Role of Antithrombotic Therapy

At the completion of this activity, the participant will be able to:
• Explain the unmet need and clinical burden of coronary artery disease/peripheral artery disease (CAD/PAD)
• Examine the evidence-based treatment guidelines for patients with CAD/PAD
• Analyze clinical data exploring therapies with the potential to improve patient outcomes and reduce complications
• Identify the role of the pharmacist in making clinical recommendations, counseling and educating patients, and managing associated comorbidities of CAD/PAD

111 Overcoming Barriers to Influenza Vaccination: Examining Available Vaccines for 2021-2022 and Addressing Hesitancy During the COVID-19 Pandemic

At the completion of this activity, the participant will be able to:
• Examine the epidemiology of the influenza virus and the challenge of increasing influenza vaccination rates during the era of COVID-19
• Determine the patient populations at elevated risk of complications related to Influenza and COVID-19 and the need to improve vaccination rates during the pandemic
• Explore the recommendations, safety, and efficacy of the available influenza vaccines for the 2021-2022 influenza season
• Investigate the growing presence of pharmacies as a site of care to improve influenza and COVID-19 vaccination rates especially during the ongoing pandemic and the role of the pharmacist as patient identifier, educator, and vaccine administrator
Social Comments

Don't miss a thing! Follow us on all your social media platforms.

This morning we’re featuring Bethany Nash, PharmD, AEMT! Nash is deeply passionate about her career and is always available to answer questions and give advice. She also works closely with @LifeFlightMaine reviewing protocols and teaching for the organization. #ThankAPharmacist

6:00 AM · Sep 28, 2021 · TweetDeck

On social media, you helped us celebrate National Pharmacists Month. Here were some of your thoughts:

**ON INSTAGRAM**

Jaime H. said on Instagram, "I’m celebrating by serving patients and their families today at the hospital.”

**ON FACEBOOK**

Aryaan T. said on Facebook, “Dispensing more and more drugs to patients.”

Tell us why you’re proud to be a pharmacist and why the profession is so important. Use #APharmacists on social media or email submissions to Aislinn Antrim at aantrim@pharmacytimes.com.
Economic Protectionism Prevents Health Care Delivery Evolution

By TROY TRYGSTAD, PHARMD, PHD, MBA, PHARMACY TIMES® EDITOR IN CHIEF

PHARMACISTS ARE READY TO PROVIDE care and get paid for their services.

The COVID-19 pandemic has shown an ability, at scale, and willingness by pharmacists in community settings to schedule patients for services, such as infusions, testing, and vaccinations, and deliver them effectively, professionally, and safely. Many COVID-19 vaccinations have been performed at pharmacies. When given a choice, patients largely prefer going to a pharmacy to receive basic health services. Pharmacists are trained to respond to public health measures, such as prescribing treatment under standardized protocols and screenings. They are undisputedly the drug therapy experts, and pharmacies are an ideal setting of care for frontline health care service delivery and referral to behavioral health, primary care, and other care team members.

However, pharmaceutical manufacturer and provider policy and politics have long suppressed the pharmacist’s ability to use their 4 years of postgraduate training, often with an additional year or 2 of residency. “Provider status” is a long-sought after umbrella phrase for a host of door-opening service and professional sustainability provisions. Lack of said “status” is less about scope of practice and more about accessing insurance coverage. No honest physician or physician advocate believes that basic health care service assessment and delivery cannot be done effectively and safely by a pharmacist practicing in a community pharmacy. If so, they would be clamoring to put a host of OTC medications back on “legend” status, requiring a prescription from a qualified health care professional before one could purchase them. Athlete’s foot, dry eyes, heartburn, and of course, seasonal allergies all necessitate a diagnosis or self-diagnosis when accessing those products over the counter. Every day, pharmacists screen hundreds of thousands of patients for a brief intervention, and either refer them to a care team member or suggest treatment. Once upon a time, these treatments, now available over the counter, were inaccessible without seeing a prescriber at a physician’s office.

Uncurious Case Example of Loratadine

Loratadine was approved by the FDA in 1993. Hailed as the first truly nonse-dating antihistamine with a nearly flawless adverse effect (AE) profile, it was destined to be a blockbuster drug. Because it did not cross the blood-brain barrier, it did not have many of the well-documented anticholinergic and seda-
tion effects of diphenhydramine. Antihistamines remain a very widely used class of drugs, with estimates of 50 million Americans using them for allergies alone.

Upon loratadine’s initial FDA approval, patients were faced with a choice to continue to using their existing OTC antihistamine, with all its known AEs and dangers, or use a clearly superior, safer medication. But they would need to have an office visit, tell the prescriber they had been using antihistamines for years, get a prescription, go to the pharmacy, and wait to have it filled to finally achieve wakefulness. Then in 2002, the same year that loratadine came off patent, it miraculously became available over the counter. A regulatory requirement was no longer needed to get a prescription from a list of qualified prescribers, which did not and still largely does not include the experts trained for years in drug therapy. So the drug went from a highly restricted prescription-only medication to a product widely available with no restrictions at all and no requirement for health care provider input or monitoring in a single day. One day at patient needed a prescription, and the next day the patient could pick it up at a truck stop while asking the cashier for medication advice, thanks solely to the loss of patent protection.

**Manufacturer and Provider Economics Drive Policy**

More effective and safer diagnostic testing and medications continue to be brought to the market. And that benefits all of us if we can access them. Billions of dollars in upfront investments by manufacturers and taxpayers require a “what-the-market-will-bear” pricing strategy, segmented by ability to pay. A combination of perceived out-of-pocket costs, price sensitivity, and product value largely determines how and when devices and drugs are paid for when health insurance is in play. If an antihistamine costs $100 but a patient only pays $30 because of insurance coverage, the patient is more likely to purchase the medication, at about the same cost if it were available over the counter. Filing for an OTC approval and taking it to market while a drug is on patent would be an outlier from a regulator’s perspective and shows negligence of the highest order to the drug is on patent would be an outlier from a regulator’s perspective and shows negligence of the highest order to the drug’s early days. Initially, many states resisted the federal government’s use of the PREP Act and neglected to follow its authorizations for pharmacists to order testing and vaccinations, while testing manufacturers were in the process of applying to the FDA for home test and OTC use for their products. Curiously, none of the laboratories, medical providers, or states were against that.

**COVID-19 Testing Available at Home**

Despite all the above, we found the economics of special interests rearing their ugly heads again during the pandemic’s early days. Initially, many states resisted the federal government’s use of the PREP Act and neglected to follow its authorizations for pharmacists to order testing and vaccinations, while testing manufacturers were in the process of applying to the FDA for home test and OTC use for their products. Curiously, none of the laboratories, medical providers, or states were against that.

**Galling Case of Remote Therapeutic Monitoring**

This brings to mind what is perhaps the most vexing coverage and qualifying provider policy about to ever take root. Remote Therapeutic Monitoring is a new service that covers “musculoskeletal system status, respiratory system status, therapy [medication] adherence, and therapy [medication] response” with billing codes (989X[1-5]) is be covered under Medicare as of 2022. Clinical psychologists, nurses, occupational and physical therapists, speech language pathologists, and other practitioners will likely be able to bill for the service but not pharmacists.

**Time to Engage Professional Associations**

There is no more critical time to engage local, national, and state professional associations. All the gains made during the pandemic so that pharmacists could serve patients in their communities, providers on the care team, and public health may be lost when the PREP Act amendments are allowed to expire. Worse, the underlying trend provides a through line that ignores the pandemic and seeks to give everyone on the care team a role in optimizing medication use, except the pharmacist. Get out there and get active.
## FDA Approvals

### Biologics License Applications, Biosimilars, Generics, and New Drug Applications

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<th>Drug name</th>
<th>Indication</th>
<th>Manufacturer</th>
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<tr>
<td>Asciminib (Scemblix)</td>
<td>Indicated for the treatment of patients with Philadelphia chromosome (Ph)-positive chronic myeloid leukemia (CML) in chronic phase who were previously administered 2 or more tyrosine kinase inhibitors</td>
<td>Novartis</td>
<td>10/29/21</td>
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<tr>
<td>Pilocarpine HCl Ophthalmic Solution 1.25% (Vuity)</td>
<td>Indicated for the treatment of presbyopia in adults</td>
<td>AbbVie</td>
<td>10/29/21</td>
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<td>Repository Corticotropin Injection (Purified Cortrophin Gel)</td>
<td>Indicated for the treatment of chronic autoimmune disorders, including acute exacerbations of multiple sclerosis and rheumatoid arthritis, in addition to excess urinary problems because of nephrotic syndrome</td>
<td>ANI Pharmaceuticals</td>
<td>11/1/21</td>
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<tr>
<td>Amphetamine extended-release (Dyanavel XR)</td>
<td>Indicated as a once-daily tablet for the treatment of individuals 6 years of age and older with attention-deficit hyperactivity disorder</td>
<td>Tris Pharma</td>
<td>11/5/21</td>
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<td>Pembrolizumab (Keytruda)</td>
<td>Indicated for the adjuvant treatment of patients with renal cell carcinoma at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions</td>
<td>Merck</td>
<td>11/18/2021</td>
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<td>Neuromark Rhinitis Neurolysis Therapy</td>
<td>Indicated as an in-office treatment to create lesions to interrupt the posterior nasal nerves for patients with chronic rhinitis</td>
<td>Neurent Medical</td>
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<td>Maribavir (Livtencity)</td>
<td>Indicated for the treatment of adults and pediatric patients aged 12 years or older and weighing at least 35 kg with post-transplant cytomegalovirus infection/disease that is refractory to treatment with ganciclovir, valganciclovir, cidovir, or foscarinet</td>
<td>Takeda Pharmaceutical Company</td>
<td>11/23/2021</td>
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</tbody>
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COVID-19 Vaccines Are Effective and Safe for Patients With Thoracic Cancer

**COVID-19 VACCINES ARE EFFECTIVE** and safe in patients with thoracic cancer and most are immunized after 2 doses, results of a study show.

After 6 to 7 months, just 8 of 283 patients with lung cancer contracted proven symptomatic SARS-CoV-2 infection with rapid favorable evolution. After 14 days following the second dose, 17 individuals were still negative and 34 were using a pseudoneutralization assay. The third dose given to 11% of individuals with persistent low antibody titers resulted in an 88% immunization rate.

The study included 306 patients with lung cancer with a median age of 67 years, and 283 received 2 vaccine doses at 28-day intervals.

The investigators measured SARS-CoV-2 spike antibodies using the Abbot Architect SARS-CoV-2 IgG immunoassay prior to the first injection of the mRNA vaccines, after the fourth week, and at 2 to 16 weeks after the second vaccine dose.

Only age, chemotherapy as last systemic treatment within 3 months, and chronic corticosteroid treatment were significantly associated with a lack of immunization. Thirty individuals received a third vaccine dose, with just 3 showing persistent negative serology.

No anaphylaxis reactions occurred among any of the individuals who received the vaccine doses, and there were no significant safety concerns.

The findings were posted in the *Journal of Thoracic Oncology.* — Ashley Gallagher

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COVID-19 Vaccines Protect Patients Treated for Cancer

**INDIVIDUALS BEING TREATED FOR** active cancer had lower immune responses to the 3 COVID-19 vaccines than healthy individuals, though they were predicted to still be protected, study results show.

“T he vaccine [adverse] effects experienced by patients with cancer were similar to those experienced by healthy controls and were generally mild or moderate, which should be reassuring to patients,” said Vivek Nanarbhai, MBChB, PhD, DPhil, a clinical fellow in medicine at Massachusetts General Hospital and Dana-Farber Cancer Institute, in a statement.

Investigators measured the individual’s concentration of antibodies against SARS-CoV-2 and neutralizing titers to determine how well the antibodies blocked the virus from entering cells.

In patients with cancer, responses to the 3 vaccines were lower compared with those in healthy individuals, but most patients had responses that are likely sufficient to protect against severe disease. Those who received treatments with immune checkpoint blockade tended to have enhanced immune responses.

The type of vaccine patients received was a major factor in inducing an immune response. Those who received the Johnson & Johnson (J&J) vaccine had lower immune responses than those who received an mRNA vaccine.

Additional doses of the vaccine induced a higher immune response in those who received the booster dose, which was safe and well tolerated. Individuals who had a prior COVID-19 infection also had higher immune responses to the vaccine, although increasing age predicted lower responses. Over time, the immunity induced by the vaccines declined.

The investigators enrolled into the trial 1001 patients with diverse hematologic and solid-organ malignancies who were treated at Massachusetts General Hospital Cancer Center. Participants had received 2 doses of the Moderna or Pfizer vaccines or 1 dose of the J&J vaccine and 32 had received a vaccine booster.

The findings were published in the *Journal of Clinical Oncology.* — Ashley Gallagher

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Flu Vaccine May Protect Against Severe Effects of COVID-19

**THE INFLUENZA VACCINE HAS** the potential to provide vital protection against severe effects of COVID-19, according to new study results from the University of Miami Leonard M. Miller School of Medicine in Florida.

The study, which analyzed 37,377 patient records on a global scale, strongly suggests that getting the annual influenza vaccine reduces the risks of deep vein thrombosis (DVT), sepsis, and stroke in patients with COVID-19.

Individuals with COVID-19 who have been vaccinated against influenza were also significantly less likely to visit the emergency department (ED) and be admitted to the intensive care unit (ICU), the study results show.

“Only a small fraction of the world has been fully vaccinated against COVID-19 to date, and with all the devastation that has occurred due to the pandemic, the global community still needs to find solutions to reduce morbidity and mortality,” said senior study author Devinder Singh, MD, chief and program director, Division of Plastic Surgery and professor of clinical surgery at the Miller School of Medicine, in a statement.

The study results show that patients with COVID-19 who had not had the influenza vaccine were up to 20% more likely to be admitted to the ICU. Further, they were significantly more likely to develop DVT (40%) or sepsis (45%), have a stroke (58%), or visit the ED (58%), and the risk of death was not reduced.

In addition, the investigators were able to calculate how many patients with COVID-19 would need to have received the influenza vaccine to avoid an adverse outcome: 176 patients would need to have received it to prevent 1 ED visit within 120 days of testing positive for COVID-19. In addition, 286 patients had to have received their influenza vaccine to prevent 1 case of sepsis. For every 440 patients who were updated on their influenza vaccine, 1 ICU admission was prevented.

Although these results suggest that the influenza vaccine may protect against several severe effects of COVID-19, the study authors strongly recommend that everyone should get a COVID-19 vaccination in addition to their annual influenza vaccine.

More research is needed, but the investigators said they hope the influenza shot can provide increased protection in countries where the COVID-19 vaccine is in short supply or help protect against new breakthrough cases in individuals who are already vaccinated against COVID-19. —Jill Murphy
Vadadustat Shows Positive Safety Data

FDA Is Reviewing a New Drug Application; Prescription Drug User Fee Act Date Is Set for Early 2022

By AISLINN ANTRIM

SEVERAL POSTERS AT THE American Society of Nephrology 2021 Kidney Week reinforced positive safety data with the use of vadadustat in patients with anemia related to chronic kidney disease (CKD), according to a statement from Akebia Therapeutics.1

The FDA is reviewing a new drug application for vadadustat in this patient population, with a Prescription Drug User Fee Act (PDUFA) date set for March 29, 2022.

There are no approved hypoxia-inducible factor prolyl hydroxylase inhibitors to treat anemia related to CKD. If approved, vadadustat would be a first-in-class drug, according to the statement.1

“We are within 5 months of vadadustat’s PDUFA date, which has the potential to be a pivotal catalyst for the company and, if approved, would mean the availability of a novel oral therapeutic for people living with anemia due to chronic kidney disease,” John P. Butler, president and CEO of Akebia Therapeutics, said in the statement.1

In an analysis of pooled safety data from 4 global, open-label, phase 3 randomized studies evaluating the use of vadadustat compared with darbepoetin alfa (DA), investigators found that vadadustat had a comparable treatment-emergent adverse event (TEAE) profile to that of DA. The most common AEs in the vadadustat and DA groups were gastrointestinal disorders (40.2% and 35.2%, respectively); infections and infestations (50.8% and 52.7%); injury, poisoning, and procedural complications (29.5% and 30.7%); and metabolism and nutrition disorders (34.6% and 36.2%).2

Furthermore, the most common drug-related TEAEs in the vadadustat group were diarrhea (2.2%) and nausea (1.2%), which led to study drug discontinuation in 0.4% and 0.2% of patients, respectively. The most frequent serious AEs in both treatment arms were infections and renal and urinary disorders, and TEAEs leading to death in both arms were cardiac arrest (1.7% in both vadadustat and DA groups), cardiorespiratory arrest (0.9% and 1%, respectively), and end-stage kidney disease (1.8% and 1.3%).2

A second poster reviewed data demonstrating that among patients receiving peritoneal dialysis in the INNO2VATE phase 3 trials (NCT02892149 and NCT02865850), the efficacy and safety of vadadustat were comparable with that of DA. Of 3923 patients randomized in the trials, 309 were receiving peritoneal dialysis, among whom the composite rates of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke were similar in both treatment groups.3

Primary and key secondary end points met the prespecified non-inferiority margin, and the incidence of overall TEAEs was 95.5% in the DA arm and 88.2% in the vadadustat arm. Similarly, the incidence of serious TEAEs was 73.2% in the DA arm and 52.6% in the vadadustat arm.3

Finally, among patients in the INNO2VATE trial with anemia and dialysis-dependent CKD, the rate of thrombotic events was similar between the vadadustat and DA treatment arms, according to a third poster.

A total of 1947 patients received vadadustat, whereas 1955 received DA in the 2 studies.4

A first thromboembolic event occurred in 148 patients in the DA arm compared with 169 patients in the vadadustat arm, according to the poster.

Furthermore, 32 patients experienced arterial thrombosis, deep venous thrombosis, or pulmonary embolism in the DA arm compared with 26 patients in the vadadustat arm. Finally, the number of patients who experienced venous thromboembolic events were 28 and 19, respectively.4

“While our review with the FDA is ongoing, we remain confident that the data we have compiled and submitted for review makes a compelling case for approval in dialysis patients,” Butler said in the statement.1

REFERENCES
1. Email.
Which OTC Products Do You Recommend?

Your clinical opinion is more important than ever.

Share the OTC products you recommend to your patients to ensure your voice is heard in our annual survey of pharmacists!

The results of this survey will be published in our annual OTC Guide® and have been featured on national television.

As a thank you for your participation, you will be entered to win a $250 visa gift card!*
Anti-Inflammatory Diet May Lower Risk of Dementia Later in Life

INDIVIDUALS WHO CONSUME AN anti-inflammatory diet, including beans, coffee, fruits, tea, and vegetables, could have a lower risk of developing dementia later in life, the results of a new study show.

After adjusting for age, education level, and gender, each 1-point increase in dietary inflammatory score was associated with a 21% increase in dementia risk.

Those in the top third of individuals who had diets of the highest inflammatory scores were 3 times more likely to develop dementia than those in the lowest third of individuals who had diets of the lowest inflammatory scores.

Individuals who participated in the study answered a food frequency questionnaire that is used to determine the inflammatory potential of an individual’s diet.

The questionnaire was used to gather information on the main food groups consumed during the previous month, including added fats, alcohol, cereals, dairy, fish, fruits, legumes, meat, stimulants, sweets, and vegetables.

A possible dietary inflammatory score can range from –8.87 to 7.98, with a higher score indicating a more inflammatory diet, which includes fewer servings of beans, coffee, fruits, tea, and vegetables.

Investigators found that during the follow-up, an average of 3 years, about 6% of respondents developed dementia. Individuals who developed dementia scored an average of –0.6 compared with the average scores of –0.70 for those who did not develop dementia.

The study was observational and shows an association between brain aging and dementia and diet. The findings were published in Neurology, the medical journal of the American Academy of Neurology.—Ashley Gallagher

Study: Cell-Based Influenza Vaccine Provides Protection in Children

THE RESULTS OF A new study show that a cell-based influenza vaccine can effectively provide protection against the disease in adolescents and children, according to a Murdoch Children’s Research Institute statement.

In the study, the cell-based quadrivalent influenza vaccine (QIVc) produced a significant immune response in children aged between 2 and 18 years. The controlled and randomized study was led by Terry Nolan, PhD, MBBS, and involved 4514 participants across Australia, Estonia, Finland, Lithuania, the Philippines, Poland, Spain, and Thailand.

Overall vaccine efficacy was 54.6%, which met the prespecified end point for success and showed benefit across 3 flu seasons and all 8 countries. QIVc uses a cell-based influenza vaccine production process, which is an alternative to traditional egg-based manufacturing, in which reference influenza viruses are grown in the yolk of fertilized hens’ eggs.

This process can result in mutation of the influenza virus, leading to an antigenic mismatch between the circulating reference and inactivated strains contained within the seasonal influenza vaccine, the study results show. —Jill Murphy

Mindfulness Is Linked to Improved Psychological Health for Cardiac Arrest Survivors

SURVIVORS OF CARDIAC ARREST who practiced mindfulness reported fewer symptoms of anxiety, depression, and posttraumatic stress disorder (PTSD) than survivors who were less mindful, according to preliminary research results presented at the American Heart Association Resuscitation Science Symposium 2021.

Cardiac arrest is often fatal if cardiac pulmonary resuscitation (CPR) or defibrillator shocks are not delivered within minutes to restore normal heart rhythm. Increased survival rates can be partially attributed to better awareness and training among health care professionals and the public to recognize and quickly treat individuals who are experiencing cardiac arrest.

The investigators assessed 129 individuals who had survived cardiac arrest for an average of 5 years and were members of the Sudden Cardiac Arrest Foundation’s online support group. Study participants completed 2 mental health surveys: the Patient Health Questionnaire-4, which assesses anxiety and depression symptoms, and the PTSD Checklist for PCL-5, which tests for PTSD. Participants completed these studies once for baseline and a second time in a 1-year follow-up.

Practicing mindfulness was associated with fewer psychological symptoms, such as anxiety, depression, and posttraumatic stress, according to the results of the study.

Baseline symptoms were moderately predictive of the psychological symptoms at the 1-year mark, meaning that participants who had a greater symptom burden at baseline had a greater number of symptoms at the 1-year evaluation.

Potential limitations of the study include the fact that all participants were White and members of the same online support group, reducing generalizability, and that investigators only measured mindfulness during a single follow-up as opposed to multiple evaluations throughout the study.—Skylar Kenney

FOR REFERENCES, GO TO PHARMACYTIMES.COM/PUBLICATIONS
Help Treat Coughs That Linger After a Cold

Pharmacists Can Advise Patients on Treatments to Find Relief From These Common Winter Ailments

By SARO ARAKELIANS, PHARMD

Colds and influenza can have similar presentations, with both making patients feel miserable, but there are key differences that pharmacists can help identify.
Colds produce gradual symptoms, with slight aches, some fatigue and weakness, mild to moderate chest discomfort and cough, sneezing, sore throat, and stuffiness, but no chills, fever, or headache. Influenza, on the other hand, produces abrupt symptoms, usually including aches, chest discomfort, chills, cough, fatigue, fever, headaches, some congestion and sneezing, and weakness. Cold symptoms may last 3 to 10 days, whereas influenza symptoms may last 7 to 14 days and can even linger for up to 3 weeks. Generally, having influenza is worse than having a cold, and a cold will not result in other serious health conditions. But influenza can lead to bacterial infections, pneumonia, and even hospitalization.¹

The CDC estimates that in the United States between 2010 and 2020, influenza has resulted in around 9 to 41 million illnesses, 140,000 to 700,000 hospitalizations, and 12,000 to 52,000 deaths annually.² With such a high number of patients affected by influenza and its complications, prevention is important. Some cold and flu symptoms can linger, including postinfectious coughs. These are usually dry coughs that may happen at various times of the day, and they can linger for about 3 to 8 weeks after the infection and be bothersome to patients.³

Coughs can linger for many reasons, aside from influenza, including adenovirus, bronchitis, pharyngitis, pneumonia, and respiratory syncytial virus. Some infections may cause the cough receptors in the body to be more sensitive and enter a state of hyper-responsiveness. When this happens, the smallest trigger or lingering infection can make the receptors activate and create a cough that does not go away easily. A lingering cough can also result from the inflammation of the lining of the airways, which could be extensive after recovery from infection. If the cough starts from the lower airways, excessive mucus production may be a responsible factor. Lingering coughs affect 1 of 4 individuals who have influenza or an infection.⁴

Other underlying conditions may also cause a cough to linger. These include asthma, laryngeal pharyngeal reflux (LRP), and obstructive sleep apnea (OSA). Asthma causes the airways to become inflamed, sensitive, and swollen. When an individual who has asthma also develops influenza, additional inflammation in the airways can create many more symptoms, including a lingering, persistent, and severe cough. The inflammation can also cause the asthma to worsen. LRP can cause the acid from the stomach to travel to the upper esophagus and into the throat area, inflaming and irritating the vocal cords, which can trigger a cough.⁴ In addition, OSA can cause aggressive gastroesophageal reflux disease (GERD), airway inflammation, and cough reflex sensitivity.⁴

Postnasal drip is another reason a cough can linger. When an individual catches a cold, mucus builds up, and that drips back into the throat, causing irritation and a need to cough, which is a natural bodily reaction to clear mucus from the system. Unless the mucus is cleared or stopped, the cough continues. The cough resolves either because the flu or infection go away on their own or medication dries up the mucus, which is often a quicker remedy.⁵

A lingering cough can take a toll on a patient, disrupting sleep, social events, and work.⁶ Antibiotics can often treat a cough, but if the cough started because of a cold, antibiotics may not make a big difference.⁶
OTC mucus drying agents are somewhat effective, but a cough may persist. If related to postnasal drip, treatments could include an antihistamine, such as chlorpheniramine maleate (Chlor-Trimeton) or clemastine (Dayhist). The provider may also suggest nasal sprays, such as azelastine (Astelin), ipratropium bromide (Atrovent nasal spray), and fluticasone propionate (Flonase). OTC allergy medications such as fexofenadine (Allegra), loratadine (Claritin), and cetirizine (Zyrtec) are other options. If the cough is related to inflammatory changes, then the provider may suggest inhaled corticosteroids, a leukotriene receptor antagonist such as montelukast (Singulair), or oral prednisone. OTC cough medications are also sometimes recommended, including cough drops, dextromethorphan (Delsym), guaifenesin, and lozenges. Home remedies might include eucalyptus oil, honey with hot water, a humidifier, or a saltwater gargle.

When such remedies do not help and the cough lingers for weeks and cannot be explained by smoking or an underlying lung condition, pharmacists should recommend that patients consult their physician. Such lingering coughs may be symptoms of other serious conditions, such as lung infections or even tuberculosis. A health care provider can evaluate the patient and suggest the best treatment approach, which could include antihistamines, inhalers, or medications for GERD, such as esomeprazole (Nexium) or omeprazole (Prisolec).

CONCLUSION
Colds and influenza can be miserable but suffering from a cough for weeks afterwards can be debilitating and limiting. Pharmacists should recommend that patients seek treatment from their physician if the cough continues for more than a few weeks and cannot be treated with home remedies or OTC medications.

REFERENCES
Here Comes Cold and Flu Season
Help Patients Prepare for These Winter Ailments and Choose the Appropriate Nonprescription Medications

By YVETTE C. TERRIE, BSPHARM, RPH

THE SEVERITY OF THE ANNUAL cold and flu season can be very unpredictable from year to year.

Each year, millions of individuals use the various nonprescription medications marketed for the management and treatment of symptoms that are generally associated with colds and influenza. Pharmacists can be indispensable resources in aiding patients in the selection and proper use of these products. For the management of mild to moderate common cold and influenza symptoms, nonprescription products include analgesics, anesthetics, antihistamines, antipyretics, antiseptics, cough suppressants, decongestants, and expectorants, available in multi-ingredient or single-entity formulations.

RECENT CLINICAL STUDIES AND NEW PRODUCTS
Findings from 2 recently published studies predicted the impact of the 2021-2022 flu season. According to the results from one, there could be 100,000 to 400,000 more influenza hospitalizations in the 2021-2022 flu season compared with a typical season. But the investigators found that the predicted increase in those hospitalizations could be avoided if the percentage of Americans vaccinated against influenza increased from the typical 50% to 75%.1 In the second study, investigators suggested that the 2021-2022 season could see a 20% increase in cases compared with a typical season and that children younger than age 2 would be particularly at risk for influenza because they are unlikely to have any previous exposure to the virus.2 The results of both studies suggested that a flu season with high activity could be avoided if vaccination rates increased by 20% to 50% compared with those in a typical year.3

On November 1, 2021, Reckitt, the manufacturer of the OTC cold, cough, and influenza product Mucinex, announced the launch of a new product line called Mucinex InstaSoothe, which includes lozenges and spray designed to numb, relieve, and soothe sore throat pain. The new products are Mucinex InstaSoothe Sore Throat + Cough Relief Lozenges, Mucinex InstaSoothe Sore Throat + Pain Relief Spray, and Mucinex InstaSoothe Sore Throat + Soothing Comfort Lozenges.4

To gain a better understanding about the impact of sore throat pain on patient quality of life, Reckitt conducted a random double opt-in survey of 2005 Americans between August 26 and August 30, 2021.
The results showed that sore throat pain is 1 of the top 3 most incapacitating symptoms, alongside fever and migraine. Despite this, 55% of individuals are most likely to “power through” a sore throat, meaning that they continue completing housework, going to school, running errands, and working while dealing with difficult sore throat pain.4

CONCLUSION
Prior to recommending any OTC cold and cough products, pharmacists should always screen for a patient’s allergy and medical history and medication profile to check for possible contraindications or interactions. Individuals with medical conditions and/or who are taking other medications should always consult with their primary health care providers before using any nonprescription medications to ascertain appropriateness. During counseling, pharmacists should remind patients to read labels prior to self-administration and to check for expiration dates and ingredients, particularly if using multiple products, to avoid therapeutic duplications or excessive dosing. Pharmacists should also remind patients to adhere to the recommended administration guidelines, dosages, and duration of use. Additionally, remind caregivers and parents to always read all labels prior to administering medications to children and use the calibrated drug measuring devices provided with the selected OTC products when administering liquid medications to ensure proper accuracy and dosage. Caregivers and parents should only give children those OTC products manufactured specifically for the pediatric population, and when in doubt regarding the appropriateness or dose of a medication should consult their pediatricians or pharmacists.

During counseling, pharmacists should stress the importance of obtaining an annual influenza vaccination, as well as suggest various nonpharmacologic measures that may provide relief of cold and influenza symptoms. These include humidifiers, nonmedicated nasal strips, saline nasal sprays, and vaporizers. Patients should also maintain adequate hydration and rest. Encourage patients to seek medical attention from their primary health care provider if a cough lasts more than 14 days, a fever is high, a sore throat persists, symptoms linger or worsen, or there are signs of infection. Study results have shown that the implementation of various preventive measures, such as avoiding direct contact with an individual with a cold or influenza, routine handwashing, and use of hand sanitizers when soap and water are not available, is effective for decreasing or preventing the transmission of colds and influenza.

Pharmacists can be indispensable resources in aiding patients in the selection and proper use of these products.

REFERENCES
Baby Probiotic
Manufactured by SmartyPants
SmartyPants has introduced a baby probiotic that is a liquid designed for newborns to children aged 24 months to support digestive and immune health through pediatric-tested probiotic strains *Pediococcus pentosaceus* KABP-041 and *Bifidobacterium longum* KABP-042. The product is free of artificial flavors and sweeteners, genetically modified organisms, gluten, and synthetic colors.

FOR MORE INFORMATION:
smartypantsvitamins.com

Liquid-filled Aspirin Capsules
Manufactured by Valzalore
PLx Pharma has developed a liquid-filled aspirin capsule that parent company, Valzalore, says is the first and only one on the market. The capsules each contain 81 mg, which is usually the dose that physicians recommend for low-dose aspirin therapy, and also come in a 325-mg dose. The liquid capsules are designed to protect the stomach but deliver fast absorption for fever reduction and pain relief.

FOR MORE INFORMATION:
vazalore.com

Alocane Maximum Strength First Aid Antiseptic Spray
Manufactured by Quest Healthcare
Quest Products has introduced a 4% lidocaine spray with Alocane Maximum Strength. The spray is designed for a no-touch application and a continuous spray. It is an alcohol-free product that kills 99% of germs while cleaning wounds. The company said the bottle can be 100% emptied.

FOR MORE INFORMATION:
questhealthcare.net

Skin Renewing Nightly Exfoliating Treatment
Manufactured by CeraVe
CeraVe has launched a Skin Renewing Nightly Exfoliating Treatment that is formulated for brighter skin. It is optimized to boost hydration and minimize the appearance of fine lines and wrinkles. The product contains 5% glycolic and lactic acids to increase cell turnover and promotes a natural exfoliate without causing flaking.

FOR MORE INFORMATION:
cerave.com
OTC Cases

Nasal Congestion

By RUPAL PATEL MANSUKHANI, PHARMD, FAPHA, NCTTP; AND AMMIE J. PATEL, PHARMD, BCACP, BCPS

CASE 1: Allergy-Related Nasal Congestion

RS is a 38-year-old woman who has nasal congestion and typically has seasonal allergies. RS has been taking loratadine 10 mg daily for the past few weeks but has had no relief. She wants to know if there is anything stronger she can take over the counter. What recommendations should the pharmacist make?

Typically, RS can use antihistamines, decongestants, or intranasal corticosteroids to treat her symptoms. Because she is already taking an antihistamine, she should try an intranasal corticosteroid. The FDA has approved the following intranasal corticosteroids for nasal symptoms: budesonide (Rhinocort Allergy Spray), fluticasone furoate (Fiorin Sensistim), fluticasone propionate (Flonase Allergy Relief), and triamcinolone acetonide (Nasacort Allergy 24HR). RS can try any of these intranasal corticosteroids, as all of them are once-daily medications. Both formulations of fluticasone are approved for ophthalmic symptoms, such as watery eyes. If her symptoms do not improve, RS should see her primary care provider.

CASE 2: Nasal Congestion With Vaccination

BL is a 10-year-old girl who comes to the pharmacy with her mother RL complaining about a runny nose, though she has no other symptoms. BL was tested by her pediatrician for COVID-19 influenza, and streptococcus, but all the test results came back negative. RL was planning on getting BL vaccinated with the newly approved pediatric COVID-19 vaccine. Although she would like BL to receive the vaccination today, she is concerned about her runny nose. What should the pharmacist advise?

The CDC says that vaccines do not affect mild illnesses, such as a cold, cough, ear infection, low-grade fever, or runny nose. In addition, the pharmacist should advise RL that mild illnesses do not affect how well the body responds to a vaccine. Vaccines have a small amount of the bacteria and viruses with which BL would normally come in contact. Therefore, her immune system can handle getting vaccinated today and fighting off her runny nose at the same time. Let RL know that vaccines can cause mild adverse effects (AEs), such as a low-grade fever or soreness or swelling at the injection site. AEs typically resolve within 24 hours, but BL can place a cool, wet washcloth on the sore area. If symptoms persist, she can also take fever- or pain-reducing medications, such as acetaminophen or ibuprofen. RL should follow package instructions on pediatric dosing.

» Continued on page 42
OTC Cases

CASE 3: Cold or Cough With Diabetes

LH is a 54-year-old man who has a dry cough and nasal congestion. He has felt sick for the past few days, so he went to see his health care provider. LH’s COVID-19 and flu tests came back negative. His physician recommended he buy an OTC medication to treat his cold and cough. LH would like a sugar-free medication, as he recently received a diagnosis of diabetes. He does not take any medications. What should the pharmacist recommend to LH?

LH is complaining of 2 symptoms: dry cough and nasal congestion. Most dry coughs are caused by postnasal drip; therefore, he can take a first-generation antihistamine, such as diphenhydramine. For the nasal congestion, LH may benefit from the antihistamine but can also use nasal decongestants, such as pseudoephedrine. If he chooses to use a nasal decongestant, he should monitor his blood glucose closely, as it may raise his blood sugar level. There are specific OTC formulations with less sugar, such as Diabetic Tussin syrup or Robitussin sugar free. However, these products would not be appropriate for LH because he does not need an expectorant at this time. If he needs cough drops or lozenges for the sore throat, he could consider sugar-free lozenges, such as those from Cepacol, Cold-Eeze, or Ricola.

CASE 4: Fever and Nasal Congestion

TY is a 38-year-old man who has had a fever and nasal congestion for the past 3 days. He also complains of occasional shortness of breath. TY went to a local pharmacy to get tested for COVID-19, but his results were negative. He still feels sick and wants recommendations on how to treat the fever and nasal congestion. What recommendations should the pharmacist provide?

Because TY is complaining of fever and shortness of breath, he should be referred to his primary care provider to be evaluated. Although he tested negative for COVID-19, he should also get tested for influenza and other viruses that may be circulating. Patients who have a fever lasting more than 3 days should be referred to a physician. Other patients who should be referred include those who complain of a cough that gets worse or lasts more than 7 days, dizziness, nasal congestion, new onset of symptoms, pain, redness, or sleeplessness. TY should also stay hydrated and use an OTC electrolyte supplement with low sugar.
IN SEASON 2 OF THE television series “Friends,” unvaccinated Phoebe contracts a childhood viral infection and gives it to her paramour. Their pruritis is so severe that they don oven mitts to keep them from disturbing the lesions. Technically, the episode should be called “The One With the Varicella,” but as the audience is laypeople, it is called “The One With the Chickenpox.” The itching creates comedy on the show. But it is no laughing matter in real life. Typically, chickenpox is considered a disease of childhood, but adults who have not had it or been vaccinated against it can also contract the disease. In healthy people, it is usually a mild and self-limiting illness.1

SPOTTY ERUPTION

The word varicella, is a derivative or diminutive of the Latin variola, which means smallpox, or “spotted.”2 Clinicians were not sure that chickenpox and smallpox were different infections until the 19th century.3,4 In many Eastern European languages, the word used for chickenpox often translates to “wind pox,” reflecting its easy, rapid spread.5-7 It can be spread by direct contact and respiratory inhalation of aerosols from vesicular fluid in skin lesions or coughing or sneezing.1

Chickenpox is very contagious. In the United States, more than 90% of individuals who have not been vaccinated or previously had the disease who are exposed to this virus will develop the disease. Contagion can occur as early as 3 days before the onset of the rash to 4 days after it erupts.8 Immunocompromised individuals, infants, and pregnant women are at increased risk.1

Chickenpox manifests as a vesicular eruption: a red spotty rash that has water-filled blisters. It is usually accompanied by low-grade fever and malaise.1 After an incubation period of 10 to 21 days, it usually starts on the back, chest, and face and then spreads to the rest of the body. A typical case lasts 5 to 7 days, at which point the lesions crust. Complications are possible (see Table 1), with bacterial skin sepsis most common in children younger than 5 years. Older children are more likely to develop acute cerebellar ataxia, and varicella pneumonia is the most common complication in adults. In general, it is a more serious condition in adults than in children.1

VACCINATION WORKS WONDERS

Since 1995, the Advisory Committee on Immunization Practices has recommended a live attenuated varicella vaccine to prevent chickenpox in healthy children as a routine vaccine.9 It may also reduce the incidence of chickenpox in healthy unvaccinated children exposed to varicella-zoster virus if administered within 3 days of exposure. Vaccinated children who develop chickenpox usually have mild disease. The recommendation is 2 doses of varicella vaccine for all children, adolescents, and adults without
evidence of immunity. If an individual misses the second dose, receiving the second dose as soon as the gap is identified provides the best protection against the disease.9

When individuals contract chickenpox, they should follow standard precautions and contact precautions until lesions are dry and crusted. Table 210,11 lists appropriate interventions for typical disease.

In addition, pharmacists and health care providers should actively counsel caregivers and patients not to use aspirin or aspirin-containing products to relieve fever from chickenpox because it has been associated with Reye syndrome. In addition, the American Academy of Pediatrics recommends avoiding treatment with ibuprofen, if possible, because it has been associated with life-threatening bacterial skin infections.

CONCLUSION
The CDC indicates that varicella vaccination prevents more than 3.5 million cases of varicella, 9000 hospitalizations, and 100 deaths every year in the United States.1 Although now less of a problem than in the past, chickenpox still occurs, and pharmacy staff members will sometimes field questions about it. In most cases, management is simple, although patients will find the infection bothersome and the itching intrusive.

REFERENCES
3. Trouseau A. Lectures on Clinical Medicine. Lindsay & Blakiston; 1873.

TABLE 1. Complications of Chickenpox

<table>
<thead>
<tr>
<th>Complications of Chickenpox</th>
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<tbody>
<tr>
<td>Most likely:</td>
</tr>
<tr>
<td>• Bacterial infections of the skin and soft tissues</td>
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<tr>
<td>• Pneumonia (adults)</td>
</tr>
<tr>
<td>Severe:</td>
</tr>
<tr>
<td>• Bacterial infections, such as bacterial pneumonia, necrotizing fasciitis, osteomyelitis, septic arthritis, septicemia, and toxic shock syndrome</td>
</tr>
<tr>
<td>• Cerebellar ataxia</td>
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<tr>
<td>• Encephalitis</td>
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<tr>
<td>• Hemorrhagic conditions</td>
</tr>
<tr>
<td>• Viral pneumonia</td>
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<tr>
<td>Potential long term:</td>
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<tr>
<td>• Shingles</td>
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</table>

TABLE 2. Management Strategies for Typical Cases of Chickenpox

<table>
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<tr>
<th>Management Strategies for Typical Cases of Chickenpox</th>
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<tbody>
<tr>
<td>• <strong>Active treatment:</strong> The antiviral acyclovir can be used for individuals at elevated risk for serious illness and should ideally be started within 24 hours after the first sign of rash.</td>
</tr>
<tr>
<td>• <strong>Cleaning:</strong> Chlorine bleach kills varicella, as do other detergents, disinfectants, and heat.</td>
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<tr>
<td>• <strong>Fever:</strong> Use nonacetaminophen to relieve fever from chickenpox.</td>
</tr>
<tr>
<td>• <strong>Itching:</strong> Calamine lotion and cool baths with baking soda or colloidal or uncooked oatmeal.</td>
</tr>
<tr>
<td>• <strong>Postexposure prophylaxis:</strong> Varicella-zoster immune globulin preparation is indicated for individuals at high risk for severe disease who lack evidence of immunity to varicella and for whom varicella vaccine is contraindicated.</td>
</tr>
<tr>
<td>• <strong>Skin integrity:</strong> Trim fingernails and avoid scratching to prevent spreading the virus and skin infections. If patients disturb a blister, they should wash their hands with soap and water for at least 20 seconds.</td>
</tr>
</tbody>
</table>
Celecoxib and Tramadol Hydrochloride (Seglentis)
Manufactured by Esteve Pharmaceuticals

The FDA has approved celecoxib and tramadol hydrochloride for the management of acute pain that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Celecoxib is a nonsteroidal anti-inflammatory drug combined with tramadol, a Schedule IV opioid analgesic. It is a cocrystal formulation that is intended to optimize the properties of each drug for the management of pain.

FOR MORE INFORMATION:
esteve.com

Pembrolizumab (Keytruda)
Manufactured by Merck

Pembrolizumab (Keytruda) has been approved for use with chemotherapy, with or without bevacizumab (Avastin). It is intended to be used for individuals with metastatic, persistent, or recurrent cervical cancer whose tumors have a programmed death-ligand 1 combined with a positive score of 1 or higher. The FDA also granted approval for pembrolizumab monotherapy for individuals with metastatic or recurrent cervical cancer whose disease progressed during or after chemotherapy.

FOR MORE INFORMATION:
merck.com

Varenicline Nasal Spray (Tyrvaya)
Manufactured by Oyster Point Pharma

Varenicline is a nasal spray approved by the FDA as the first and only nasal treatment for signs and symptoms of dry eye disease. It is a solution to bind the cholinergic receptors to activate the trigeminal parasympathetic pathways and increases the basal tear film. The treatment is a new option for individuals who may have difficulties administering eye drops.

FOR MORE INFORMATION:
oysterpointrx.com

Naloxone HCL Injection (Zimhi)
Manufactured by Adamis Pharmaceuticals Corporation

The FDA has approved Adamis’ Naloxone HCL Injection, Zimhi 5 mg/0.5 mL/. It is a high-dose naloxone injection used to treat opioid overdose. Naloxone blocks and reverses the effects of the opioid and is widely considered treatment for immediate administration. Zimhi is intended to be administered immediately by a caregiver but should not replace emergency medical care following injection.

FOR MORE INFORMATION:
adamispharmaceuticals.com
Saphnelo From AstraZeneca

By MONICA HOLMBERG, PHARMD, BCPS

THE FDA HAS APPROVED ANIFROLUM-AB-FNIA injection (Saphnelo; AstraZeneca) for the treatment of adults with moderate to severe systemic lupus erythematosus (SLE) who are receiving standard therapy. The approval carries the limitation that the efficacy of Saphnelo has not been evaluated in patients with severe active central nervous system lupus or severe active lupus nephritis and is not recommended in these situations.1

Symptoms of SLE include fatigue, fevers, joint swelling, pain, and rashes. Approximately 5 million individuals worldwide have a form of lupus, and more than half of those with SLE develop permanent organ damage.2

PHARMACOLOGY AND PHARMACOKINETICS

Saphnelo is a fully human IgG1κ monoclonal antibody that binds to subunit 1 of the type 1 interferon-α/β receptor (IFNAR) with high affinity and specificity, which causes the biologic activity of type 1 IFNs to be blocked. Saphnelo also reduces the levels of cell surface IFNAR1 available for receptor assembly. By blocking receptor-mediated type 1 IFN signaling, IFN-responsive gene expression and downstream inflammatory and immunological processes are inhibited. Type 1 IFN inhibition also blocks plasma cell differentiation and normalizes peripheral T-cell subsets. Type 1 IFNs are involved in the pathogenesis of SLE, with approximately 60% to 80% of adults with active SLE demonstrating elevated levels of type 1 IFN inducible genes.1,2

Saphnelo displays nonlinear pharmacokinetics. Steady-state plasma concentration is observed by day 85, and the estimated systemic clearance is 0.193 L/day.1

DOSE AND ADMINISTRATION

The recommended dose of Saphnelo is 300 mg administered as a 30-minute intravenous infusion every 4 weeks. It is supplied as a 300-mg/2 mL solution in a single-dose vial. Saphnelo requires dilution prior to administration.1

CLINICAL TRIALS

Saphnelo was evaluated in 3 double-blind, multicenter, placebo-controlled, randomized studies in adults with moderate to severe SLE who were receiving standard therapy. In trial 1, 305 patients were randomized 1:1:1 to receive Saphnelo 300 mg, Saphnelo 1000 mg, or a placebo for up to 52 weeks. The primary end point was a combined assessment of the SLE Responder Index (SRI-4) and the sustained reduction in oral corticosteroid use at week 24. Both groups receiving Saphnelo showed improvement compared with those using the placebo.

Trial 2 randomized 457 patients 1:2:2 to receive Saphnelo 150 mg, Saphnelo 300 mg, or a placebo. The primary end point was improvement in disease activity as measured by SRI-4 at week 52, which the trial did not meet.

In trial 3, 362 patients were randomized 1:1:1 to receive Saphnelo 300 mg or a placebo. The primary end point was improvement in disease activity as assessed by the British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) at week 52. The trial found Saphnelo to be more effective than the placebo.1,2

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Treatment with Saphnelo is contraindicated in patients with a history of anaphylaxis to the medication. Patients using Saphnelo have experienced serious and sometimes fatal infections. In controlled trials, Saphnelo increased the risk of herpes zoster and respiratory infections. The medication should not be initiated in patients with an active infection, and the individual benefits and risks should be considered in patients with a chronic or severe infection. Interruption of treatment should be considered if a new infection occurs. Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported after administration of Saphnelo. If a serious hypersensitivity or infusion-related reaction occurs, the infusion of Saphnelo should be stopped immediately and appropriate therapy initiated. Because there is an increased risk of malignancies with the use of immunosuppressants, the individual benefits and risks in patients with known risk factors for malignancy should be considered before beginning treatment. The concomitant use of live or live-attenuated vaccines should be avoided. The combination of Saphnelo and other biologic therapies has not been evaluated and is not recommended. The most common adverse reactions are bronchitis, cough, herpes zoster, infusion-related reactions, nasopharyngitis, and upper respiratory tract infections.1

REFERENCES


December 2021 pharmacytimes.com
Watch for 3 Types of Errors With Transdermal Patches

Clonidine, Estradiol, Fentanyl, and Scopolamine Are Involved Most Frequently, an ISMP Review Shows

BY MICHAEL J. GAUNT, PHARMD

AN INFLUX OF REPORTS INVOLVING transdermal medication patches submitted to the Institute for Safe Medication Practices (ISMP) National Medication Errors Reporting Program (MERP) prompted ISMP to look at all patch-related reports it had received within the past 4 years.

More than 50 reports associated with 12 different transdermal medication patches were analyzed. Patches most frequently involved in reported errors included clonidine (n = 10), estradiol (n = 6), fentanyl (n = 16), and scopolamine (n = 7). Three of the error types identified during the analysis are described below.

LACK OF AWARENESS

The ISMP has received 7 reports associated with practitioners failing to identify patches on the patient’s or resident’s skin (which had been applied prior to admission), finding multiple patches on patients that had been left on longer than prescribed, and/or not removing an old patch when applying a new patch. Five of these events involved fentanyl patches. In 1 case, 2 patches were found on an unexpectedly somnolent patient during rounds. In another case, 3 100-mcg/hour fentanyl patches were found on an oversedated patient with respiratory depression. We have also received reports of finding multiple nicotine patches and rivastigmine (Exelon) patches used to treat Alzheimer disease on patients during their admission. Because many patches are beige or clear, they might easily be missed on the skin of some patients.

WRONG-DOSE DISPENSING ERRORS

The ISMP received 6 reports of dispensing the wrong dose of patches that are available in more than 1 strength. One of these errors was published in the December 2020 issue of Pharmacy Times®. An order for 50-mcg/hour fentanyl patches included “72 hours” for the duration of patch application. The “72” was mistaken as the strength, leading to the erroneous dispensing of a 75-mcg/hour instead of the intended 50-mcg/hour fentanyl patch. Including the duration of controlled drug delivery (ie, 72 hours) in the order and the drug description field contributed to this dispensing error. In another event, a pharmacy technician filling an order for rivastigmine patches 9.5 mg/24 hour for a long-term care (LTC) resident prepared 13.3-mg/24-hour patches and failed to notice the error because he had bypassed
the usual barcode scanning process. The pharmacist verifying the product did not notice a discrepancy between the 13.3-mg/24-hour patches and the image of the 9.5-mg/24-hour patches on the computer screen and dispensed the patches.

**PATCH COVER APPLIED WITHOUT THE MEDICATION PATCH**

The ISMP received 5 reports of applying a clonidine patch adhesive cover directly to the skin without first applying the clonidine patch. In 1 case, only the adhesive cover was retrieved from the carton and applied. In all other cases, the active medication patch was accidentally discarded. The errors contributed to uncontrolled blood pressure. The clonidine transdermal system (Catapres-TTS) is packaged in a carton containing individually labeled pouches of 4 clonidine patches and 4 adhesive covers. Once removed from the pouches, the clonidine patch is a different color, shape, and size than the adhesive cover, but the patch and cover do not specify which is which. Application of the adhesive cover is optional. The cover should be applied directly over the clonidine patch only if the patch begins to separate from the skin.

**RECOMMENDATIONS**

Treating patients receiving medication patches can be challenging, given the variety of patch characteristics. To prevent the types of errors described above, consider the following recommendations:

- Build a medication administration record note to remind LTC nurses to apply the clonidine medication patch and not just the cover. If the adhesive cover is used over the medication patch, it is best for nurses to label the adhesive cover with the drug name, strength, and date, before applying it.
- Create electronic prescribing medication patch order sentences that include the appropriate application frequency.
- Dispense the clonidine medication patch and adhesive cover in a zipper storage bag with a label explaining the 2 components of the product for LTC patients.
- Do not include the duration of medication delivery in the patch drug description field, which could be confused as the dose, for fentanyl patches. The patient’s dosing instructions should communicate the frequency of changing the patch.
- Employ barcode scanning during dispensing to ensure correct product selection.
- Explore ways to assist patients to maintain an up-to-date record of all their medications (including any OTC products and patches), such as providing them with a current medication list at each encounter.
- Give LTC nurses a documentation prompt each shift to verify placement of each medication patch and to record the location, if necessary.
- Provide verbal and written education to caregivers and patients about the use of patches. Verify the patient’s understanding of the information.
- Use scripted prompts or questions to collect a detailed medication history from each patient. Specifically ask patients about the use of any type of patch.

**REFERENCE**

Pharmaceutical Manufacturers Pay Hundreds of Millions to Settle Price-Fixing Charges

Apotex, Sandoz, and Taro Allegedly Cause an Increase in Drug Costs for Federal Health Care Programs and Beneficiaries

By SKYLAR KENNEY

THREE PHARMACEUTICAL MANUFACTURERS HAVE AGREED to pay a combined total of $447.2 million to resolve alleged violations of the False Claims Act related to price-fixing conspiracies for several generic drugs, according to the US Department of Justice (DOJ).

The 3 companies—Apotex Corporation, Sandoz Inc, and Taro Pharmaceuticals USA, Inc.—allegedly caused drug prices to increase for federal health care programs and beneficiaries.

“Conspiring to raise prices on generic medications is illegal and could prevent patients from being able to afford their needed prescription drugs,” said Special Agent in Charge Maureen R. Dixon of the Philadelphia Regional Office of the Department of Health and Human Services, Office of the Inspector General (HHS-OIG), in a statement.

“Americans have the right to purchase generic drugs set by fair and open competition, not collusion,” she said. “HHS-OIG along with our law enforcement partners will continue to investigate allegations of companies engaging in actions that put the public and the Medicare program at risk.”

The government alleges that the 3 companies paid and received compensation through arrangements on price, supply, and customer allocation with other pharmaceutical manufacturers for certain generic drugs manufactured by the companies, which is not allowed under the Anti-Kickback Statute. That statute prohibits companies from making or receiving payments in return for arranging the purchase or sale of items, including drugs, for which payment may be made by a federal health care program.

“Protecting TRICARE, the health care system for US military members and their dependents, is a top priority for the Department of Defense, Office of Inspector General, Defense Criminal Investigative Service (DCIS),” said Special Agent in Charge Patrick J. Hegarty, DCIS Northeast Field Office, in a statement.

“When pharmaceutical corporations artificially inflate prices, they undermine the integrity of TRICARE and place an unnecessary financial burden on the program,” he said. “The settlement agreements announced today are the result of a joint effort and demonstrate the ongoing commitment of DCIS to work with our law enforcement partners, DOJ Civil Frauds and the USAO-EDPA [US Attorney’s Office-Eastern District of Pennsylvania], to investigate health care fraud.”

Apotex Corporation has agreed to pay $49 million in connection with its sale of pravastatin, a drug used to treat high cholesterol and triglyceride levels. Sandoz Inc has agreed to pay $185 million. The drugs at issue produced by Sandoz include benazepril HCTZ, which is used to treat hypertension, and clobetasol, a corticosteroid used to treat skin conditions. Taro Pharmaceuticals USA, Inc, has agreed to pay $213.2 million. The Taro drugs allegedly implicated in this scheme include etodolac, a nonsteroidal anti-inflammatory drug used to treat arthritis and pain, and nystatin-triamcinolone cream and ointment, a combination of an antifungal medicine and steroid used to treat certain types of skin infections. All 3 companies previously entered into deferred prosecution agreements with the federal Antitrust Division to resolve related criminal charges.

“These civil settlements are another achievement in my office’s efforts to hold generic drug companies accountable for the consequences arising from price-fixing schemes, including the harm to federal health care programs,” Acting US Attorney Jennifer Arbittier Williams for the Eastern District of Pennsylvania, said in a statement. “We will continue to aggressively pursue these violations of the Anti-Kickback Statute and the False Claims Act and obtain significant recoveries.”

In addition to these settlement agreements, each company also entered a 5-year corporate integrity agreement with OIG. The provisions of these agreements include unique internal monitoring and price transparency provisions, as well as a requirement that the companies implement compliance measures, including risk assessment programs, compliance-related certifications from company board members and executives, and executive recoupment provisions.

“These kickback schemes harm Medicare, Medicaid, and patients,” Chief Counsel Gregory E. Demske for the Inspector General at HHS, said in a statement. “The [corporate integrity agreements] promote transparency and accountability by requiring the companies to report price-related information to OIG and mandating individual certifications by key executives involved in pricing and contracting functions.”
Everolimus
Marketed by Biocon Ltd

Compare To: Afinitor
Biocon has developed Everolimus tablets, a generic version of Novartis’ Afinitor. The dose strengths are 2.5, 5, 7.5, and 10 mg, with the 10 mg as a day 1 launch. Everolimus treats certain types of cancers and tumors, and the company states that its aim is “affordable, lifesaving medicines.”

FOR MORE INFORMATION:
biocon.com

Vortioxetine
Marketed by Zydus Cadila

Compare To: Trintellix
Zydus Cadila has released vortioxetine tablets in 5-, 10-, and 20-mg dose strengths. The drug is a generic for Trintellix that is used to treat depression. Vortioxetine is a serotonin receptor modulator and selective serotonin reuptake inhibitor. The medication is used to restore the balance of serotonin in the brain.

FOR MORE INFORMATION:
zyduscadila.com
**Generic Product News**

**Vigabatrin for Oral Solution**
Marketed by Aurobindo Pharma

**Compare To:** Sabril
Vigabatrin for oral solution is used as the generic of Sabril. It is a 500-mg oral solution from Aurobindo Pharma approved by the FDA for patients 10 years and older. It is an adjunctive therapy that is used to treat refractory complex partial seizures but can also be used for monotherapy for pediatric individuals aged 1 month to 2 years with infantile spasms.

FOR MORE INFORMATION:
aurobindousa.com

**Carmustine for Injection**
Marketed by Dr. Reddy’s Laboratories

**Compare To:** BiCNU
Dr. Reddy’s Laboratories has launched carmustine as a generic version of BiCNU. Carmustine is used to treat symptoms of brain tumors, Hodgkin disease, multiple myeloma, and non-Hodgkin lymphoma. It is an injectable lyophilized powder packaged in single-dose vials containing 100 mg of carmustine and 3 mL sterile diluent.

FOR MORE INFORMATION:
dreddys.com

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Wrongful Death Case Is Tied to Additive Effects of Multiple Drugs

Trial Court Judge Places Limits on Testimony of Widow’s Pharmacy Expert Witness and Dismisses Lawsuit

By JOSEPH L. FINK III, JD, DSC (HON), FAPHA, BSPHARM

Pharmacy Law

ISSUE OF THE CASE

A patient who allegedly had consumed a mixture of 3 prescription medications met his demise, and the judge dismissed the widow’s lawsuit against the chain pharmacy. Was that the correct decision, and what was the proper role of the widow’s expert witness pharmacist?

FACTS OF THE CASE

A worker at a factory in a Midwestern state had completed his usual night shift and returned home at 7:30 AM. He met his wife in the driveway and spoke for about an hour. At that time, the wife noticed nothing unusual about his communication or conduct. She left for her place of employment, and her husband entered the house. He died at approximately 3 PM while sleeping. The cause of death was identified as alprazolam, fentanyl, and oxycodone intoxication.

Prior to his death, a pharmacist at a national pharmacy chain had dispensed fentanyl patches to him pursuant to a prescription issued by his treating physician. The widow filed a wrongful death lawsuit against both the pharmacy chain and the prescriber.

The crux of the argument advanced regarding the pharmacy chain was that the pharmacist employed by the chain responsible for the transaction “violated the standard of care to be expected of a reasonably competent pharmacist under the circumstances by filling the prescription knowing that [the husband] worked in a high-heat environment and that he had succumbed to an increased level of fentanyl due to heat exposure at work.”

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The surviving spouse had lined up a pharmacist to testify as an expert witness about how a high-temperature working environment could potentiate the effects of the fentanyl. The trial court judge limited the testimony and prevented the witness from testifying that the patient had “succumbed to an increased level of fentanyl due to heat exposure.”

An expert witness is typically brought in during a trial to explain the issues at hand in an understandable fashion to allow the jurors to make an informed decision. Usually, the expert witness is asked to indicate whether another pharmacist with similar education, experience, and skill who is
operating under similar circumstances would rea-
sonably reach the same conclusion or take the same
action as the actual pharmacist under review did.
Either side, or both, can proffer an expert witness,
but the judge must deem the individual’s back-
ground acceptable for him or her to participate.
The attorney for the pharmacy chain made a
motion to dismiss the lawsuit by asking for a sum-
mary judgment. A summary judgment motion asks
the trial court judge to decide and declare that there
is no genuine dispute regarding any material fact at
issue in the lawsuit and that the party making the
motion is entitled to judgment. The trial court judge
granted the motion and dismissed the lawsuit. The
surviving spouse filed an appeal with the relevant
state court of appeals, arguing that the decision of
the trial court judge was erroneous.

THE RULING
The court of appeals judges agreed with the trial
court and upheld the dismissal of the lawsuit.

THE COURT’S REASONING
The appellate court judges pointed out that the
plaintiff/spouse presented no evidence regarding
her husband’s working conditions on the day of
his death. Despite that, the plaintiff had presented
during pretrial proceedings the deposition of the
pharmacy expert witness that contained his expert
opinions regarding the relationship between the
fatality and working conditions.
The attorney for the surviving spouse did not
challenge the trial court’s decision to limit the tes-
timony of the expert witness when the appeal was
filed. The appellate judges pointed out that the trial
court had “prohibited him from testifying that [the
husband] had succumbed to an increased level of
fentanyl due to heat exposure.”

The attorney for the pharmacy chain made a
motion to dismiss the lawsuit by asking for a sum-
mary judgment.

Further, the trial court additionally specified
that the proffered expert witness “could not
discuss the factual circumstances surround-
ing his use of the patch while at work” because
he did not know specific details regarding the
deceased husband’s job.

When the trial court judge was considering
the motion for dismissal made by the defendant
pharmacy chain, the plaintiff/spouse submitted
2 affidavits from the proposed pharmacy expert
supporting her position that the summary judg-
ment should not be granted and the case should
not be dismissed. The trial court judge did not
accept the 2 additional submissions by the phar-
macist expert witness in support of the position
of the plaintiff/spouse, and that decision by
the presiding officer in the court below was not
challenged on appeal.

The appellate judges concluded that though
the widow “argues that the record contains sub-
stantial evidence that creates a genuine issue
of material fact as to the pharmacy’s liability,”
they did not concur.
The judges stated that “we have thoroughly exam-
ined the record, and we conclude that there are
no admissible facts to support [the widow’s] claim
that the cause of death was tied to a duty [the chain
pharmacy] had breached by filling [the husband’s]
 prescription for fentanyl patches.”
They affirmed the trial court’s “grant of summary
judgment for the [pharmacy chain].”
Legislative Focus

Pharmacists Play Role in Preventing DUIDs
Offering Individual Advice and Counseling to Patients Can Help Combat the Risks of Driving Under the Influence of Prescription Drugs

By CHLOE M. LINDSEY AND JOSEPH L. FINK III, BSPHARM, JD, DSC (HON), FAPHA

MOST OF US KNOW ABOUT the dangers of driving under the influence (DUI) of alcohol, which is also known as driving while intoxicated (DWI). In 2018 alone, the US alcohol-related impaired driving death toll reached an estimated 10,511 individuals, according to the CDC.1 But in addition to alcohol and illicit substances, medications commonly prescribed to patients can also impair driving.

The National Highway Traffic Safety Administration (NHTSA) has started a campaign called “There’s More Than One Way to Be Under the Influence,” to enhance awareness about the effects that OTC and prescription medications can have on driving.2

Information found on the NHTSA website states that “10% of weekday, daytime drivers surveyed tested positive for prescription and/or over-the-counter drugs.”2

Although this information demonstrates the large portion of drivers using OTC or prescription medications, it did not test for driving impairment, which is where the real risk lies. Medications commonly known to cause impairment include, but are not limited to, antianxiety medications, antidepressants, antihistamines, antihypertensives, and benzodiazepines.3

Furthermore, there is a common misconception that if driving impairment is caused by a prescription drug then it must have been caused by the patient’s incorrect usage or overdosing, which is not always the case. Even if taken properly, some prescription medications can still affect coordination and judgment, cause nausea, and induce drowsiness.4 All these adverse effects can impair one’s ability to drive and pose a risk for patients who drive and those around them.

In many states, laws are in place that recognize driving under the influence of certain medications as driving impairment. These are known as driving under the influence of drugs (DUID) per se laws.4 In July 2010, a report by the NHTSA reviewed 15 states in which these specific laws had been enacted. The laws are unlike alcohol-impairment laws in that there is no acceptable limit at which these drugs can be found in the system, and the report compared them to zero-tolerance laws.4

Although these DUID per se laws vary state by state, each lays out a list of which medications are considered unacceptable to use while driving. So what happens to patients who take these medications legally and as prescribed? In many of these laws there is a section that either exempts the person from guilt if the medication was taken in accordance with a valid prescription or if a valid prescription can be used as an affirmative defense against the charge.4

Some of these states, such as Iowa, have even specifically included pharmacist-related exemptions of their per se laws, stating “...or if the substance

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was dispensed by a pharmacist without a prescription pursuant to the rules of the board of pharmacy examiners, if there is no evidence of the consumption of alcohol and the medical practitioner or pharmacist had not directed the person to refrain from operating a motor vehicle."  
Pharmacists can help combat the growing problem of DUID by offering individual patient counseling and education. Although labels on prescription bottles alert patients that a medication alone or in combination with alcohol may impair their ability to drive, there is no guarantee that they are reading these warnings. Pharmacists should use their positions in the community to verbally inform patients of the risks, ensuring they understand that they should not get behind a wheel before knowing how their medications affect their ability to drive.  

Another way that pharmacists can help in this regard is to provide information and share resources with their communities. Those in states with DUID per se laws could post the list of medications the law applies to in an area of the pharmacy where patients can read it as they wait to pick up their prescriptions. Pharmacists can also share resources such as the American Automobile Association Foundation for Traffic Safety’s Roadwise Rx online tool, which allows patients to check their medications for driving impairment–related adverse effects for free. In addition, pharmacists can use journals, newspapers, and social media platforms to spread awareness of medication-related driving impairment and reach the patient audience.  

REFERENCES
CARL WILHELM SCHEELE (1742-1786) was a pharmaceutical chemist who discovered chlorine, manganese, and oxygen.

Born in an area of Germany that was under Swedish jurisdiction, he became a pharmacist’s apprentice in Gothenburg, Sweden, at age 15 years. During his apprenticeship, he developed an interest in chemistry and spent much time experimenting with and reading about chemicals available in the pharmacy. Several years later, he moved to Malmö, Sweden, to work at a pharmacy and also began working with scientists at Lund University.

He moved several times to work in different pharmacies with various scientists. Scheele settled in a small town calling Köping to become an apothecary with his own business. He studied at the Royal Swedish Academy of Sciences.

Scheele was known for his outstanding analytical skills in studying gases, despite his lack of equipment. He did not have a proper oven for generating heat and analyzing minerals. Scheele also used simple instruments that were borrowed or improvised.

He first contributed to the discovery of tartaric acid, later discovering chlorine and barium oxide. Scheele worked with black magnesia and manganese but was unable to isolate the manganese.

Working in all fields of chemistry, he studied mineral acids, including arsenic, molybdcic, and tungstic. Scheele determined the properties of hydrofluoric acid and its salts, distinguished graphite and molybdenite, studied the effect of light on silver salts, and worked on phosphorous and its compounds.

He also studied and isolated for the first time many organic acids, including citric, lactic, and malic acids, as well as other organic substances, such as aldehyde, casein, and glycerol.

Scheele is most famous for his role in the discovery of oxygen, which he made independently but at the same time as scientist Joseph Priestley. Scheele used his own experiments to prove the prevailing phlogiston theory, discovering chlorine and oxygen in this manner.

He worked with fellow scientist Torbern Bergman for many years. During this time, Scheele frequently consulted Bergman and did not take regular laboratory notes. Because of this, Bergman and many other chemists profited heavily from Scheele’s work on 15,000 to 20,000 experiments.

Scheele’s early death in 1786 was likely because of damage from frequent experiments with arsenic and cyanide without proper ventilation. While on his deathbed, he married his housekeeper and transferred the pharmacy and other assets to her.

REFERENCE
Consider Constructive Changes in 2022

Industry Consultant Bruce Kneeland Shares Ideas on How Pharmacies Can Refresh for the New Year

By KAREN BERGER, PHARMD

As 2022 approaches, what are some changes independent pharmacies can implement to stay at the top of their game? Bruce Kneeland is an independent pharmacy consultant based in Prescott, Arizona. He has worked with independent community pharmacies for more than 40 years and shares some ideas.

Brainstorm New Product Ideas

Kneeland encourages pharmacists to expand their thinking about what a pharmacy could be, beyond filling prescriptions. Look around and see what else the pharmacy could stock that is consistent with its health care image. For example, because healthy lifestyle changes are in vogue and compatible with a pharmacy’s focus on health care, consider stocking products such as bathroom scales, electronic toothbrushes, hand weights, and yoga mats. Kneeland also noted that sales of clean air products are exploding, making it a great opportunity for pharmacies to offer high-end air or water purifiers and filters for the home and office.

Consider the Emotional and Social Needs of Employees

Kneeland said that team-bonding activities are great, but a strong foundation and team morale are key. “Examine and rethink how you are building a team spirit. It’s an invisible competitive advantage. You can feel the atmosphere when you walk into a store; you can see how the employees feel and treat each other,” Kneeland said. He proposes occasional staff meetings, where employees are encouraged to share ideas, suggestions, and thoughts without having to defend them or be criticized. “Let them talk first. Once the boss talks, no one wants to disagree,” Kneeland said.

In addition, he recommended instilling “in employees the idea of a noble cause; we aren’t just filling prescriptions, we are improving people’s lives and caring for our patients,” Kneeland said. He also recommended that pharmacists create a feeling of “we are all in this together,” saying, “If Sally’s child gets sick, it is great when someone will step up and help. The staff makes sure Sally can go home and be with her child.”

Author Bio

Karen Berger, PharmD, is a pharmacist at an independent pharmacy in northern New Jersey.
LOOK AT NEW TECHNOLOGY
Kneeland encouraged pharmacies to look at new technology that can increase customer satisfaction and efficiency. One new technology that is becoming more widely available is automated drug delivery systems (ADDS), such as the Pharmaself24 unit. Kneeland said he is doing some consulting work for the company and describes the unit as a reverse robot that can stock already filled prescriptions that are stored in the pharmacy and then deliver them to patients via a portal, like an automated teller machine, when the patient enters a personal identification number that the system texts to the patient. Other types of systems are coming on the market, as well. Some are being produced by major pharmacy technology companies. Part of the rationale for ADDS is that independent pharmacies typically have shorter hours than their chain competitors. Installing an ADDS can give patients the ability to pick up their prescriptions even when the pharmacy is closed. Of course, they work during normal hours, too, and in some cases, an ADDS could replace the need for curbside service, Kneeland said.

SAY THANK YOU
A thank you letter program can be very powerful. Kneeland suggested involving all staff members who work with patients. Each employee can pen a hand-written note to a patient about something positive. For example, "Dear Mrs. Jones, I appreciated your smile and your kindness when you came into the pharmacy. It makes it a pleasure to work here." Kneeland recommended that the employee gets a $5 bonus when they turn in their note that week for mailing. "It's a great way to build relationships," he said.

START A NEW CUSTOMER PROGRAM
"New customers are the lifeblood of the business. Train employees to recognize every new customer," Kneeland said. When an employee takes in a prescription, he or she should welcome the patient and express appreciation that the patient has chosen the pharmacy. While the prescription is being filled, the pharmacy manager can step out and greet the patient. When the patient is paying for the prescription, hand the patient a brochure about the pharmacy and point out something unique about the pharmacy’s services, such as delivery or medication flavoring. Ask patients how they heard about the pharmacy. "Train your employees, so all of this happens automatically when there is a new patient," Kneeland said.

Keep a list of new patients, and at the end of each week, mail each a “new patient kit,” which can include a bounce back coupon, a brochure, and a welcome letter from the pharmacist. "The bounce back coupon entices the patient to return to the pharmacy and does not require a prescription. The coupon can be for a free item worth about $10, such as a box of chocolates, something that gets the patient off the couch and into the store," Kneeland said.

THINK ABOUT WHAT IS MISSING
Kneeland suggested that pharmacists first go back to basics. "The story is told of a famous football coach who, every year, when practice started for the new season, would gather the team around in the locker room and hold up a ball and say, 'This is a football.' Then he'd start to build the team from that foundation," Kneeland said.

Kneeland encourages pharmacists to take an honest look at the store: Is it clean, neat, and well-organized? Be sure to look at the outdoor appearance; does it make a good impression? A flowerpot and some fresh paint can go a long way, Kneeland said. He also advises owners to come into work at least once a month the same way that customers come in. "Instead of entering the pharmacy through the back door, come in the front door and look around, viewing the store from the customer’s perspective," Kneeland said.

Independent pharmacies have an opportunity to implement some of these ideas in 2022, as it is important to always stay ahead of the curve. Have a happy new year! ■
Pharmacists Can Develop Their Own Business Models for Patient Care
They Can Create Innovative Face-to-Face and Virtual Medication Therapy Management Practices

By JENNIFER GERSHMAN, PHARMD, CPH, PACS

MEDICATION THERAPY MANAGEMENT (MTM) PROGRAMS offer pharmacists expanded opportunities to use their clinical skill set as drug information experts to provide patient care services, but there are challenges to integrating MTM services into the community pharmacy practice setting.¹ Medicare Part D MTM delivery has increased to approximately 65% of plans using community pharmacists through MTM vendor contracts.¹ However, many prescription drug plans are not using pharmacists as the primary providers for Part D MTM services. Pharmacists are in a unique position to develop their own business plans to create innovative face-to-face and virtual MTM practices.

DEVELOPING A PRACTICE
Incorporating MTM services into a community practice setting may not be feasible because of a lack of pharmacy staff members, limited training opportunities, and obstacles integrating shared electronic health record systems.¹ Aligning MTM with value-based care delivery through the development of payment models that reward positive outcomes is critical for building a sustainable business model.¹ When developing an MTM business plan, determining the location where services will be offered is crucial.² Possibilities include a home office with virtual services, offering consults on site at employers’ locations, or renting space at a physician’s practice.² Additionally, other pharmacies in the region could contract with MTM pharmacists to provide services for patients enrolled in their Medicare Part D programs.² Pharmacists should ensure that they become familiar with the terms of the agreement and carefully review all contracts.² Further, they should ensure that a lawyer reviews all the contract information before they sign any documents.² It is important to determine the costs associated with initiating and providing services including accountant fees; computer, including billing, documentation, and technology support; home office expenses; legal fees; liability insurance; marketing costs; mortgage or rent for office space; office supplies; patient supplies; postage; support staff; and travel expenses.²

On January 1, 2017, the Centers for Medicare & Medicaid Services launched a pilot program to evaluate changes to the traditional MTM model.³⁴ Enhanced MTM includes program changes, such as increased payment incentives and regulatory flexible patient enrollment requirements, which provide pharmacists with additional opportunities.³ Stand-alone basic prescription drug plans in selected regions can offer innovative MTM programs, with the ultimate goal of improving the quality of patient care while reducing costs.³ The following Part D sponsors are participating in the enhanced MTM model: Blue Cross Blue Shield Northern Plains Alliance, Blue Cross and Blue Shield of Florida, CVS Health (SilverScript Insurance Company/CVS Insurance Company), Humana, UnitedHealthcare (UnitedHealth Group), and Wellcare Prescription Insurance.³⁴

» Continued on page 66
The first evaluation during the initial 20 months of the enhanced MTM program showed that there was an expanded pool of eligible beneficiaries who could receive tailored services. Predictive analytics was used to identify patients at high risk of experiencing drug-related problems, high spending, and hospital admissions. Based on these parameters, patients were risk stratified to determine which services they should be offered. These expanded targeted criteria allow for more patients to qualify for services versus the traditional MTM parameters of drug spending, number of chronic conditions, and quantity of medications. Services provided include comprehensive and targeted medication reviews, medication reconciliation, and patient education. The enhanced MTM model provides more opportunities for innovative data-sharing systems, new partnerships, and novel programs for data reporting.

CLOSER LOOK

In an interview, Jamie Wilkey, PharmD, founder of PGx Consulting Confidence Academy, discussed her pharmacogenomics consulting practice. She is a functional wellness pharmacist who is certified in pharmacogenomics and provides patient care using precision medicine.

“One test will change [the whole of] medicine,” Wilkey said, when discussing the important role that pharmacogenomics plays in MTM services.

As the CEO and founder of Arches Health, she manages patients individually in her clinical practice, both in person and virtually, and educates leaders in various clinical settings about strategies (see Figure) to integrate pharmacogenomics testing into their programs.

“Believe your knowledge can help others,” Wilkey said, who provides this motivating tip to others starting their own businesses. She noted that having a business degree is not a requirement for developing a consulting practice.

Through the PGx Consulting Confidence Academy program, she educates pharmacists and other health care professionals about strategies to start their own consulting practices. The course is a 1-year self-paced program in which Wilkey walks pharmacists through a step-by-step process of starting a pharmacogenomics consulting practice. The company also includes a social network of like-minded health care professionals discussing the latest developments in MTM pharmacogenomics.

REFERENCES
Pharmacists Can Be Invaluable in Identifying Chest Pain
Help Patients Choose Appropriate Medications and Direct Them to a Physician, When Necessary

By ABIMBOLA FARINDE, PHD, PHARMD

MANY PATIENTS WHO EXPERIENCE CHEST pain are unsure whether the discomfort indicates a serious or life-threatening condition, but pharmacists can help guide them to the appropriate medications or to a physician, when necessary.\(^1\)

Chest pain is the reason for more than 6.5 million visits to the emergency department and 4 million outpatient clinic visits every year.\(^2\) Individuals aged 45 to 64 years have chest pain most often, though the presentation differs between men and women.\(^2\) Women are more likely to present with discomfort in their jaws, epigastric symptoms, and palpitations than men. Chest pain is also a common occurrence in primary care settings. Given pharmacists’ accessibility, they can serve as effective educators and help inform patients about the signs and symptoms of chest pain and the importance of taking immediate action when they experience it. Although chest pain can vary in degree of severity from a benign presentation to a life-threatening condition, it is important for patients to be aware that thorough assessments of both are necessary.\(^3\)

When it comes to educating patients on the proper identification of chest pain, pharmacists can make them aware of key symptoms, including heaviness, pain, or tightness that radiates to the arms, back, jaw, and neck.\(^1\) Other notable symptoms include lightheadedness, nausea, shortness of breath, vomiting, and weakness.\(^1\) The goal of management and treatment is to help control these symptoms and reduce progression of any underlying conditions.\(^4\) Pharmacists can ask a few key questions about a patient’s medical history and physical condition to help evaluate the pain, but it is important to direct a patient to a physician or even an emergency department if the situation is dire. Questions to ask of
Women are more likely to present with discomfort in their jaws, epigastric symptoms, and palpitations than men.

References


Patients include the characteristics and location of the chest pain, how long the symptoms have lasted, time of onset, and whether they have risk factors that predispose them to development of the chest pain.1,4

Prior to the development of chest pain, it is important to educate patients about potential causes of chest pain, which may result from cardiac, gastrointestinal, musculoskeletal, psychological, and respiratory issues.1,4 Each presents with unique symptoms that can alert health care professionals and patients to the severity of the presentation and whether immediate medical attention is required. For example, stable angina can present with chest pressure or heaviness that can be an indicator of a serious situation, whereas fibromyalgia that can cause widespread pain even to the anterior chest may not be as time sensitive in terms of seeking care.

Pharmacists are invaluable members of the health care team in terms of chest pain identification and management because they can provide interventions by offering advice on drug information and instructions for the use of medications that target chest pain.3 Additionally, pharmacists can provide counseling to patients who are taking medications to address their specific chest pain. Research findings have shown that the involvement of pharmacists in the multidisciplinary team has been able to reduce morbidity and mortality rates.4,8 The involvement of pharmacists in education related to chest pain and the identification of its symptoms can have a significant impact on the quality of care delivered to patients.
WITH MILLIONS OF HEALTH CARE professionals heroically fighting COVID-19 on the front lines, battle fatigue has kicked in for many.

This battle fatigue transcends mere tiredness and is more specifically referred to as burnout.

“Burnout” as a concept was first proffered by clinical psychologist Herbert J. Freudenberger, who, in the 1970s, volunteered at a free clinic and observed that the demands of the job had left many of the workers feeling emotionally drained, resulting in cynicism, fatigue, and frustration.1

This concept was further refined by social psychologist Christina Maslach, who defined burnout as consisting of decreased feelings of personal accomplishment, as well as depersonalization and emotional exhaustion.2 The idea of burnout is particularly important to individuals who work in the pharmacy field, including pharmacy technicians, because of the impact that it can have not only on the health professional’s well-being but also on the health outcomes of the patients they serve. Burnout can also lead to lapses in judgment, resulting in medical errors.3 In the field of pharmacy, eliminating medication errors and providing efficient customer service are 2 of the highest priorities. The results of a 2017 study focusing on pharmacists showed that the rate of burnout among clinical pharmacists was 61.2%, which can surely spill over to technicians.4

Mitigating the likelihood of burnout requires a multifactorial approach. Some of the precipitating causes of burnout include an increased level of bureaucratic responsibilities, poor relationships with supervisors, and spending too many hours at work per week.1,5 As such, addressing burnout is a concern among individual employees and organizational leaders and supervisors.

On an individual level, there are several things to consider. The results of a 2018 study examining PGY1 pharmacy residents showed that participating in enjoyable activities, spending time with family and friends, and staying optimistic were some of the most effective coping strategies used to mitigate feelings of burnout throughout their residencies.6 These findings are validated by a meta-analysis conducted by Shin et al.7 Their study analyzed 2 kinds of coping strategies, emotion-focused and problem-focused, and the relationship that these strategies have with the 3 dimensions of burnout defined by Maslach.7

Problem-focused coping attempts to solve the stressful situation directly targeting the stressor to decrease or minimize it.8 Emotion-focused coping attempts to manage stress by focusing on the negative emotional reactions to the stressful situation and instead of taking actions to alter the stressor, uses tools such as meditation, positive reframing, prayer, or relaxation techniques to change perspective.8

Both strategies serve particular uses and help to mitigate feelings of burnout.

With these results in mind, pharmacy professionals can develop their own stress-reducing strategies to guard themselves against burnout in the workplace.

On an organizational level, a progressive strategy to mitigate employee burnout was taken at Stanford Medicine in California, which several
years ago created a position called chief wellness officer. This position takes on the responsibility of creating initiatives to combat physician burnout within the institution. With this idea in mind, institutions and pharmacy practices can also consider taking a more intentional approach toward combating burnout in the workplace. Because pharmacy professions also demonstrate high rates of burnout, developing an organizational leadership approach would be in the collective best interest. To assist health care workers, organizations can consider expanding or implementing access to mental health and self-care resources. Providing education about the symptoms of burnout, so that individuals can recognize it within themselves or their coworkers, can also help create a culture within practices or institutions that allows people to mitigate the negative outcomes that burnout can have on themselves, coworkers, and patients. Additionally, given that burnout often stems from stress in dealing with managers, those in supervisory positions can take heed and be more mindful of their verbal engagements with employees, making sure they understand that their contributions are valuable to the organization.

CONCLUSION

Avoiding burnout is contingent upon developing effective coping strategies at the individual and organizational level. It requires intentional efforts from both employees and supervisors. Some coping strategies are more effective than others, but no one size fits all. For some individuals, this may involve leaning on the social and spiritual atmosphere of religious faith. For others, it may involve directly intervening in the stressors of the workplace to mitigate stress. For many, it likely involves a combination of emotion- and problem-focused approaches to deal with the everyday stresses faced at work. Regardless of the approach, pharmacy professionals must confront the reality of burnout and the implications it has on their well-being and the health outcomes of patients. This way, they can begin to make changes in their own lives and lobby for organizational changes to create a positive workplace environment. In doing so, they can help revitalize themselves as they continue to provide efficient patient care during the COVID-19 pandemic and beyond.

REFERENCES

**Condition State Management**

**DIABETES**

**Gestational Diabetes**

**Study Suggests Eating Habits Barely Change After Diabetes Diagnosis**

**INVESTIGATORS AT THE NATIONAL** Institutes of Health (NIH) found that pregnant women made only slight changes to their diet after receiving a gestational diabetes diagnosis.

The investigators analyzed an existing data set from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Fetal Growth Studies, which included surveys on diet and exercise from a diverse patient population at 12 hospital centers across the United States. The analysis on diet included 1371 women, of whom 72 had gestational diabetes. The study team further examined exercise habits among 1875 women, of whom 84 had gestational diabetes.

In the study, women with gestational diabetes cut their daily carbohydrate intake to 48 g primarily by limiting juice consumption by approximately 0.096 L per day. They also decreased their added sugar consumption by approximately 16 mL per day.

Conversely, their consumption of cheese increased by 0.3 cups per day, and artificially sweetened beverages increased by 72 mL per day, according to the NIH.

Further, the team found that women with gestational diabetes did not decrease their consumption of whole fruit or grains, nor did they compensate for the dietary changes by increasing saturated fats. The study authors noted that these observations are reassuring, because complex carbohydrates from whole fruits or grains may be beneficial for gestational diabetes, whereas saturated fats can worsen health outcomes by promoting excessive fetal growth.—**Jill Murphy**

**Link Is Seen to Commonly Screened Protein During Pregnancy**

**NEW RESEARCH FINDINGS SHOW** that low levels of a protein often seen in screening tests for chromosomal disorders during the first trimester of pregnancy are associated with adipose tissue remodeling, gestational diabetes, and glucose resistance in pregnant women. The study results were published in *Science Translational Medicine*.

The data highlight a new role for pregnancy-associated plasma protein A, known as PAPP-A, in gestational diabetes, with translational potential as both a diagnostic tool and therapeutic target, according to the investigators.

Investigators ran a series of RNA screens on adipose tissue from pregnant women after cesarean delivery so they could identify possible differences in gene expression. They also ran RNA screens on adipose tissue from non-pregnant women undergoing bariatric surgery, using the samples to elucidate differences between adipose tissue growth in response to overnutrition or pregnancy.

One finding was the elevated presence of insulin-like growth factor-binding protein 5 (IGFBP5) in fat from pregnant women. This traps the protein IGF-1, which is necessary for cell proliferation and tissue growth.

The investigators suggested that the high levels of IGFBP5 in adipose tissue may be connected to the protein PAPP-A. Previous research results have shown that pregnant women produce this protein, which is not normally found circulating in the blood.—**Jill Murphy**

**Research Shows Increased Risk of Heart Disease for Women**

**NEW RESEARCH RESULTS SUGGEST** that women with a history of gestational diabetes are twice as likely to develop calcium in the heart arteries by midlife, even if healthy blood glucose levels were attained many years after pregnancy. This is a strong predictor of heart disease, according to the authors of the findings, which were published in *Circulation*.

The new analysis includes approximately 1100 women without type 1 or type 2 diabetes (T2D) who subsequently gave birth at least once during the 25-year study period, which ended in 2011. Blood tests were performed from before to after pregnancies at 5-year intervals to determine whether the women had developed overt T2D or had normal blood glucose levels or intermediate elevations in blood glucose levels. Heart scans were performed to measure coronary artery calcium at 15, 20, and 25 years after the baseline first exam of the study.

Notably, attaining healthy blood glucose levels after pregnancy did not decrease the risk of developing cardiovascular disease in midlife for women with a history of gestational diabetes. Of women with previous gestational diabetes, 36% developed prediabetes and 26% developed T2D compared with 35% and 9%, respectively, of women with no history of gestational diabetes.

Furthermore, 25% of women with a history of gestational diabetes had some level of coronary artery calcium versus 15% of women who never had gestational diabetes.—**Aislinn Antrim**
Pet Peeves

Wrong Place, Wrong Time
When patients ask to transfer medications and give the information to the wrong pharmacy at a different location.

Pointless Prior Authorization
When the pharmacist does all the work for a prior authorization that the patient wants filled elsewhere.

Trivial Transfer
When patients ask to transfer medications that have no refills.

Check Online
PharmacyTimes.com will offer Pet Peeves, brought to you by the Sassy Pharmacist in coming months.

What's Bothering You?
Bossy patients, abandoned prescriptions, drive-through demands? We want to know! Send your pet peeves to cmollison@pharmacytimes.com. We'll share them here and online.
Case Studies
By STEFANIE C. NIGRO, PHARMD, BCACP, CDCES; AND NICHOLAS BOEMIO, PHARMD, BCPS

CASE 1

The pharmacist on duty receives a call from BB, a 65-year-old woman with type 2 diabetes who says that her primary care provider (PCP) increased her dose of metformin from extended-release (ER) 750 mg daily to ER 1000 mg daily approximately 1 month ago. Since then, BB has noticed a metallic taste in her mouth, which she did not experience at the lower dose. She says that she did not start any new medications during that time, nor did she have any additional dose changes. BB’s other chronic medications include a daily multivitamin and amlodipine 5 mg daily, both of which she has taken for years without incident. She wants to know if the situation could be related to metformin and what advice, if any, the pharmacist has.

How should the pharmacist respond?

CASE 2

SW, a 34-year-old man, has started on the following insulin regimen: 22 units of neutral protamine Hagedorn (NPH) and 10 units of regular insulin before breakfast and 5 units of regular insulin and 10 units of NPH before dinner. He brings in his glucometer for review at a follow-up visit 2 weeks later, noting that he tests his sugar once daily in the morning before breakfast. A review of SW’s glucometer data shows a 7-day average of 150 mg/dL. Individual daily readings include 147 mg/dL, 176 mg/dL, 156 mg/dL, 161 mg/dL, 138 mg/dL, and 145 mg/dL. SW denies any signs or symptoms of hypoglycemia.

What changes to his insulin regimen should the pharmacist recommend to help the patient reach his glycemic goals?
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Before the advent of modern anesthesia, humans tried multiple avenues for effectively rendering others unconscious before surgeries. Some cultures found certain drugs had a similar benefit to anesthesia, such as hashish in Ancient China and opium in Ancient Egypt. During the Middle Ages, physicians used a method they referred to as the “soporific sponge,” which involved soaking a sponge in hemlock, henbane, mandrake, and opium; letting it dry in the sun; rinsing it in hot water; and then squeezing it and stuffing it firmly under a patient’s nose.

Fun Facts

Q: What ailments did the color green supposedly cure in the 1940s?
A: While working as a stage manager in a theater in Bombay, India, Dinshah P. Ghadiali began to read about the potential of color therapy to cure disease. He taught his students some basic principles of color therapy, which was founded on the idea that every element represents 1 of 7 prismatic colors. Ghadiali explained that humans are made of carbon, hydrogen, nitrogen, and oxygen, which each correspond with a color: yellow, red, green, and blue, respectively. If an individual is sick, then 1 of their colors is imbalanced, requiring the color to be amplified or subdued in them. Green was supposedly used to cure ailments of the pituitary glands.

Q: What clinical research flourished for decades before criminalization?
A: Despite the illegality of most psychedelic drugs at the federal level in the United States, the US government has not always been averse to the exploration and funding of research into the benefits of psychedelic medicine. Lysergic acid diethylamide (LSD) took a primary role in the research conducted from the 1940s through the 1960s into the potential therapeutic benefit of psychedelic medicine. Despite these efforts and several international conferences regarding the effects of psychedelic medicine and its impact as a treatment in the field of psychiatry, by the late 1960s, negative associations with psychedelic medicine persisted within the social consciousness of the United States. These public attitudes led to the criminalization of psychedelic drugs in 1968. With this criminalization, all federal funding for further research was eliminated, and drugs such as LSD and psilocybin were classified as Schedule I drugs, which establishes them on a federal level as having no accepted medical use and a high risk for potential abuse.
A Review of Novel Antifungal Therapies for Vulvovaginal Candidiasis to Improve Patient Outcomes and Prevent Recurrent Infections

**Pharmacists Educational Objectives**

At the completion of this activity, the participant will be able to:

- Determine the pathophysiology, epidemiology, risk factors, and clinical presentation associated with vulvovaginal candidiasis (VVC).
- Compare the mechanisms of action, dosing, administration, potential adverse effects, and challenges associated with standard -azole therapies including available over-the-counter and prescription agents for VVC.
- Examine the newly approved and emerging antifungals for VVC including mechanisms of action, dosing, administration, efficacy and safety data, and clinical benefits.
- Identify the role of the pharmacist in counseling patients at risk for or with VVC about novel therapies to reduce recurrent infections, and improving patient adherence and clinical outcomes.

**Pharmacy Technicians Educational Objectives**

At the completion of this activity, the participant will be able to:

- Recall the burden of vulvovaginal candidiasis (VVC) or vaginal yeast infections, and associated risk factors and symptoms.
- Recognize standard -azole therapies including available over-the-counter and prescription agents for VVC including the dose, route, and potential challenges associated with these therapies.
- Review the newly approved and emerging antifungals for VVC including the dose, route, potential adverse effects, and benefits.
- Clarify the role of the pharmacy technician in identifying patients at risk for or with VVC and referring appropriate patients to the pharmacist for additional counseling on novel therapies.

**Target Audience:** Pharmacists and pharmacy technicians.

**Activity Type:** Application for pharmacists; knowledge for pharmacy technicians.

**Release Date:** November 30, 2021.

**Expiration Date:** December 15, 2022.

**Estimated Time to Complete Activity:** 2.0 hours.

**Fee:** This lesson is offered for free at www.pharmacytimes.org.

**Introduction**

Vulvovaginal candidiasis (VVC), also referred to as vaginal candidiasis or vaginal yeast infection, is a type of infectious vaginitis. Vaginitis is one of the most common reasons that women visit their health care providers and is a general term for disorders of the vagina caused by infection, inflammation, or changes in the normal vaginal flora. Vaginitis can be classified as infectious or noninfectious. Noninfectious vaginitis may include irritant, allergic, or inflammatory vaginitis and accounts for 5% to 10% of vaginitis cases. Other common types of conditions that fall under the umbrella of infectious vaginitis include bacterial vaginosis and trichomoniasis vaginalis. There are some overlapping symptoms among the types of vaginitis but each has specific characteristics, complications, and medication management. According to the Centers for Disease Control and Prevention (CDC), trichomoniasis is a common sexually transmitted disease (STD).
external vaginal itching, soreness, discharge, and discomfort.4 Resulting in internal and Candida environment can lead to overgrowth of Candida, resulting in internal and external vaginal itching, soreness, discharge, and discomfort.4 Changes in the vaginal environment can lead to overgrowth of Candida, resulting in internal and external vaginal itching, soreness, discharge, and discomfort.4 Being that VVC is a very common infection among women, many of them attempt to self-treat with nonprescription products before visiting their health care provider. In the early 1990s, several of the prescription topical vaginal antifungals switched to over-the-counter status, allowing for ease of symptom management. Approximately $317 million was spent annually on the use of nonprescription vaginal products for itch and yeast treatment in 2020.8 Unfortunately, misdiagnosis happens often and only an estimated one-third of women purchasing nonprescription antifungals accurately identify their condition.7 It is important to confirm an accurate diagnosis as inappropriate self-treatment could lead to RVVC or drug resistance, which makes curing the infection challenging.

Pharmacists play an essential role in identifying those patients who meet the criteria for self-treatment as well as those who require referral to their health care provider. This involves obtaining a thorough medical history and asking the patient key questions about their lifestyle habits. Pharmacists can also help to identify those patients at higher risk for developing VVC and recommend additional testing or screening for underlying conditions. The primary management of VVC includes the class of prescription and nonprescription azole antifungals, which are available in a variety of formulations. Most recently a new non-azole oral antifungal therapy, ibrexafungerp (Brexafermee), has been approved, making it the first new antifungal class in more than 2 decades. Pharmacists are in a unique position to counsel patients on appropriate use of the various treatments, prevention, and adherence to therapy. Understanding the signs and symptoms of VVC, risk factors, and management will help pharmacists educate and advise patients appropriately.

**Pathophysiology**

In approximately 90% of VVC cases, the Candida species identified is *C albicans*.12-13 However, it is suggested that due to the incidence of inappropriate self-management with nonprescription products, health care providers are identifying more non-Candida albicans Candida species (NCAC). NCAC species are generally associated with higher resistance to first-line treatments, making VVC more difficult to treat.13 Another common Candida species associated with VVC is *C glabrata*, which is the second most common after *C albicans*. Additional common Candida species include *C tropicalis*, *C parapsilosis*, and *C krusei*. In a small percentage of women (1%-10%), there may be coinfection of two or more Candida species.8 There are numerous bacterial flora that inhabit the healthy vagina during a woman’s reproductive years, most notably the Lactobacillus species. The most common are *L iners*, *L crispatus*, *L gasseri*, *L acidophilus*, *L casei*, and *L vaginalis*.4,10 Lactobacilli primarily produces lactic acid, in addition to hydrogen peroxide and acetic acid, by converting it from glycogen which is stored in the cells of the vaginal epithelium. This helps to maintain a normally low vaginal pH (3.8-4.5).49 Vaginal pH can fluctuate with age, vaginal hygiene products, sexual activity, menstrual cycle, and pregnancy.3 The acidic environment produced by Lactobacilli is a defense mechanism, whereby it helps

### Table 1. Distinguishing Types of Vaginitis

<table>
<thead>
<tr>
<th></th>
<th>VVC</th>
<th>Bacterial vaginosis</th>
<th>Trichomoniasis vaginalis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
<td>Fungi</td>
<td>Anaerobic bacteria</td>
<td>Protozoan parasite</td>
</tr>
<tr>
<td><strong>Discharge</strong></td>
<td>Thick, white, curd-like</td>
<td>Thin, gray, increase in volume</td>
<td>Yellow/green</td>
</tr>
<tr>
<td><strong>Odor</strong></td>
<td>None</td>
<td>Fishy, foul, or unpleasant</td>
<td>Fishy</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>Vaginal itching, vulvar redness, burning, painful urination, inflammation</td>
<td>Itching sometimes present; some inflammation</td>
<td>Itching, burning, and painful urination usually present, strawberry colored cervix</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>&lt;4.5</td>
<td>&gt;4.5</td>
<td>&gt;4.5</td>
</tr>
</tbody>
</table>

VVC, vulvovaginal candidiasis.
inhibit growth of fungi (yeast) and other pathogens such as viruses, protozoa, and vaginitis-associated bacteria.\textsuperscript{10} It is estimated that 20\% of women have \textit{Candida} as part of their normal vaginal flora without having any symptoms.\textsuperscript{1,11} However, as a result of various predisposing factors or triggers, there can be overgrowth of \textit{Candida}, causing an imbalance between the “good” normal flora and yeast.\textsuperscript{1,4}

Overgrowth of \textit{Candida} can result in vulvar soreness, itching or irritation, pain with urination or intercourse, abnormal vaginal discharge, vaginal redness, edema, and discomfort, all of which are the common symptoms of VVC.\textsuperscript{2} Normal physiologic vaginal discharge is clear to milky white in color, odor-free, and nonirritating. As a woman goes through her menstrual cycle and hormone levels fluctuate, the quality and quantity of discharge may change.\textsuperscript{2} Normal discharge can vary from thin watery discharge to a thicker cloudy discharge.\textsuperscript{2} Although some women may not present with a change in discharge, VVC typically presents as an odorless thick, white, and curd-like discharge.\textsuperscript{2} TABLE 1\textsuperscript{1-3,9,12} illustrates the comparison among VVC, bacterial vaginosis, and trichomoniasis with respect to the causative microbes as well as the clinical presentation. The odorless curd-like discharge is one of the hallmark signs of VVC compared with other vaginal infections.\textsuperscript{2} Upon examination, women with RVVC may present with significant edema and thickening of the skin of the vulva as well as severe itching, burning, and irritation.\textsuperscript{9}

TABLE 1. RISK FACTORS FOR VVC\textsuperscript{14}

<table>
<thead>
<tr>
<th>Category</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral</td>
<td>Personal hygiene habits</td>
</tr>
<tr>
<td></td>
<td>Lifestyle habits</td>
</tr>
<tr>
<td></td>
<td>Use of spermicides or douching</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td></td>
<td>Uncontrolled diabetes</td>
</tr>
<tr>
<td>Hormonal</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Oral or intrauterine contraceptives</td>
</tr>
<tr>
<td>Other medications</td>
<td>Antibiotics</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
</tr>
</tbody>
</table>

VVC, vulvovaginal candidiasis.

<table>
<thead>
<tr>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are numerous predisposing factors or triggers that can cause a change to the vaginal environment causing the overgrowth of \textit{Candida}, some of which are reviewed in TABLE 2.\textsuperscript{1,4} Select risk factors include the use of antibiotics, chronic diseases, genetics, hormone-related factors, altered immune systems, lifestyle habits, and sexual activity.</td>
</tr>
</tbody>
</table>

**Antibiotics**

Antibiotics, which may reduce the amount of normal vaginal flora, are a common risk factor for developing VVC. Antibiotics are thought to deplete the amount of \textit{Lactobacillus} species, which usually protects against the growth of \textit{Candida}. Not all women who take antibiotics will develop VVC but studies show that those already colonized with \textit{Candida} may be at increased risk.\textsuperscript{4,11} Although no particular antibiotic has shown to be of a higher risk, broad-spectrum antibiotics such as tetracyclines, cephalosporins, and ampicillin may have a higher incidence.\textsuperscript{4,9} In addition, the risk of developing VVC has shown to increase with the duration of antibiotic use.\textsuperscript{4}

**Chronic Diseases**

Underlying chronic disease states such as diabetes are predisposing factors for VVC, RVVC, and NCAC, especially in those patients with uncontrolled diabetes. The incidence of VVC in women with diabetes ranges from 32\% to 67.5\% as compared with patients without diabetes ranging from 11\% to 23\%. Hyperglycemia may cause impaired defense mechanisms, thickening of the vaginal epithelial wall, and enhanced adherence of \textit{Candida} to vaginal skin cells. As corticosteroids can cause hyperglycemia, the mechanism by which they increase the risk of VVC is similar to that of individuals with diabetes. It is also speculated that \textit{C. albicans} has glucose and corticosteroid binding proteins at its surface, which further promotes adhesion of \textit{Candida} to vaginal cells.\textsuperscript{4}

**Genetics**

For those women with no underlying risk factors, there may be a possible genetic predisposition to VVC. The literature has shown that African American women are more likely to have \textit{Candida} as part of their vaginal flora and have an increased incidence of VVC compared with Caucasian and Hispanic women. Genetic mutations and overexpression of proinflammatory markers have also been identified in women with RVVC.\textsuperscript{4}

**Hormonal**

Pregnancy is another common cause of VVC, with an estimated 33\% of pregnant women being affected worldwide.\textsuperscript{9} The higher levels of progesterone and estrogen in pregnancy may cause an accumulation of glycogen in the vaginal epithelial cells, thick-
ening the vaginal epithelium and increasing glycogen production. This results in increased adhesion of *Candida* to the vaginal epithelium, lowering of vaginal pH, and suppression of protective vaginal flora. This is speculated to be the same mechanism for those taking hormone replacement therapy, high-dose estrogen oral contraceptives, and using intrauterine contraceptives.

**Immune System**
Women with altered immune systems, including HIV infection, organ transplant, corticosteroid use, undergoing chemotherapy, or taking other immunosuppressants are at increased risk of VVC, RVVC, and NCAC infections. Depressed T-cell immunity and dysfunction of protective immune responses are speculated to be a contributing factor to VVC in these patients.

**Lifestyle Habits**
Lifestyle habits also play a significant role in the development of VVC by introducing bacteria to the vaginal area (eg, cleansing from the anus toward the vagina), altering the balance of normal flora (eg, excessive douching, use of perfumed hygiene vaginal products and spermicides) or increased vaginal moisture and temperature to allow for *Candida* overgrowth (eg, wearing poorly ventilated underwear, tight-fitting clothing, and remaining in damp clothes for long periods of time). Identifying risk factors for VVC, especially those that can be modified, can aid in the prevention of RVVC.

**Sexual Activity**
The link between VVC and sexual activity is still debatable because VVC can occur in those women who are not sexually active. However, those who are sexually active may be at a higher risk due to increased *Candida* entrance to the vagina. According to the CDC, VVC is not usually acquired through sexual transmission and therefore treatment of sexual partners has no effect on a woman’s risk of recurrence.

**Classification and Diagnosis Considerations**
VVC is classified into 2 categories including uncomplicated and complicated. Uncomplicated VVC usually presents in immunocompetent women, can be sporadic or infrequent, mild to moderate in severity, and is usually due to *C albicans*. Complicated VVC can be recurrent (RVVC) or severe and is typically due to NCAC species in immunocompromised women or those with underlying medical conditions and additional risk factors. RVVC can either be idiopathic (unknown cause) or defined as secondary where it is related to underlying risk factors. Uncomplicated VVC is defined as fewer than 4 episodes per year and complicated or recurrent VVC is defined as 4 or more episodes per year (the CDC defines RVVC as 3 or more episodes per year).

Suspected VVC caused by *C albicans* is usually based on the presence of clinical factors (both signs and symptoms), vaginal pH, and a vaginal wet-mount test. The wet-mount test involves a microscopic examination of vaginal discharge mixed with either saline or potassium hydroxide (KOH preparation) to look for the presence of yeast. The KOH preparation also allows for detection of an odor (Whiff test) to decipher among VVC, bacterial vaginosis, and trichomoniasis. According to the CDC, all women with signs and symptoms of VVC should have a wet mount with KOH preparation performed and those with a positive result should be treated. Providers should consider vaginal cultures for women with negative wet-mount results but still presenting with signs and symptoms. However, if cultures cannot be performed, then the CDC recommends empiric treatment. There is no indication for wet-mount tests for retesting without the presence of signs and symptoms, as *Candida* can be part of a woman’s normal vaginal flora. Women with suspected complicated VVC due to NCAC species should have a vaginal culture performed with susceptibility testing to determine the best course of treatment.

Testing vaginal pH is another method used in the diagnosis of VVC and to rule out other infectious forms of vaginitis. VVC does not alter the vaginal pH and therefore upon testing should remain less than 4.5. At-home screening kits for vaginal infections only test vaginal pH. Women who identify an abnormal vaginal pH or have symptoms even in the presence of normal pH should follow up with their health care provider.

Other reasons for provider referral include presenting with a foul-smelling discharge, discharge with an abnormal color, presence of fever, nausea, vomiting, or pain in the abdomen, back, shoulder, or pelvis, pregnancy, breastfeeding, or aged younger than 12 years.

Those who have self-treated for an appropriate length of time without symptomatic relief within 7 days or suspect they are experiencing their first infection should consult their provider. Women with underlying medical conditions, VVC episode once per month or 3 episodes in 6 months should seek medical care. Noninfectious forms of vaginitis could easily be confused with the symptoms of VVC, especially complaints of vaginal redness, itching, and irritation. However, noninfectious vaginitis does not typically present with a significant change to the vaginal discharge. These symptoms could be a result of a vaginal product hypersensitivity, allergy to latex condoms or spermicides, use of scented feminine products, or frequent douching. Taking a thorough medical history that includes inquiring about patient symptoms and use of vaginal hygiene products is important because noninfectious vaginitis requires different management.
Management of VVC
The goals of treating VVC infection include relief of symptoms, eradication of infection, reestablishing normal flora, and preventing recurrence. Treatment considerations are based on classification and whether the patient presents with complicated or uncomplicated VVC. The mainstays of management for VVC are topical intravaginal and oral azole preparations, which achieve cure rates of 85% to 95%.\(^9\) Nonprescription and prescription medication treatment regimens approved for the management of VVC are listed in TABLE 3\(^{1,2,9,16}\) and TABLE 4\(^{1,2,9,16}\).

There are 2 classes of azoles for the management of VVC, including the imidazoles (eg, miconazole, itraconazole, clotrimazole, butoconazole) and triazoles (eg, fluconazole, terconazole). Other azoles within these classes not approved for VVC include ketoconazole and itraconazole. The azole class works by inhibiting the cytochrome P450-dependent enzyme lanosterol 14-α-demethylase, which is necessary for the synthesis of ergosterol, a primary component of the fungal cellular membrane.\(^{17,18}\) The azole class possesses fungistatic activity, whereby it limits and stops the growth of Candida species.\(^{17}\)

| TABLE 3. REGIMENS FOR UNCOMPLICATED VVC\(^{1,2,9,16}\) |
|---------------------------------|-------------|------------------|
| **Ingredient** | **Brand name** | **Dosing** |
| Clotrimazole vaginal | NA | 1% cream, 5 grams (g) intravaginally daily for 7 days 2% cream, 5 g intravaginally daily for 3 days |
| Miconazole | Monistat 1 | 1200-mg vaginal suppository, 1 suppository for 1 day |
| | Monistat 3 | 200-mg vaginal suppository, 1 suppository daily for 3 days |
| | Monistat 7 | 2% cream, 5 g intravaginally daily for 7 days OR 100-mg vaginal suppository, 1 suppository daily for 7 days |
| | Vagistat 3 | 4% cream, 5 g intravaginally daily for 3 days  |
| | | Note: Combination products are available with 2% external cream. |
| Tioconazole | Monistat 1-day | 6.5% ointment 5 g intravaginally in a single application |
| | Vagistat 1 |  |

| TABLE 4. REGIMENS FOR COMPLICATED VVC\(^{1,2,9,16}\) |
|---------------------------------|-------------|------------------|
| **Severe acute** | Oral fluconazole 150 mg every third day for a total of 2 or 3 doses |
| **RVVC** | 10-14 days with a topical azole OR oral fluconazole followed by 150 mg weekly for 6 months |
| **C glabrata unresponsive to azoles** | Topical intravaginal boric acid (in a gelatin capsule), 600 mg daily, for 14 days OR nystatin intravaginal suppositories, 100,000 units daily for 14 days OR 17% flucytosine cream alone or in combination with 3% amphotericin B cream once daily for 14 days |

RVVC, recurrent vulvovaginal candidiasis; VVC, vulvovaginal candidiasis.

VVC, vulvovaginal candidiasis.
The risk of adverse effects (AEs) with the topical intravaginal azoles is minimal, including localized vaginal burning and irritation. Women should not mistake these AEs with worsening of their condition or the medication not working. Educating women on these AEs is important to ensure adherence to the regimen and cure of their infection. Oral azoles, specifically fluconazole, can cause nausea, abdominal pain, and headache, and rare elevation in liver enzymes has been noted. Fluconazole has the potential for drug interactions and should not be coadministered with other drugs known to prolong QT interval or those metabolized by CYP3A4. As previously mentioned, azole-resistant *C. albicans* is a growing issue possibly due to inappropriate or unnecessary use of nonprescription topical azoles. In recent years, other theories of the mechanism of azole resistance have been investigated at the molecular level of fungi. One such mechanism is overexpression of efflux pumps, whereby the resistant *Candida* species transports and removes the azole out of the cell. It still remains unknown why there is an overexpression of certain transporters within efflux pumps causing azole resistance. In vitro studies show a possible genetic component and there may be certain transporters present within certain *Candida* species leading to specific azole resistance.

**Uncomplicated VVC**

According to the CDC and Infectious Diseases Society of America (ISDA) Clinical Practice Guidelines for the Management of Candidiasis, first-line therapy for uncomplicated VVC includes a short course (eg, 1 or 3 day) of topical intravaginal azoles or single dose of oral fluconazole (TABLE 3).

Topical azoles should provide a cure rate of 85% to 95% in patients who are adherent and complete therapy. Per the treatment guidelines, no particular product or length of therapy (1, 3, or 7 day) has shown to be superior to another. Therefore, product selection is based on patient preference, convenience of the chosen treatment, ease of use, cost, and previous treatments.

The CDC recommends a 7-day topical azole treatment regimen for pregnant women and they should avoid oral azole therapy due to the risk of miscarriage or fetal abnormalities. There are advantages and disadvantages to the different topical formulations available as well as to oral therapy. Women should be aware that the topical azole formulations are oil based and may weaken latex condoms and diaphragms. Due to the localized effects of the topical formulations, some women may experience an immediate relief of their symptoms compared with the oral formulations. However, in some cases, topical products could possibly exacerbate current VVC symptoms, including vaginal itching or burning. Topical azoles are available as suppositories, creams, and ointments all administered intravaginally with either filled or prefilled applicators depending on the patient’s preference. Some products are also available as a combination preparation containing a small tube of antifungal cream for the relief of external itching and irritation. Medication leakage is very common with the topical azoles and therefore it is recommended to use them at bedtime. Oral medications are more convenient but have the potential for causing systemic AEs and possible drug interactions. Common AEs associated with fluconazole include headache, nausea, diarrhea, and abdominal pain. Based on available data and given that VVC is not acquired through sexual intercourse, the CDC does not support the treatment of sex partners for uncomplicated or complicated VVC. For the minority of male sex partners who do have penile irritation, redness, and itching, a topical antifungal would be first-line treatment.

**Complicated VVC**

The management of complicated VVC is guided by the classification of either severe acute VVC, RVVC, or NCAC VVC (TABLE 4). Longer courses of either topical or oral therapy are typically needed for higher response rates in complicated cases. If a patient does not respond to therapy and resistance is suspected, a vaginal culture may be necessary to determine the specific *Candida* species as well as refer the patient to an infectious disease specialist. Immunocompromised patients or those with uncontrolled diabetes usually require longer duration of treatment from 7 to 14 days. Other regimens for complicated VVC, especially NCAC, may include use of boric acid, nystatin, and a combination of fluconazole with amphotericin B.

**Boric Acid**

The exact mechanism of boric acid in the management of VVC is unknown but it is thought that its antiseptic and antifungal properties prevent the fungus from growing, giving it fungistatic activity. Studies show that AEs of intravaginal boric acid include vaginal burning, watery discharge, and vaginal redness. A review of 14 studies showed that when boric acid was compared with nystatin, fluconazole, and various medications in the azole class, mycologic cure rates (negative lab cultures) ranged from 40% to 100% with statistically significant clinical cure rates.

**Non-azole Antifungals**

The use of non-azole antifungals such as nystatin and fluconazole have been shown to be effective against NCAC, especially *C. glabrata*. Nystatin works by binding to the fungal cell membrane and interfering with the membrane permeability, creating a hole. This causes intracellular substances to leak from the fungal cells,
stopping its growth and killing the fungi.18 Compared with the azoles, which have an 85% to 95% cure rate, nystatin has a 75% to 80% cure rate.9 Fluconosine works by entering the fungal cell wall and ultimately interfering with the fungal RNA and protein synthesis.18 Approximately 10% of C. albicans presents with resistance to fluconosine.18 Despite the limited studies available for use of non-azoles in the management of complicated VVC, they remain a second-line option for patients whose azole therapy has failed.16

Other Azole Antifungals
As a result of fluconosine resistance, other oral azoles in new drug delivery systems have been studied in the management of VVC including ketoconazole and itraconazole.18 In one study, an intravaginal formulation (gel-flakes) of ketoconazole was compared with intravaginal terconazole.20 The gel formulation of ketoconazole showed comparable results to terconazole with respect to mycological and clinical cure.20

<table>
<thead>
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<th>STAR</th>
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<tbody>
<tr>
<td>How does the mechanism of action of ibrexafungerp differ from the mechanism of action of medications in theazole class?</td>
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Emerging VVC Therapies
Approved Prescription Agent
Ibrexafungerp is the newest oral prescription antifungal approved for VVC in more than 20 years in a new class called fungerp. Ibrexafungerp is a triterpenoid antifungal that inhibits the enzyme 1,3-β-glucan synthase, which is involved in the formation of an essential component of the fungal cell wall.21,22 This compromises the fungal cell wall integrity, killing the fungi, thereby giving this novel oral drug fungicidal activity. This provides an advantage over the azoles, which have fungistatic activity. Of note, ibrexafungerp has the same mechanism of action as the class of echinocandins antifungals (eg, caspofungin, micafungin), which are used in the management of invasive Candida infections and fluconazole-resistant patients in the hospital setting.16,21,22

Current data show that ibrexafungerp has activity against C. albicans and most fluconazole-resistant Candida species such as C. glabrata and C. krusei. Ibrexafungerp is administered as 300 mg (two 150-mg tablets) twice a day for 1 day, for a total treatment dosage of 600 mg. It is available as a 4-tablet pack taken by mouth over the course of 24 hours with or without food. Ibrexafungerp is approved for the treatment of VVC in adults and only approved for pediatric females who already started their first menses. It is contraindicated in pregnancy as it may cause fetal harm.22 It is recommended that a negative pregnancy test be documented before administering ibrexafungerp to women of childbearing age.23

Ibrexafungerp is a substrate of CYP3A4; therefore, drugs that inhibit or induce CYP3A may alter the concentration levels of ibrexafungerp. Data show that administration with strong CYP3A4 inhibitors such as ketoconazole and itraconazole can significantly increase levels of ibrexafungerp. In this case, the dose of ibrexafungerp should be decreased to 150 mg twice a day (12 hours apart) for 1 day.22 No dosage adjustment has shown to be needed when coadministering a weak or moderate CYP3A4 inhibitor. Concomitant use of strong and moderate 3A4 inhibitors (eg, rifampin, carbamazepine, phenytoin) with ibrexafungerp have not been studied but are likely to cause significant reduction in concentration levels affecting efficacy and therefore should be avoided. The most frequent AEs (>2%) experienced are gastrointestinal related, including diarrhea, nausea, vomiting, and abdominal pain as well as dizziness.22

Recent FDA approval of ibrexafungerp is based on 2 phase 3 studies, VANISH 303 and VANISH 306.24-26 Both trials compared ibrexafungerp in two 300-mg oral doses given 12 hours apart with placebo and evaluated clinical cure, reported as no signs and symptoms of VVC, on days 8 to 14. Clinical cure was seen in 50.5% of patients receiving ibrexafungerp versus 28.6% with placebo (P = .001) in VANISH 303 and VANISH 306 reported clinical cure of 63.3% versus 44% (P = .009) with ibrexafungerp and placebo, respectively.24,25 Mycological cure rates, reported as negative Candida cultures, were statistically significant (P <.001) in both trials for ibrexafungerp compared with placebo. Furthermore, both studies also evaluated clinical response at follow-up on day 25. Data from the VANISH 303 study showed resolution of symptoms were sustained with ibrexafungerp compared with placebo (59.6% vs 44.9%; P = .007).24,25 Similar results were observed in VANISH 306 with a statistically significant complete clinical response at day 25 (72.5% vs 49.4% with ibrexafungerp vs placebo, P = .006).24,25,26 AEs were predominately gastrointestinal related including nausea, abdominal pain, diarrhea, and vomiting. Another study, specifically looking at the activity of ibrexafungerp against C. albicans, took vaginal and blood samples from 144 women with suspected VVC.27 Susceptibility of these samples to ibrexafungerp, fluconazole, and other antifungals was investigated. Overall, the results showed good in vitro activity of ibrexafungerp against azole-susceptible and azole-resistant C. albicans.27

A recent phase 2 randomized study compared the percentage of patients with clinical and mycological VVC cure at day 10 and
day 25 between ibrexafungerp 300 mg dosed twice for 1 day and fluconazole 1 dose of 150 mg for 1 day. At day 10, the clinical cure rates for ibrexafungerp and fluconazole were 51.9% and 58.3%, respectively, and mycological cure was 63.0% versus 62.5%, respectively. However, at day 25, patients continuing with no signs or symptoms of VVC were 70.4% in the ibrexafungerp group and 50.0% in the fluconazole group. Overall, ibrexafungerp was concluded to be equally efficacious to the FDA-approved dosing of fluconazole with respect to mycological cure but with continued efficacy.

While there are other antifungals in the pipeline, ibrexafungerp is the only oral formulation approved for VVC specifically targeting Candida species. The IDSA and CDC have not updated their clinical management guidelines since the approval of ibrexafungerp; however, this new antifungal may play a role as a second-line agent for VVC or when azole resistance is suspected.

Investigational Agents

An investigational emerging therapy for VVC includes oral oteseconazole (VT-1161), which is undergoing phase 2 and 3 trials targeting Candida species. Oteseconazole is a tetrazole with possible greater Candida selectivity, fewer AEs and drug interactions, and improved efficacy compared with the currently approved azoles. In vitro studies suggest that oteseconazole is active against fluconazole-resistant Candida strains. A current phase 3 study is investigating oteseconazole versus placebo for women with RVVC. Women eligible for this study will first be treated with three 150-mg doses of fluconazole to treat the current VVC episode over 2 weeks. This will be followed by oteseconazole 150 mg once daily for 7 days at day 1 followed by once weekly for 11 weeks. There will be a 36-week follow-up period in which the investigators will look to see the percentage of women with one or more acute VVC episodes during the maintenance phase with oteseconazole.

Another phase 3 study is evaluating the safety and effectiveness of oteseconazole compared with fluconazole in the management of both acute and recurrent VVC. During the first 2 weeks of the study, participants will either randomly receive oteseconazole 150 mg once daily for 2 days or fluconazole 150 mg 3 doses (every 72 hours) for a current VVC episode. For the following 11 weeks, participants will either receive oteseconazole 150 mg once weekly for 11 weeks or placebo with a follow-up at 37 weeks. Outcome measures are percentage of subjects with one or more acute VVC episodes during the 50-week study time frame and resolution of the acute VVC episode at day 14. Results from both of these studies are still pending but a new drug application has been issued to the FDA and the manufacturer is preparing for a drug launch in early 2022.

Alternative Therapies for Symptom Management

Nonprescription azoles are the only products available without a prescription to treat and cure a yeast infection. There are other products available without a prescription that are used only to relieve external itching and irritation related to VVC and not provide a cure (TABLE 5).

It is important for pharmacists to educate patients on these products because they will more than likely still require an antifungal to cure their infection. Homeopathic products, which use the theory of treating certain conditions with very small, diluted doses of similar natural substances, are also available for the relief of symptoms associated with VVC. Although these products are available for use, pharmacists should counsel patients that they have not been reviewed for safety and effectiveness and should be used with caution. Women should not use any of these products for more than 1 week with no relief and should be referred to their provider if symptoms worsen or do not improve.

Due to conflicting evidence in the literature, there continues to be a growing debate about the use and benefits of probiotics in the management and prevention of VVC. Probiotics are live microorganisms that can be formulated into foods, drugs, and dietary supplements. They may contain a single microorganism or a mixture of several species and have been studied in maintaining and recovering the imbalance of normal vaginal flora that is seen in VVC. Proposed mechanisms for probiotics include preventing Candida adhesion and growth to vaginal epithelial

### TABLE 5. SELECT ALTERNATIVE THERAPIES FOR EXTERNAL ITCHING AND IRRITATION

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Brand</th>
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<tbody>
<tr>
<td>Benzocaine 5%, benzalkonium chloride 0.13%</td>
<td>Vagi Care Cream</td>
</tr>
<tr>
<td>Benzocaine 20%, resorcinol 3%</td>
<td>Vagisil Maximum Strength Cream</td>
</tr>
<tr>
<td>Borax 3X, Collinsonia Canadensis 3X, Berberis Vulgaris 6X, Hamamelis Virginiana 6X</td>
<td>Yeast Gard Advanced suppository (homeopathic)</td>
</tr>
<tr>
<td>Candida albicans 30X, Kreosotum 30X, Natrium muriaticum 12X, sulphur 12X</td>
<td>Azo Yeast Plus (homeopathic)</td>
</tr>
<tr>
<td>Hydrocortisone 0.1%</td>
<td>Cortizone 10 Intensive Healing Feminine Relief Anti-Itch Cream</td>
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*This list is not all inclusive.*
The Role of the Pharmacist and Pharmacy Technician

Pharmacists play a key role in educating patients on prevention, as well as appropriate medication administration and adherence. This is an important part of the management of acute VVC and eliminating the chances of recurrence. Encouraging changes in lifestyle and hygiene habits can be helpful in taking preventive measures, especially for patients with RVVC. Yeast thrive in warm and moist environments; therefore, avoiding tight-fitting clothing, synthetic underwear, and not staying in damp clothes (eg, bathing suit) for long periods of time can prevent growth of vaginal yeast. Instead, recommend cotton undergarments and loose-fitting clothes. Certain hygiene products, such as scented sanitary pads or tampons, perfumed soaps, vaginal sprays, and douches can cause irritation and potentially alter the balance of normal flora or vaginal pH. For these reasons, nonscented hygiene products are preferred and women should be counseled on avoiding excessive douching. Monitoring underlying conditions is also key in preventing chronic infections. Patients with diabetes should be encouraged to test their blood glucose regularly and all patients should avoid unnecessary use of antibiotics.

It is important for the pharmacist to take a thorough medical history, including past medical history and current medications, and to obtain specific information about symptoms. Taking patient preferences into consideration regarding treatment is also important; some patients may be more comfortable with or prefer one dosage form over another, for example. This information will help to determine which patients require referral as well as identifying those who may have an underlying condition that warrants additional follow-up. The CASE and CASE FOLLOW-UP highlight a patient with VVC and how the pharmacist may be able to assist the patient.

**CASE**

Patient SZ is a 43-year-old woman with a past medical history of recurrent VVC infections. She presents to your pharmacy with complaints of internal and external vaginal itching and a thick white discharge with no odor. She seems to constantly get yeast infections around the time of her period. During her last episode, her provider prescribed fluconazole. She cannot reach her provider and would like to know if she can purchase anything without a prescription to help her symptoms.

**RESPONSE:** In this situation, the patient should not self-treat their symptoms. The patient should be referred to their provider since they have a history of recurrent VVC infections. The patient should be counseled to discuss an appropriate prescription treatment with their provider. The patient should be asked about their other chronic disease states that could be causing the frequent VVC infections as well as hygiene and lifestyle habits.

**CASE FOLLOW-UP**

Patient SZ returns to your pharmacy the next day with a prescription for ibrexafungerp 150 mg 2 tablets twice a day. The patient has never heard of this medication and would like information on it. The technician fills the prescription and refers the patient to the pharmacist for counseling.

**RESPONSE:** The patient was given a total daily dose of ibrexafungerp 600 mg, which is indicated for VVC and especially for those who may be resistant to fluconazole. Ibrexafungerp is available as a pack of 4 oral tablets. The patient will take two 150-mg tablets (300 mg) twice a day approximately 12 hours apart with or without food. If the first 2 tablets are taken in the morning, the second 2 tablets should be taken that same day in the evening. If the first 2 tablets are taken in the afternoon or evening, the second 2 tablets should be taken the following morning. If a dose is missed, the patient should take it as soon as they remember. The patient should also make sure to let their provider know if they take any other medications while on ibrexafungerp. The most common AEs include diarrhea, nausea, vomiting, abdominal pain, and dizziness. While the AEs should go away, the patient needs to speak to their provider if they worsen.

The pharmacy technician may often be the first person a patient will approach when inquiring about nonprescription products for VVC. Understanding the “red flags” or reasons for referral to a prescriber (eg, foul-smelling discharge, discharge with an abnormal color, presence of fever or younger than 12 years) can help technicians identify those who require further work-up by the pharmacist. Technicians can also help to identify those patients at risk of VVC and refer them to the pharmacist for counseling.
In addition, technicians can ensure that patients with RVVC are refilling their medications on time. Those who appear to be nonadherent should be referred to the pharmacist.

While it is advised to abstain from sexual intercourse during treatment of VVC, patients should be reminded that topical intravaginal antifungals can weaken the effectiveness of condoms, diaphragms, or other barrier devices.\textsuperscript{1,3} Patients should avoid the use of tampons during treatment with topical intravaginal antifungals as they may absorb the medication. This could decrease medication efficacy and cause additional internal vaginal irritation. Appropriate medication administration of vaginal suppositories and intravaginal creams and ointments should also be discussed with the patient to ensure appropriate use. Patients should be encouraged to wear pads to avoid vaginal leakage and staining of undergarments that can occur with the topical formulations. Instructing the patient to lie down after inserting the medication-filled applicator can help to avoid the leakage that is experienced.\textsuperscript{15}

Pharmacists and pharmacy technicians can assist with raising awareness of the importance of treating and preventing VVC, and educate patients regarding the available prescription therapies as appropriate. All prescribed medications should be continued for the full course of therapy even if symptoms resolve quickly. The dosing of the 2 available oral prescription therapies differs, so it is important for pharmacists to review specific instructions to minimize any confusion. Additionally, patients should be counseled that their symptoms may worsen before they get better due to the AEs that mimic VVC and they should not discontinue their medication. If being treated for recurrent VVC infection, patients should adherence to their regimen and complete their entire course of therapy even if they do not present with symptoms.

Conclusion

There are numerous factors and mechanisms that can alter the vaginal environment and the makeup of the normal flora that inhabit the vagina, resulting in VVC. Management of VVC involves eliminating the signs and symptoms by treating the infection but also identifying the underlying risk factors. Pharmacists should educate those patients who have modifiable risk factors in order to prevent recurrence. It has been speculated that nonadherence to therapies, misuse of nonprescription products, and molecular changes to Candida species have caused an increase in the prevalence of azole-resistant Candida. This has warranted a look at new and emerging antifungal therapies, such as ibrexafungerp, to treat NCAC and those with complicated VVC. Isolating specific targets on fungal species or identifying overexpression of transporters within the fungi will help to continue the advances in developing oral and topical fungicidal antifungals for the management of VVC, RVVC, and NCAC.

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study of oral ibrexafungerp vs fluconazole in vulvovaginal candidiasis
27. Published online October 21, 2021. doi:10.1093/cjphj/2021.0.10.2708
14. 1/11:1471-0528.16972
INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.

Go to www.pharmacytimes.org/go/VVC-antifungal (technicians: www.pharmacytimes.org/go/VVC-antifungal-tech) to access the online version of this activity.

Click “Proceed,” then complete the online pretest.

Once completed, click “Next” until reaching the activity posttest.

Complete the online posttest and activity evaluation form.

After successfully completing the posttest and evaluation form, this information will be uploaded to CPE Monitor. You must complete these steps before the activity expires in order to receive your credit.

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SYSTEM REQUIREMENTS FOR COMPLETION:
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POSTTEST QUESTIONS*

1. Uncomplicated vulvovaginal candidiasis (VVC) is thought to be caused by which of the following Candida species?
   A. Candida tropicalis
   B. Candida glabrata
   C. Candida albicans
   D. Candida krusei

2. Which of the following is a clinical feature of VVC?
   A. Foul-smelling discharge
   B. Curd-like discharge
   C. Vaginal pH greater than 4.5
   D. Gray-like color discharge

3. Which of the following patients should be referred to their primary care physician for further evaluation of their symptoms?
   A. A 10-year-old female with white discharge and internal and external vaginal itching
   B. A 28-year-old woman who just completed a course of antibiotics and was treated for a yeast infection last year
   C. A 30-year-old woman presenting with external vaginal itching and irritation who was diagnosed with VVC last year
   D. A 16-year-old female who had a yeast infection 6 months ago and currently has symptoms again during her period

4. The CDC recommends which topical antifungal length of therapy for pregnant women?
   A. 1 day
   B. 3 days
   C. 7 days
   D. 14 days

5. Which treatment regimen would be considered appropriate for a woman with recurrent VVC?
   A. Terconazole 0.8% cream, 5 g intravaginally daily for 3 days
   B. Butoconazole 2% cream, 5 g intravaginally in a single-dose application
   C. Terconazole 0.4% cream, 5 g intravaginally daily for 10 to 14 days
   D. Fluconazole 150 mg single dose

6. Which statement is true regarding topical azole formulations?
   A. Use at bedtime to minimize medication leakage.
   B. They are compatible with latex condoms and diaphragms.
   C. They should be discontinued if they cause burning or irritation.
   D. The 1- and 3-day treatments are more effective than the 7-day treatment.

7. Which of the following is true of ibrexafungerp?
   A. Dosage adjustment is needed when coadministering with weak or moderate CYP3A4 inhibitors.
   B. It is a triterpenoid antifungal that inhibits the enzyme 1,3-glucan synthase.
   C. It is an intravaginal therapy administered once daily for 3 days.
   D. Total treatment dose is 300 mg within 24 hours.

8. Which is true regarding a phase 2 study comparing ibrexafungerp and fluconazole?
   A. The study included a single dose of ibrexafungerp and fluconazole oral tablets.
   B. At day 10, the clinical cure rates for ibrexafungerp and fluconazole were 30%.
   C. At day 25, patients continuing with no signs or symptoms of VVC were 50% in the ibrexafungerp and fluconazole groups.
   D. Ibrexafungerp was concluded to be equally efficacious to the FDA-approved dosing of fluconazole with respect to mycological cure but with continued efficacy.
9. A 19-year-old female presents to your pharmacy with complaints of curd-like discharge and vaginal itching. She is a lifeguard at the local day camp. Upon questioning, she tells you she had a yeast infection 5 months ago with the same symptoms. At the time, she was prescribed oral fluconazole by her physician. She asks you if there is anything over the counter she can use. What do you recommend for this patient?

A. Tell her to see her physician because she had an infection diagnosed 5 months ago.
B. Recommend any of the OTC topical azoles for either 1, 3, or 7 days.
C. Recommend a 7-day OTC topical azole only because they are most effective.
D. Tell her to see her physician for fluconazole 150 mg weekly for 6 months.

10. Which of the following is the most common adverse effect of ibrexafungerp that pharmacists should counsel patients on?

A. Leg cramps
B. Abdominal pain
C. Taste disturbances
D. Headache

*Questions for pharmacy technicians are available at www.pharmacytimes.org/go/VVC-antifungal-tech (pharmacists please see this link: www.pharmacytimes.org/go/VVC-antifungal)
Addressing the Challenges of Managing CAD/PAD and Associated Comorbidities: The Role of Antithrombotic Therapy

EDUCATIONAL OBJECTIVES
At the completion of this activity, the participant will be able to:
• Explain the unmet need and clinical burden of coronary artery disease/peripheral artery disease (CAD/PAD)
• Examine the evidence-based treatment guidelines for patients with CAD/PAD
• Analyze clinical data exploring therapies with the potential to improve patient outcomes and reduce complications
• Identify the role of the pharmacist in making clinical recommendations, counseling and educating patients, and managing associated comorbidities of CAD/PAD

TARGET AUDIENCE: Pharmacists
ACTIVITY TYPE: Application
RELEASE DATE: December 6, 2021
EXPIRATION DATE: December 6, 2022
ESTIMATED TIME TO COMPLETE ACTIVITY: 3.0 hours
FEE: This lesson is offered for free at www.pharmacytimes.org.

Background
Atherosclerosis is a major vascular disease, characterized by plaque formation in arteries and capillary beds that can lead to significant morbidity and mortality. Atherosclerosis develops over time as lipid material deposits in the subendothelial space of blood vessels. As pathological lipid material accumulates, inflammation, driven by cells such as macrophages, T-helper cells, and lymphocytes, further upregulates lipid deposition and development of the atherosclerotic plaque. As the atheroma increases in depth, the vessel narrows and can restrict blood flow to muscles and major organs such as the heart or brain. As these vessels narrow, specifically in the myocardial vascular bed, oxygen supply may not adequately meet the demands of the downstream target. Coronary artery disease (CAD) is defined by the development of atherosclerosis in the major coronary arteries, whereas peripheral artery disease (PAD) is defined as the presence of atherosclerosis in the peripheral vasculature. As lipid accumulation progresses, the intimal layer of the endothelium can undergo erosion, consequently causing platelet activation, aggregation, and ultimately occlusion of the artery. Severe narrowing or complete occlusion of these vessels blocks oxygen delivery to downstream targets such as the myocardium, leading to acute coronary syndrome (ACS), acute limb ischemia in patients with PAD, or noncardioembolic ischemic stroke. With thrombus formation playing a significant role in the progression of atherosclerotic disease, antithrombotic therapies such as antiplatelet agents and anticoagulants have been a major target for reducing morbidity and mortality associated with CAD and PAD. This article will focus on not only the management of antithrombotic therapies, but also the comorbidities and risk factors associated with the development of CAD and PAD in high-risk patient populations.
The Burden of CAD and PAD

**CAD**

CAD remains the leading cause of mortality in the United States with more than 650,000 deaths each year. In 2017, 18 million people older than 20 years had been diagnosed with CAD in the United States. Each year, it is estimated that myocardial infarction (MI) occurs in approximately 605,000 patients, with 200,000 of those occurring in someone who has already had a previous MI. After an initial MI, patients are not only at risk for a recurrent MI at a rate of 16.2% within 7 years, but for patients over age 65 years,

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>General management</th>
<th>Treatment goals</th>
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| Hyperlipidemia | • Lifestyle modifications  
• Pharmacologic therapies  
• Moderate-intensity statin in patients with T2D aged 40-75; or patients aged 40-75, LDL-C 70-189 mg/dL and ASCVD risk ≥7.5%-20%  
  + Atorvastatin 10-20 mg/day or rosuvastatin 5-10 mg/day  
• High-intensity statin in patients if LDL-C ≥190 mg/dL, ASCVD risk ≥20%, T2D and high ASCVD risk, or established ASCVD  
  + Atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day  
  + Ezetimibe 10 mg/day or PCSK9 inhibitor (alirocumab or evolocumab) may be reasonable for patients who have progression of CAD or PAD while on maximally tolerated statin therapy. | Moderate-intensity statin goal: 30%-49% reduction from baseline LDL-C values  
High-intensity statin goal: at least 50% reduction from baseline LDL-C values |
| Hypertension | • Lifestyle modifications  
• Pharmacologic therapies in CAD or PAD  
  + First-line therapies: ACEi or ARB, thiazide or thiazide-like diuretics, and DHP CCB  
  + Adjunctive therapies for specific indications or refractory hypertension: β-blockers, non-DHP CCB, spironolactone or nitrates | • Target blood pressure <140/90 mm Hg in patients >65 years  
• Target blood pressure <130/80 mm Hg in patients <65 years, those with high risk of ASCVD events (score ≥10%), or established ASCVD |
| T2D | • Lifestyle modifications  
• Pharmacologic therapies  
  + First-line: metformin  
  + Preferred therapies in CAD/PADa  
    ▪ Dulaglutide 0.75 mg SC weekly  
    ▪ Liaglutide 0.6 mg SC daily x1 week, then 1.2 mg SC daily  
    ▪ Semaglutide 0.25 mg SC weekly  
    ▪ Empagliflozin 10 mg/day  
    ▪ Canagliflozin 100 mg/day  
  + Preferred therapies in CHFa  
    ▪ Empagliflozin 10 mg/day  
    ▪ Canagliflozin 100 mg/day  
    ▪ Dapagliflozin 10 mg/day | Target hemoglobin A1c <7%-8% |
| Tobacco use | • 5 A’s – Ask, Advise, Assess, Assist, and Arrange  
• NRT  
  + Patch – 21 mg daily for ≥10 cigarettes/day; 14 mg daily for <10 cigarettes/day  
  + Gum or lozenge – 4 mg if first tobacco use is ≤30 minutes from awakening; 2 mg if first tobacco use is >30 minutes from awakening  
  + Bupropion SR 150 mg daily for 3 days, then 150 mg twice daily (in combination with NRT)  
  + Varenicline 0.5 mg daily for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily for 3-6 months | Sustained cessation |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; DHP, dihydropyridine; GLP-1, glucagon-like peptide-1; LDL-C, low-density lipoprotein cholesterol; NRT, nicotine replacement therapy; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin/kexin 9; SGLT2, sodium-glucose cotransporter-2; SC, subcutaneous; SR, sustained release; T2D, type 2 diabetes.

aInitial doses are listed for reference. Further dose modifications are required for continuation of treatment.
one in 40 will develop a stroke within the first 6 months after an initial MI, and nearly 20% of patients will die of cardiac causes within the first year.³ CAD also remains a significant economic burden, costing nearly $220 billion annually from direct costs associated with health care utilization, medication, and indirect costs such as loss of productivity. The average cost for each MI averages $18,931, with an additional $8037 added during the first year for repeat hospitalizations and emergency department visits.⁶

PAD

Although CAD is often the focus of atherosclerosis, PAD is also a large burden on the US health care system. Approximately 8.5 million Americans older than 40 years and more than 200 million individuals worldwide have some degree of PAD. PAD predominantly affects older individuals; approximately 6% to 7% of people older than 40 years have PAD, whereas 29% of those 70 years or older are affected.³⁴ Significant racial differences are also seen in the prevalence of PAD; just 5.5% of Caucasians are affected, but more than 10% of non-Hispanic Blacks have PAD. Although PAD is the direct cause of death in a small number of those affected (57,000 deaths in 2018), patients with PAD are 2.5 times more likely to develop an MI than those without PAD. Additionally, patients with PAD have a 35% higher risk of having a stroke. One of the most traumatic complications of PAD occurs in the setting of acute limb ischemia requiring lower extremity amputation. Between 2000 and 2008, 186,338 amputations occurred in patients hospitalized with PAD. These patients experience almost a 2 times higher rate of mortality than those who do not require an amputation for PAD.⁶

The evaluation for PAD is completed by obtaining the patient’s brachial and ankle artery blood pressure and determining the ratio of ankle to brachial blood pressure or ankle-brachial index (ABI). The diagnosis of PAD is confirmed when the ABI is lower than 0.9.⁹ Patients with PAD may initially have minimal to no symptoms, but can progress to severe pain due to intermittent claudication that is caused by severe reduction in blood flow due to arterial atherosclerosis, thus limiting oxygen delivery to the lower extremities while ambulating.⁵

### Risk Factors and Prevention of Atherosclerotic Cardiovascular Disease (ASCVD) Events

The presence of CAD, PAD, previous MI, or stroke are collectively referred to as clinical ASCVD. Major modifiable risk factors for the development of atherosclerosis include elevated blood lipid levels, specifically low-density lipoprotein cholesterol (LDL-C), hypertension, tobacco use, elevated body mass index (BMI), and type 2 diabetes (T2D) (TABLE 1⁵⁻¹⁵ and TABLE 2⁶⁻¹²,¹⁵). Additionally, alcohol, premature family history of heart disease, and sedentary lifestyle are also predictors for the development of atherosclerosis.¹⁰

### Hyperlipidemia

Due to the significant role LDL-C plays in the development and progression of ASCVD, statin therapy remains a cornerstone for reducing the risk of ASCVD events. In patients without ASCVD, statin therapy is indicated in 4 high-risk groups, as listed in TABLE 1.¹⁰⁻¹⁵ The most recent guidelines for secondary prevention and risk reduction of ASCVD recommend initiating high-intensity

<table>
<thead>
<tr>
<th>TABLE 2. LIFESTYLE MODIFICATIONS FOR Atherosclerotic Cardiovascular Disease(ASCVD)¹⁰⁻¹⁵</th>
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<tbody>
<tr>
<td><strong>Lifestyle modifications for hypertension, hyperlipidemia, and type 2 diabetes</strong></td>
</tr>
<tr>
<td><strong>Salt reduction</strong></td>
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<td><strong>Diet</strong></td>
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<td><strong>Physical activity</strong></td>
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<tr>
<td><strong>Alcohol consumption</strong></td>
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</table>

### STAR*⁻⁸

★ What therapies reduce the risk of ASCVD events in patients with hyperlipidemia, hypertension, and/or T2D and concomitant CAD or PAD?

*S = Stop; T = Think; A = Assess; R = Review
Hypertension

Hypertension is strongly associated with the development of vascular injury in CAD and PAD. Definitions of hypertension vary slightly among different guidelines but generally fall between greater than 130-140/80-90 mm Hg during at least 2 separate occasions. Over time, hypertension leads to endothelial hypertrophy and vascular smooth muscle growth, ultimately causing a reduction in the vascular lumen diameter. These pathological changes cause damage to vascular walls and further increase the risk of MI, stroke, and arterial thrombosis.

The American College of Cardiology (ACC) and American Heart Association (AHA) 2017 guidelines identify a blood pressure of greater than 130/80 mm Hg along with either clinical ASCVD or an ASCVD 10-year risk of greater than or equal to 10% as the threshold for initiating pharmacologic therapy, whereas the International Society of Hypertension (ISH) 2020 guidelines recommend pharmacologic therapy once blood pressure is greater than or equal to 140/90 mm Hg. Blood pressure goals in patients with CAD and PAD also vary according to the presence of comorbidities. In patients with stable CAD and PAD, ISH and ACC/AHA guidelines recommend a blood pressure target of at least less than 130/80 mm Hg in patients without compelling indications, and a goal of lower than 120/80 mm Hg for patients with ASCVD, chronic kidney disease (CKD), or diabetes, as more stringent blood pressure targets have been shown to reduce the risk of CV complications by 25%. Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) are a cornerstone of antihypertensive therapies in all patients and are strongly recommended as first-line therapy in patients with stable CAD and PAD. Gradual titration to the maximum recommended dose should occur to achieve the target blood pressure within 3 months. β-blockers and non-dihydropyridine calcium channel blockers (CCBs) (verapamil and diltiazem) may be indicated and necessary for patients with stable CAD who develop or continue to experience angina after maximizing first-line antihypertensive therapies. In the absence of angina or other compelling indications, thiazide or thiazide-like diuretics and dihydropyridine CCBs such as amlopidine or nifedipine are additional first-line therapies if target blood pressure is not achieved. Both the ACC/AHA and ISH guidelines recommend initiating combination drug therapy consisting of 2 first-line treatment agents for patients with severely uncontrolled blood pressure (>160/90 mm Hg) and a history of CAD or PAD, although cautious application of this approach should be used in elderly patients or those at risk for developing significant adverse effects. All patients should be educated on lifestyle modifications to achieve target blood pressure goals.

T2D

It is estimated that approximately 26 million adults in the United States have a diagnosis of T2D, and in 2018, 1.5 million adults were newly diagnosed with T2D. T2D is associated with a 67% to 85% increased risk of CV death due to stroke, MI, or heart failure compared with patients without diabetes. Since the late 1990s, the rate of atherosclerotic complications of diabetes has decreased substantially, yet diabetes remains one of the strongest predictors of MI, stroke, or need for amputation in patients with PAD. Hyperglycemia, even in the “prediabetes” stage, augments lipid deposition in the endothelium of vascular smooth muscle, even in the setting of well-controlled lipid levels. Over time, as diabetes progresses, increased oxidative stress and inflammation cause accelerated atheroma calcification and destabilization of atherosclerotic plaques, increasing the likelihood of atherothrombosis. These pathological changes highlight the importance of aggressive lipid control in patients with T2D. For patients aged 40 to 75 years with T2D with low-ASCVD risk (<7.5%), moderate-intensity statin therapy should be used in addition to lifestyle modifications. In high-ASCVD risk (≥20%) patients with T2D, high-intensity statin therapy is reasonable for the prevention of CV events. All patients with T2D and a history of ASCVD events should receive high-intensity statin therapy and if target LDL-C level of lower than 70 mg/dL cannot be achieved with statin therapy alone, the use of ezetimibe or PCSK9 inhibitors (alirocumab or evolocumab) may be considered.

For patients with T2D and ASCVD, a target hemoglobin A1c of lower than 7% to 8% should be achieved by implementation of life-
### TABLE 3. ANTITHROMBOTIC THERAPY LANDMARK TRIALS50–34

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Patient population</th>
<th>Intervention</th>
<th>Outcomes (HR [95% CI])</th>
</tr>
</thead>
</table>
| ARRIVE    | ASCVD primary prophylaxis | Aspirin daily vs placebo | • MACE: 0.81 (0.64-1.02)  
  • MI: 0.53 (0.36-0.79)  
  • GI bleeding: 2.11 (1.36-3.28) |
| ASCEND    | T2D without known ASCVD | Aspirin daily vs placebo | • MACE: 0.88 (0.79-0.97)  
  • Major bleeding: 1.29 (1.09-1.52) |
| ASPREE    | Healthy patients aged ≥70 years without a history of CAD or ASCVD | Aspirin daily vs placebo | • All-cause death: 1.14 (1.01-1.29)  
  • CV death: 0.82 (0.62-1.06)  
  • Major hemorrhage causing death: 1.13 (0.66-1.94) |
| CHANCE    | Patients aged ≥40 years and acute minor ischemic stroke or TIA | Clopidogrel-based DAPT x21 days then aspirin until day 90 vs aspirin x90 days | • Stroke: 0.67 (0.57-0.81)  
  • MACE: 0.69 (0.58-0.82)  
  • GUSTO severe bleeding: 0.94 (0.24-3.79)  
  • Any bleeding: 1.41 (0.95-2.10) |
| COMPASS   | Patients with stable CAD aged ≥65 years, or <65 years with at least 2 additional risk factors: smoking, diabetes, CKD, HF; or non-lacunar ischemic stroke ≥1 month prior  
Excluded patients at a high risk of bleeding, recent stroke, or indications for Dalteparin, antiocoagulation, or other antithrombotic therapies | Rivaroxaban 5 mg twice daily vs rivaroxaban 2.5 mg twice daily plus aspirin vs aspirin alone | • MACE (rivaroxaban 2.5 and aspirin vs aspirin alone): 0.76 (0.66-0.86)  
  • Major bleeding (rivaroxaban 2.5 and aspirin vs aspirin alone): 1.70 (1.40-2.05)  
  • Nonfatal, non-ICH, symptomatic major bleeding (rivaroxaban 2.5 and aspirin vs aspirin alone): 1.43 (0.89-2.29)  
  • Net clinical benefit (rivaroxaban 2.5 and aspirin vs aspirin alone): 0.80 (0.70-0.91) |
| GLOBAL LEADERS | Patients with CAD requiring PCI ≥47% of patients presenting with ACS  
Excluded patients at heightened bleeding risk or other antithrombotic therapies | Ticagrelor-based DAPT x1 month then ticagrelor x12 months vs DAPT x12 months, then aspirin x12 months | • All-cause death or MI: 0.87 (0.75-1.01)  
  • BARC bleeding ≥3: 0.97 (0.78-1.20) |
| HOST-EXAM | Patients with PCI and stable on DAPT for 6-18 months | Clopidogrel 75 mg daily vs aspirin 100 mg daily | • MACE: 0.73 (0.59-0.90)  
  • BARC bleeding ≥2: 0.70 (0.51-0.98) |
| MASTER DAPT | Patients with CAD requiring PCI at high risk for bleeding based on history of bleeding, indication for OAC, or PRECISE-DAPT score ≥15  
Excluded patients ≥60% of patients presenting with ACS | DAPT x1 month vs DAPT for at least 3 months | • MACE: 1.0 (0.76-1.32)  
  • Any BARC bleeding: 0.64 (0.54-0.76)  
  • Net adverse clinical events: 0.94 (0.76-1.15) |
| PEGASUS-TIMI 54 | Patients with an MI within 3 years aged ≥50 years and 1 additional high-risk feature: age ≥65 years, diabetes, recurrent MI, multivessel CAD or CKD | Ticagrelor 90 mg twice daily and aspirin vs ticagrelor 60 mg twice daily and aspirin vs aspirin alone | • MACE (ticagrelor 60 and aspirin vs aspirin alone): 0.84 (0.74-0.95)  
  • TIMI major bleeding (ticagrelor 60 and aspirin vs aspirin alone): 2.32 (1.68-3.21)  
  • TIMI minor bleeding (ticagrelor 60 and aspirin vs aspirin alone): 3.31 (1.94-5.63)  
  • Fatal bleeding or nonfatal ICH (ticagrelor 60 and aspirin vs aspirin alone): 1.20 (0.73-1.97) |
| POINT | Patients with minor ischemic stroke or high-risk TIA | Clopidogrel-based DAPT x90 days vs aspirin x90 days | • MACE: 0.75 (0.59-0.95)  
  • Major hemorrhage: 2.52 (1.04-6.87)  
  • Minor hemorrhage: 3.12 (1.67-5.83) |
| SMART-CHOICE | Patients with CAD requiring PCI Most patients with stable angina, small proportion with ACS | DAPT x3 months; then P2Y12 vs DAPT x12 months | • MACE: 0.40 (0.29-0.54)  
  • BARC bleeding ≥2: 0.58 (0.36-0.92) |
| THALES | Patients aged ≥40 years and acute minor to moderate ischemic stroke or TIA | Ticagrelor-based DAPT x30 days vs aspirin x30 days | Stroke or death: 0.83 (0.71-0.96)  
  Stroke: 0.81 (0.69-0.95)  
  Severe bleeding: 3.99 (1.74-9.41)  
  ICH or fatal bleeding: 3.66 (1.48-9.02) |
| THEMIS | Patients with T2D and stable CAD aged ≥50 years  
Excluded patients with history of MI or stroke ≥80% of patients had received either PCI and/or CABG | Ticagrelor 60 mg twice daily plus aspirin alone | • MACE: 0.90 (0.81-0.99)  
  • BARC bleeding ≥3: 2.36 (1.96-2.84) |
| TWILIGHT | Patients with CAD requiring PCI ≥63% of patients presenting with ACS | Ticagrelor-based DAPT x3 months; then ticagrelor vs ticagrelor-based DAPT x12 months | • MACE: 0.97 (0.76-1.24)  
  • BARC bleeding ≥2: 0.56 (0.45-0.68) |
| VOYAGER | Patients aged ≥50 years with documented symptomatic PAD requiring revascularization  
Excluded patients at heightened bleeding risk or duration of clopidogrel therapy expected to extend past 6 months | Rivaroxaban 2.5 mg twice daily plus aspirin vs aspirin alone | • ALI, major amputation for vascular cause, MI, ischemic stroke, or CV death: 0.85 (0.76-0.96)  
  • TIMI major bleeding: 1.43 (0.97-2.10)  
  • ISTH major bleeding: 1.42 (1.10-1.84)  
  • BARC bleeding ≥3: 1.29 (0.95-1.76) |

ACS, acute coronary syndrome; ALI, acute limb ischemia; ASCVD, atherosclerotic cardiovascular disease; BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; DAPT, dual antiplatelet therapy; GI, gastrointestinal; GUSTO, Global Use of Strategies to Open Occluded Arteries; HF, heart failure; ICH, intracranial hemorrhage; ISTH, International Society of Thrombosis and Haemostasis; MACE, major adverse cardiovascular event; MI, myocardial infarction; OAC, oral anticoagulation; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; TIMI, Thrombolysis in Myocardial Infarction; T2D, type 2 diabetes.
style changes, and the use of pharmacologic therapies with proven CV risk-reducing qualities.19 The American Diabetes Association (ADA) recommends metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, or glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as first-line treatment options for patients with T2D and ASCVD. The SGLT2 inhibitors empagliflozin and canagliflozin, but not dapagliflozin, have been shown to reduce the risk of major adverse cardiac event (MACE) outcomes. Only empagliflozin was shown to explicitly reduce the risk of CV and all-cause mortality when compared with placebo.19

The primary benefit of the SGLT2 inhibitors is the reduced risk of hospitalization for heart failure in patients with T2D. Alternatively, particular GLP-1 RAs have demonstrated benefit in reducing events such as CV death, stroke, and microvascular complications in patients with T2D. Liraglutide, injectable semaglutide, and dulaglutide are associated with significantly lower rates of MACE in patients with T2D. While all of these specific GLP-1 RAs require once-weekly subcutaneous injection with the exception of liraglutide which requires a daily injection, semaglutide is also available as an oral product. The injectable formulation of semaglutide was associated with a reduction of CV events compared with placebo, but the oral formulation did not show a lower rate of MACE compared with placebo, and is not indicated for reduction of CV events in patients with T2D.19 Lixisenatide and exenatide have not been shown to reduce cardiovascular events in patients with T2D.19

Antithrombotic Therapies

Antiplatelet therapies are a cornerstone of medical therapy in patients with CAD and PAD due to the significant role platelet activity has in causing MI, stroke, and arterial thrombus formation. The timing, combination of agents, and duration of their use are highly complex due to the interplay of various patient risk factors and populations. TABLE 3 includes a summary of the major trials discussed in the following sections.

CAD

For several decades, aspirin therapy has been recommended for the primary prevention of ASCVD events primarily due to its well-documented efficacy in secondary prevention; however, a more critical evaluation of aspirin for primary prevention has developed on the basis of several recent randomized controlled trials showing an increased risk of adverse effects that may outweigh benefits.20-22 The 2019 Primary Prevention of Cardiovascular Disease guidelines include low-dose aspirin for primary prevention as a IIb recommendation to patients aged 40 to 70 years who have a greater than 10% estimated risk of ASCVD and do not have increased risk of bleeding. Recently, the US Preventive Services Task Force (USPSTF) released draft recommendations limiting the use of aspirin for primary prevention to patients aged 40 to 59 years with a greater than or equal to 10% ASCVD risk score. Specifically, they suggest not initiating aspirin therapy for primary prevention in patients 60 years or older due to the increased risk of bleeding.35

Despite appropriate medical therapy, a significant proportion of patients with CAD or PAD may experience an ACS event. For patients who develop ACS and are medically managed without percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 inhibitor (clopidogrel or ticagrelor) is recommended for 12 months.36-38 Patients with ACS who undergo PCI with stenting are also indicated to receive DAPT for 12 months, although
the P2Y<sub>12</sub> inhibitor prasugrel may be used in these settings (FIGURE 2). For patients who require CABG in the setting of ACS, DAPT with clopidogrel for 12 months is listed as a Ia recommendation. Continuation of DAPT past 1 year is supported by a IIb recommendation in current guidelines specifically in those who received a drug-eluting stent, but careful patient selection should be conducted to avoid use in patients at an elevated risk of bleeding. At the completion of DAPT therapy, it is recommended to discontinue the P2Y<sub>12</sub> inhibitor therapy, while aspirin is continued indefinitely (FIGURE 2). Indefinite aspirin therapy is recommended by the AHA and ACC for all patients with stable CAD to prevent the development of MI or stroke. Alternatively, clopidogrel is recommended for those with a contraindication to aspirin.

Although DAPT reduces the risk of cardiovascular death and recurrent MI within the first year of PCI and stenting, it also carries a relatively high risk of bleeding. New approaches to the management of DAPT and antiplatelet therapy have produced promising results to maximize the efficacy and minimize the bleeding risks in several phases of CAD management.

P2Y<sub>12</sub> monotherapy

Recently, several trials have addressed alternative DAPT regimens aimed at reducing bleeding events while still preventing ischemic events. The TWILIGHT trial evaluated the use of ticagrelor monotherapy after 3 months of DAPT, compared with continuation of DAPT after PCI in a high-risk patient population. The results of this simple, yet novel approach showed a noninferior rate of ischemic outcomes but a significantly lower rate of minor and major bleeding in patients randomized to ticagrelor monotherapy. The SMART-CHOICE, GLOBAL LEADERS, and MASTER DAPT trials also evaluated P2Y<sub>12</sub> inhibitor monotherapy after 1-3 months of DAPT, revealing similar rates of MACE outcomes and similar or lower rates of bleeding compared with continuation of DAPT. Prasugrel has yet to be studied on a similar large scale, but one trial has shown similar outcomes by reducing the dose of prasugrel to 5 mg after 1 month of DAPT. These current studies along with future trials such as the TALOS-AMI trial will likely play an important role in guideline recommendations regarding the management of DAPT for patients who require PCI.

Continuation of P2Y<sub>12</sub> Inhibitor

Due to the relatively high percentage of patients developing recurrent ischemic events after completion of DAPT, it was theorized that continuation or addition of a P2Y<sub>12</sub> inhibitor would reduce the risk of ischemic events in patients with a remote history of MI or stroke or stable CAD, PAD, or at least an array of atherosclerotic risk factors, including elevated blood pressure in the presence of antihypertensive therapy, hyperlipidemia, or diabetes. The CHARISMA trial failed to show any meaningful benefit in ischemic or CV death with the addition of clopidogrel to aspirin over aspirin alone (6.8% with DAPT, 7.3% with aspirin; \( P = .22 \)) in patients with stable CAD. Moderate bleeding was increased by 38% in the DAPT-treated patients.

Similar to the CHARISMA trial, in the PEGASUS-TIMI 54 trial, patients with a history of MI who were at high risk for recurrent ACS were randomized to either 2 doses of ticagrelor and aspirin or aspirin alone. In this study of high CV risk patients, the use

**FIGURE 2. ANTITHROMBOTIC THERAPY AFTER ASCVD EVENTS**

<table>
<thead>
<tr>
<th>PCI with stent for STEMI or NSTEMI</th>
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<tbody>
<tr>
<td><strong>Guideline Recommendations</strong></td>
</tr>
<tr>
<td>DAPT for 1 year</td>
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<tr>
<td>Aspirin 81 mg daily plus</td>
</tr>
<tr>
<td>- Clopidogrel 75 mg daily OR</td>
</tr>
<tr>
<td>- Ticagrelor 90 mg twice daily OR</td>
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<tr>
<td>- Prasugrel 10 mg daily*</td>
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<tr>
<td>*<em>Alternative Regimen</em></td>
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<tr>
<td>Initial 3 Months</td>
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<tr>
<td>DAPT with Aspirin 81 mg daily plus</td>
</tr>
<tr>
<td>- Ticagrelor 90 mg twice daily</td>
</tr>
<tr>
<td><strong>Months 3-12</strong></td>
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<tr>
<td>Continue ticagrelor monotherapy or</td>
</tr>
<tr>
<td>change to aspirin plus</td>
</tr>
<tr>
<td>clopidogrel 75 mg to complete 12</td>
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<tr>
<td>months from event</td>
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<tr>
<th>Stable CAD Treatment Options</th>
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<tr>
<td>Continue DAPT in patients at</td>
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<tr>
<td>highest risk of recurrent events</td>
</tr>
<tr>
<td>and low bleed risk</td>
</tr>
<tr>
<td>Continue aspirin or clopidogrel</td>
</tr>
<tr>
<td>monotherapy</td>
</tr>
<tr>
<td>Continue aspirin and add low-dose</td>
</tr>
<tr>
<td>rivaroxaban 2.5 mg twice daily</td>
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</tbody>
</table>

ACC, American College of Cardiology; AHA, American Heart Association; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

*Alternative regimen of shortened duration DAPT and continuation of either ticagrelor monotherapy or changing to clopidogrel and aspirin is based on the results of recent randomized controlled trials. It has not been included in current ACC/AHA or ESC guidelines.

¶For patients older than 75 years or weighing <60 kg, consider reducing dose to 5 mg daily.

^If continuing ticagrelor, dose reduction to 60 mg twice daily is recommended.
of either dose of ticagrelor significantly lowered the incidence of CV death, MI, or stroke compared with aspirin monotherapy. While major bleeding was similar between treatment groups, more patients discontinued ticagrelor due to bleeding compared with the placebo group. There was no significant difference in the rates of fatal bleeding or nonfatal intracranial hemorrhage (ICH). When ticagrelor displayed beneficial effects on ischemic events, the elevated bleeding risk observed diminished the overall benefit seen with using ticagrelor and aspirin long term, even at a reduced dose of 60 mg twice daily. Preference for this approach may be used in patients at a particularly high risk of CV events with a low bleeding risk based on a validated scoring tool such as the DAPT-Score.30,43

Alternatively, the HOST-EXAM trial studied the effect of clopidogrel 75 mg monotherapy compared with aspirin 100 mg monotherapy in patients with stable CAD after receiving PCI. During the 24-month follow-up period, all-cause death, nonfatal MI, stroke, readmission for ACS, and serious bleeding were significantly lower in those treated with clopidogrel compared with those treated with aspirin (P = .003). Interestingly, although clopidogrel may exert greater antiplatelet effects leading to increased bleeding, the incidence of serious bleeding and minor gastrointestinal bleeding were also significantly lower in the clopidogrel treatment arm. While no difference in all-cause or CV death was observed in this trial, the results suggest clopidogrel may be a reasonable maintenance antiplatelet therapy regimen in patients who are categorized as high CV risk who prioritize avoidance of ischemic events.29

**PAD**

The AHA/ACC guidelines for the management of PAD provide a Ia recommendation for aspirin at a dose of 75 to 325 mg daily or clopidogrel 75 mg daily for the treatment of symptomatic patients (FIGURE 9,10,35).9 The use of these agents in patients with symptomatic PAD has shown a significant reduction in the risk of developing stroke, MI, and vascular death. For patients with asymptomatic PAD, antiplatelet therapy is given a slightly lower recommendation, as limited data suggest that it provides similar benefit. DAPT is often initiated in patients with PAD, particularly after endovascular intervention to prevent morbidity and mortality, although its use remains a point of controversy due to inconsistent results across several trials, thus it is only provided a IIa recommendation.9 In a subgroup analysis of the CHARISMA trial, 3096 patients with PAD, most of whom were symptomatic, were evaluated for the development of CV death, MI, or stroke. The primary composite outcome occurred in 7.6% of patients treated with DAPT versus 8.9% in patients treated with aspirin monotherapy (P = .18). The rate of fatal and nonfatal MI was significantly reduced by approximately 38% (P = .028) and the rate of hospitalization for unstable angina, transient ischemic attack (TIA), or need for revascularization was reduced by about 18% (P = .011). Minor bleeding was substantially increased by the addition of clopidogrel. Although there was no significant benefit of DAPT in the primary outcome, the reduction of MI may outweigh the increased observance of minor bleeding in patients with PAD.34

Ticagrelor has also been evaluated in patients with PAD. The EUCLID study compared the effectiveness of ticagrelor compared with clopidogrel as monotherapy for patients with an ABI of lower than or equal to 0.80 or who had previously received revascularization of the lower limbs. No significant difference was observed in the primary outcome of cardiovascular death, MI, or stroke between ticagrelor- and clopidogrel-treated patients.35 Notably, current AHA/ACC PAD guidelines do not address ticagrelor for antiplatelet treatment in patients with PAD.9

**Anticoagulation in CAD and PAD**

Although anticoagulation with vitamin K antagonists has been used in patients with CAD and PAD for a number of years, several trials highlighted the adverse risks associated with their use. While in several large-scale trials, the addition of warfarin provided a reduction in MACE, these benefits were strongly outweighed by the upwards of 50% relative risk increase in major bleeding and is not routinely recommended.46

With the advent of the direct acting oral anticoagulants (DOACs), a re-emergence of interest in the role of anticoagulation has surfaced over the past decade. Two trials, the APPRAISE-2 trial and the ATLAS AC 2-TIMI 51 trial, evaluated the use of apixaban and rivaroxaban, respectively, in addition to DAPT in patients with ACS.47,48 In both trials, rates of bleeding were significantly higher in patients receiving DAPT and DOAC therapy. While apixaban did not lead to any CV benefit, low-dose rivaroxaban was associated with a lower rate of CV death, MI, or stroke.48 Ultimately, due to risk of bleeding with the addition of apixaban or rivaroxaban, this antithrombotic approach was not incorporated into the treatment of patients during the acute and late phase (<12 months from event) management of ACS.57,48 Follow-up studies would be required to determine whether rivaroxaban could demonstrate similar CV benefits with lower rates of bleeding in patients who had stable CAD.

COMPASS was a large, randomized, double-blinded, placebo-controlled trial evaluating the addition of rivaroxaban in 27,395 patients with stable CAD and/or PAD.25 Patients with CAD were included, but patients younger than 65 years were required to have additional ASCVD risk factors (TABLE 3).25 The primary efficacy composite outcome of CV death, MI, or stroke was
lowered by 15% with the combination of rivaroxaban 2.5 mg twice daily and aspirin compared with aspirin alone ($P = .007$). Rivaroxaban 5 mg twice daily did not provide significant benefit over the aspirin monotherapy. Each of the individual outcomes of the composite, with the exception of MI, was statistically lower with the addition of low-dose rivaroxaban. There were statistically more major bleeds in patients treated with a combination of rivaroxaban and aspirin (3.1%) compared with aspirin alone (1.9%). Fatal bleeding, nonfatal symptomatic ICH, or symptomatic bleeding into a critical organ did not differ in those receiving rivaroxaban and aspirin versus aspirin alone. With any study evaluating augmented antithrombotic regimens, there will always be a need for careful examination of the benefit from the addition of an additional agent to reduce ischemic events and how this compares to increases in clinically important bleeding episodes. When looking at the net clinical benefit outcome in the COMPASS trial, there is a net 20% relative risk reduction in overall adverse effects (ischemic outcomes and bleeding events). While this may seem impressive, some experts suggest the overall benefit derived from the addition of rivaroxaban is not robust enough to treat a large proportion of this patient population. While the net clinical benefit outcome attempts to include bleeding events (fatal or bleeding into critical organs) that share a similar severity to CV death, MI, or stroke, this approach may minimize the impact on quality of life that patients experience from minor bleeding episodes. Additionally, in instances where patients had multiple major bleeding episodes, only the most severe form of bleed was included, thus minimizing the impact of bleeding in the overall net clinical benefit analysis.\textsuperscript{25} Despite the critiques and controversies presented, clinicians have been provided with an additional therapeutic agent that can provide benefit in reducing the morbidity and mortality associated with CAD. A discussion with patients sharing the risk and benefit of low-dose rivaroxaban can help guide the decision-making process as some patients may find the increased risk of bleeding reasonable to prevent the ischemic events that have a high rate of fatal and nonfatal sequelae.

In a subgroup analysis of the COMPASS trial including patients with symptomatic PAD or carotid artery disease, similar CV benefits were observed as the original trial. Because the complications of PAD are not confined to an MI, CV death, and stroke, an additional composite outcome of major adverse limb events (MALEs) including acute and chronic limb ischemia and major amputations was evaluated. Use of rivaroxaban 5 mg twice daily alone in comparison to aspirin alone did not reduce the risk of CV death, stroke, or MI but did significantly lower the risk of MALE events. In addition to reducing CV death, stroke, or MI, rivaroxaban 2.5 mg twice daily and aspirin also reduced the risk of MALE events by 46%. Specifically, major amputations, although rare in this subgroup, were reduced by 70%. With the addition of MALE events, the net clinical benefit was slightly higher than seen in the overall COMPASS population at 22%.\textsuperscript{49}

The VOYAGER PAD trial further measured the potential benefits of rivaroxaban. Patients were required to have had lower extremity revascularization within 10 days of randomization.\textsuperscript{34} Of the patients randomized to rivaroxaban plus aspirin, 15.5% experienced the primary outcome of acute limb ischemic, major amputation, MI, stroke, or CV death, compared with 17.8% of patients receiving aspirin only ($P = .009$). Of these individual outcomes, only major amputation was statistically lower in the rivaroxaban- plus aspirin-treated patients. Additional outcomes associated with lower extremity ischemia or revascularization were also significantly lower in patients randomized to rivaroxaban plus aspirin. Unsurprisingly, major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) and the Bleeding Academic Research Consortium (BARC) were significantly higher in the rivaroxaban and aspirin group compared with the aspirin group.\textsuperscript{34} Currently, the AHA/ACC and European Society of Cardiology (ESC) guidelines for the management of PAD do not include recommendations for the use of rivaroxaban, but it has gained FDA approval to reduce the risk of major CV events in patients with CAD or PAD.\textsuperscript{3,50}

**Antithrombotic Therapies in Specific Patient Populations**

**CAD/PAD and Diabetes**

**Mechanisms of Platelet Dysfunction**

Diabetes is associated with upregulation of platelet activity during vascular injury. This occurs through several mechanisms such as increased platelet adhesion molecules, von Willebrand factor antigen, and clotting factors.\textsuperscript{51,52} Insulin resistance can cause upregulation of the adenosine diphosphate P2Y\textsubscript{12} pathway and impaired fibrinolysis.\textsuperscript{52}

The combination of these effects leads to platelet hyperreactivity and increases the incidence of platelet-mediated thrombosis, the cause of MI, stroke, and arterial thrombosis in patients with CAD and PAD, and may contribute to the increased risk of MI, stroke, and CV death in patients with T2D compared with the general population.\textsuperscript{53}

**Antithrombotic Therapy**

Due to the significant interplay of diabetes and platelet function, extensive research has been conducted evaluating various antithrombotic regimens in patients with diabetes. Similar to primary prevention in the general population, aspirin use in patients with diabetes but without prior vascular events has yielded under-
whelming outcomes, resulting in varying national guideline recommendations. The ADA provides a level C recommendation for aspirin as a primary preventive strategy for patients with diabetes who have an elevated ASCVD risk such as those aged 50 years or older with at least 1 additional ASCVD risk factor (hypertension, family history of premature ASCVD, smoker, CKD, or hyperlipidemia) only if the risk of bleeding is low due to increased risk of bleeding seen in more recent studies.19,20 The ACC/AHA guidelines do not provide any specific recommendations for aspirin in patients with diabetes without CAD as a primary preventive measure, but do recommend aspirin as a reasonable strategy for select patients who are at an elevated risk for ASCVD events.19 The ESC guidelines also provide IIb recommendation for aspirin therapy in patients with diabetes at high or very high ASCVD risk in absence of any contraindications.54 High-risk patients are defined as those who have had diabetes for 10 or more years and have at least 1 other risk factor such as hypertension, hyperlipidemia, active smoker, or obesity. Very-high-risk encompasses patients with diabetes who have 3 or more of the previous risk factors, or evidence of end-organ dysfunction such as left ventricular hypertrophy, estimated glomerular filtration rate (eGFR) less than or equal to 30 mL/min/1.73m², proteinuria, or retinopathy.54

Due to the enhanced platelet activity associated with diabetes, a number of trials have evaluated various antithrombotic regimens at different stages of CAD. THEMIS was one of the largest studies evaluating an augmented antithrombotic regimen in patients with diabetes and CAD.22 Patients with a history of known MI or stroke were excluded. The composite outcome of CV death, MI, or stroke was not reduced in the ticagrelor treatment group, but MI and stroke were statistically lower in those receiving ticagrelor compared with placebo. Conversely, major bleeding according to TIMI, PLATO, and BARC criteria were all significantly higher in patients receiving ticagrelor. Although small, a significantly higher incidence of trauma-related ICH was also noted in those receiving ticagrelor.55 Collectively, the lack of benefit in the composite ischemic outcome, the small difference in reduced ischemic events did not outweigh the increased rate of adverse effects, thus ticagrelor cannot be recommended for primary prevention even in patients with diabetes who have an increased risk of MI and stroke.

In a subgroup analysis of the TWILIGHT trial, patients with diabetes treated with ticagrelor were significantly less likely to experience a major bleeding event compared with those who continued to receive DAPT (1.1% vs 3.1%, respectively; \( P = .001 \)). Additionally, no significant difference was observed in the composite ischemic end point of CV death, MI, or stroke.53 This approach may be a suitable alternative regimen for those patients who are at a particularly high risk of bleeding to ensure ongoing antithrombotic therapy is provided to patients after PCI.

Another decision point occurs after 12 months of antithrombotic therapy from PCI. Two large-scale trials found clopidogrel monotherapy to be a reasonable antithrombotic strategy for patients with diabetes and stable CAD. In CAPRIE, patients were randomized to receive clopidogrel 75 mg daily or aspirin 325 mg daily after either an MI or stroke, or those with symptomatic PAD.56 In the patients with diabetes, those who received clopidogrel had an improved net clinical benefit compared with those who received aspirin.57 Unfortunately, patients with diabetes only represented about 20% of the trial population, and the use of higher dose aspirin limits conclusions regarding the safety and efficacy in current day practice. In the HOST-EXAM trial’s prespecified analysis of patients with diabetes treated with clopidogrel, the composite of all-cause death, nonfatal MI, stroke, readmission for ACS, and major bleeding was lower compared with those treated with aspirin.58 The ESC guidelines provide a IIb recommendation for the use of clopidogrel for secondary prevention over aspirin in patients with ASCVD.54

Although a focus on antithrombotic therapies predominates in patients with diabetes, anticoagulation may still be a therapeutic option to minimize ischemic outcomes. In the COMPASS trial, CV death, stroke, and MI were 21.5% lower in patients with diabetes treated with rivaroxaban and aspirin, and the incidence of stroke was statistically lower in those treated with rivaroxaban and aspirin (1.2%) versus those only receiving aspirin (2.1%). While major bleeding was significantly higher in the rivaroxaban-treated patients \( (P = .0006) \), no significant difference in fatal bleeding was observed. When fatal bleeding or bleeding into a critical site was included in the net clinical benefit outcome, the addition of rivaroxaban showed a 22% benefit, whereas when major bleeding was included, no significant benefit was observed.58 This again suggests patients should be informed about the overall risk-benefit profile from the addition of rivaroxaban and should play a role in the decision to initiate this therapy.

**CAD/PAD and Stroke**

**Mechanisms of Platelet Dysfunction**

Patients with CAD and PAD are at a heightened risk for noncardioembolic ischemic stroke.5 Intracranial and carotid artery stenosis follows a similar pathophysiological process as in CAD and PAD. As the carotid arteries and intracranial arteries supply specific areas of the brain, blockage of these vessels can cause catastrophic neurologic consequences.59 Neurologic symptoms of stroke (e.g., facial or limb numbness or weakness, altered mental status, aphasia, vision...
changes) can develop within seconds to minutes of artery occlusion. More than 7.6 million adult Americans have had a stroke and rates are expected to increase to nearly 11 million adults by the year 2030. After an initial stroke, 16% to 21% of patients will experience a recurrent stroke. Unsurprisingly, the risk factors for CAD and PAD are also predictors for the development of stroke. Glycemic, blood pressure, and lipid control as outlined previously can significantly reduce the risk of an initial and recurrent ischemic stroke by 25% to 65%.

Antithrombotic therapy
As the pathophysiology of ischemic stroke closely resembles that of CAD and PAD, the use of antiplatelet therapies remains a mainstay of treatment in patients with noncardioembolic stroke. DAPT has shown greater efficacy than aspirin monotherapy in patients with TIA or minor ischemic stroke. In the CHANCE and POINT trials, patients were randomized to either early DAPT with clopidogrel for 21 to 90 days, respectively, or aspirin monotherapy for 90 days. Patients receiving only aspirin had a higher rate of ischemic stroke compared with those receiving initial DAPT in both trials. A small but significant difference in major bleeding was observed in the POINT trial and may be related to the longer duration of DAPT compared to only 21 days of DAPT in the CHANCE study.

Although prasugrel has been limitedly evaluated in the setting of ischemic stroke, the results from the TRITON-TIMI 38 trial identified a higher risk of major bleeding and CV death in patients with a history of ischemic stroke or TIA and thus should be avoided in these patients. Ticagrelor-based DAPT for 30 days after a mild to moderate stroke (National Institutes of Health Stroke Scale score ≤5) was found to reduce the incidence of stroke or death by 17% compared with patients treated with only aspirin in the THALES study. While severe bleeding was rare, the incidence of ICH or fatal bleeding was significantly higher in those receiving ticagrelor. While direct comparisons cannot be made between clopidogrel- and ticagrelor-containing DAPT regimens, clopidogrel-based DAPT, particularly when used for a short time period, appears to be the most optimal DAPT regimen to avoid adverse safety events.

Patients with a minor, noncardioembolic ischemic stroke or high-risk TIA should be initiated on clopidogrel-based DAPT within 12 to 24 hours of symptom onset based on the AHA and American Stroke Association 2021 guidelines for secondary prevention of ischemic stroke. DAPT should be continued for 21 to 90 days, although no specific duration within this time period is recommended and should depend on overall bleeding risk. Ticagrelor-based DAPT may be considered for patients with minor-moderate stroke or high-risk TIA but carries a slightly weaker IIb recommendation due to the increased risk of ICH and serious bleeding. After completion of DAPT, indefinite single antiplatelet therapy with either aspirin or clopidogrel is recommended by current guidelines. The use of aspirin 25 mg and dipyridamole 200 mg twice daily is also reasonable for the secondary prevention of ischemic stroke.

In patients with significant but stable CAD, rivaroxaban may be a suitable antithrombotic agent to prevent a first or recurrent stroke. A sub-analysis of the COMPASS trial found rivaroxaban 2.5 mg twice daily and aspirin was associated with a 42% lower risk of stroke and 49% lower risk of ischemic stroke when compared with aspirin alone. In patients with a previous history of stroke, the combination of rivaroxaban and aspirin was found to reduce the incidence of ischemic or unknown stroke by 67%. Unfortunately, the beneficial effect on stroke reduction was not observed in the VOYAGER PAD trial and with just 27% of patients in the COMPASS trial having PAD, the use of rivaroxaban in these patients cannot be recommended specifically for stroke prevention in patients with PAD.

Optimizing Outcomes in the Management of CAD/PAD and Associated Comorbidities

Role of the Pharmacist
Pharmacists can play an imperative role in the management of patients with CAD and PAD. Given the risk of bleeding events associated with antithrombotic therapies, pharmacists should regularly inform patients about the potential for bleeding and assess them for significant bleeding such as epistaxis, genitourinary bleeding, or melena. Additionally, due to the potential for drug–drug interactions that may cause enhanced or diminished effects of the antithrombotic therapies discussed, pharmacists should regularly assess patients for any changes to their prescribed medications and appropriate use of over-the-counter products.

Despite the demonstrable evidence for using therapies such as lipid-lowering agents, some studies have shown shockingly low rates of statin usage. Even when initiated, just 25% of patients with clinical ASCVD have been reported to attain appropriate LDL-C goals. Regular contact with patients allows pharmacists in the community setting to regularly assess and educate patients through medication therapy management (MTM) services. MTM is a wide-ranging array of services centered on optimization of therapeutic outcomes through the review of medication profiles, creation of a medication treatment plan, monitoring of effective-
ness, and provision of education and support services. Community pharmacy-based education for patients with diabetes has directly demonstrated improvement in medication usage, adherence to clinical practice guideline recommendations, attainment of goal A1c, LDL-C, and blood pressure targets.67

Additionally, several studies have documented the direct impact the community pharmacist has in early disease state recognition through initial and follow-up monitoring. Over the past 2 decades, community-based screening has grown and produced a substantial evidence base for the positive impact pharmacists can have in early recognition of hypertension, diabetes, hyperlipidemia, and increasing rates of sustained smoking cessation.68-70 These programs help not only identify patients with modifiable risk factors but can also lead to initiation of appropriate medications to reduce ischemic events.

Pharmacists working in the hospital setting also have the opportunity to recognize risk factors and optimize the medication therapy regimens patients receive. Unfortunately, more than 25% of Americans do not have a primary care physician. 71 A hospital admission may be a patient’s first encounter with a health care system and the transitions of care (TOC) period may serve as an optimal time to educate patients about indications for various medications and initiate life-saving guideline-directed medical therapies. Various TOC programs have not only demonstrated reduction in hospital readmissions but have also been shown to improve medication adherence and patients’ understanding of their therapies.72,73 The optimization of antithrombotic therapy by pharmacists for patients with CAD and PAD is an area in need of attention and further evaluation.

**Pharmacist Interventions**

Although various interventions may be appropriate for a patient, it may be difficult to determine those that have the most significant impact. The CDC’s Million Hearts 2022 Campaign has sought to reduce the number of MI's and strokes by 1 million in the next 5 years. The ABCS of heart health center around 4 primary recommendations: taking aspirin as directed, controlling blood pressure, managing cholesterol, and smoking cessation.74 Pharmacists, with their frequent patient interactions, can identify patients who may benefit from aspirin therapy based on comorbid disease states. Additionally, for patients who require DAPT therapy after PCI, several tools, such as the DAPT Score and PRECISE-DAPT Score, are available to assess the likelihood of benefit from prolonged duration of DAPT.75-76 While these calculators may provide an estimate of whether patients may benefit from longer periods of DAPT, it is important to recognize that these tools have limitations in their ability to predict bleeding events.

The Million Hearts campaign has created a blood pressure log and educational pamphlet that pharmacists can provide to any patient. Assisting patients with control of blood pressure and understanding their therapies is pivotal; of the 116 million adults with hypertension in the United States, more than 73% of them have not met guideline blood pressure targets.77 Pharmacists can also provide blood pressure measurement services for those who may not be able to afford in-home blood pressure monitors. Pharmacists are also perfectly poised to assist with medication adherence and identify opportunities for medication consolidation and reducing polypharmacy. With the risk factors for CAD and PAD addressed earlier, many medication therapies are available as single-pill combinations. While these products may not be suitable during episodes of medication titration, once stable doses are obtained, adherence may be improved by up to 20% by switching to single-pill combination therapies.78,79 Pharmacists should also identify medication products with extended or sustained-release formulations so once-daily medication administration can be achieved.

Similarly, pharmacists can help recognize patients who may be candidates for statin therapies and discuss with the patient’s provider to recommend initiating therapy. Collaborative practice agreements may also serve as an avenue for pharmacists to increase their scope of practice and initiate and monitor therapies, such as statins or antihypertensive therapies, in conjunction with medical practices and physicians. Lastly, tobacco cessation plays a tremendous role in reducing CV events in patients with CAD, PAD, or high-risk patients. Community pharmacists are key players in helping patients avoid tobacco products. Fourteen states have statutes or regulations that allow pharmacists to prescribe tobacco cessation therapies.80 Again, due to frequent contact with a community pharmacy, the pharmacist can assist with not only helping patients decide when and which therapies would be most effective, they can regularly follow up with patients regarding relapses and potential modification of therapeutic regimens to achieve sustained cessation. Several resources through national and state pharmacy organizations are available to help navigate implementing smoking cessation and other CV risk reduction services.

**Conclusion**

As CAD and PAD continue to cause significant morbidity and mortality in the United States, the pharmacist’s role continues to evolve and expand. It is important for all pharmacists to recognize the importance of antithrombotic therapies available for patients with a variety of comorbidities. At a minimum, single antiplatelet therapy should be used for all patients with stable CAD or PAD
in the absence of contraindications. For patients requiring PCI with stent placement, innovative DAPT regimens may become more common to improve the safety profile and ensure patients are able to remain on beneficial antiplatelet therapies for the appropriate durations. Anticoagulation with rivaroxaban may also provide benefits to select patients who have stable CAD or PAD with additional CV events, although identifying patients at high risk of bleeding remains an important aspect in determining the overall clinical benefit. Outside of antithrombotic therapy management, pharmacists should regularly engage with patients to identify therapeutic opportunities for medication optimization for those with hypertension, hyperlipidemia, diabetes, and those who are active tobacco users.

ADDITIONAL RESOURCES

American College of Cardiology
www.acc.org/clinical-topics/acute-coronary-syndromes/atherosclerotic-disease-cad-pad

Take a Stand Against Amputation
https://standagainstamputation.com/resources-for-physicians/

Tobacco Cessation
quitassist.com

Million Hearts Campaign
https://millionhearts.hhs.gov

REFERENCES


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INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.

Go to www.pharmacytimes.org/CAD-PAD to access the online version of this activity.

Click “Proceed,” then complete the online pretest.

Once completed, click “Next” until reaching the activity posttest.

After successful completion of the online interactive patient simulation, posttest, and activity evaluation, your credit will be uploaded into CPE Monitor. You must complete these steps before the activity expires in order to receive your credit.

You may view your credit within 48 hours at www.mycpemonitor.net.

NOTE: Your CE credit will be automatically uploaded to CPE Monitor.

NABP e-profile ID number and your date of birth. Participation data will not be uploaded into CPE Monitor if you do not have your NABP e-profile ID number and date of birth entered into your profile on www.pharmacytimes.org.

SYSTEM REQUIREMENTS FOR COMPLETION:
Computer or smartphone with internet-access web browser (IE7.0+ or Webkit-/Mozilla-compatible) with JavaScript enabled.

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POSTTEST QUESTIONS

1. JB, a 66-year-old woman, was recently discharged from the hospital after experiencing a myocardial infarction (MI) and receiving percutaneous coronary intervention (PCI) with stent placement. She has a past medical history significant for hypertension and hyperlipidemia, and a gastrointestinal bleed that occurred 2 years ago. She reports her physician prescribed her aspirin 81 mg daily and ticagrelor 90 mg twice daily for 3 months and is planning to have her continue ticagrelor after that for an additional 9 months. She reports her husband was on aspirin and clopidogrel for an entire year and is wondering why her regimen is different. Which of the responses related to the TWILIGHT trial is correct related to JB’s regimen?
   A. In high-risk patients, ticagrelor monotherapy reduced the risk of ischemic events and had a similar risk of bleeding.
   B. In high-risk patients, ticagrelor monotherapy had a similar risk of ischemic events and a lower risk of bleeding.
   C. In low-risk patients, ticagrelor monotherapy had a similar risk of ischemic events and had a similar risk of bleeding.
   D. In low-risk patients, ticagrelor monotherapy had a similar risk of ischemic events and a lower risk of bleeding.

2. Which of the following goals of therapy is the most appropriate for patients with hypertension with established coronary artery disease (CAD) and history of MI?
   A. Blood pressure of <150/90 mm Hg
   B. Blood pressure of <120/80 mm Hg
   C. Blood pressure of <130/80 mm Hg
   D. Blood pressure of <140/90 mm Hg

3. Which of the following antithrombotic regimens is appropriate for a patient with stable CAD and low risk of bleeding?
   A. Aspirin 81 mg daily and rivaroxaban 5 mg twice daily
   B. Aspirin 81 mg daily and warfarin titrated to a goal international normalized ratio of 2-3
   C. Aspirin 81 mg daily and apixaban 5 mg twice daily
   D. Aspirin 81 mg daily and rivaroxaban 2.5 mg twice daily

4. Which of the following P2Y₁₂ inhibitors is reasonable to initiate based on the results of the PEGASUS-TIMI 54 trial?
   A. Ticagrelor 60 mg twice daily
   B. Prasugrel 5 mg daily
   C. Clopidogrel 75 mg daily
   D. Ticagrelor 90 mg twice daily

5. Which of the following events are patients at risk for after an MI?
   A. Cardiovascular (CV) death
   B. CV death and MI
   C. Stroke and MI
   D. MI, stroke, and CV death

6. In the VOYAGER trial, the addition of rivaroxaban to aspirin specifically reduced the rate of which of the following outcomes?
   A. Major amputation for vascular causes
   B. Acute limb ischemia
   C. CV death
   D. Stroke
POSTTEST QUESTIONS (CONTINUED)

7. Which patient would most benefit from high-intensity statin therapy for primary prevention of atherosclerotic cardiovascular disease (ASCVD)?
   A. 52-year-old man with a past medical history significant for MI
   B. 40-year-old woman with a past medical history of type 2 diabetes with an ASCVD risk score of 6%
   C. 90-year-old man with an ASCVD risk score of 5%
   D. 60-year-old woman with peripheral artery disease (PAD) and an ASCVD risk score of 22%

8. Which initial antithrombotic regimen would be most appropriate for a patient presenting with a minor acute noncardioembolic ischemic stroke?
   A. Aspirin 81 mg daily and prasugrel 10 mg daily for 21 days
   B. Aspirin 81 mg daily and clopidogrel 75 mg daily for 30 days
   C. Aspirin 81 mg daily and rivaroxaban 2.5 mg twice daily indefinitely
   D. Ticagrelor 90 mg twice daily for 30 days

9. Which of the following antihyperglycemic medications is most likely to reduce the risk of major cardiac adverse event outcomes in a patient already taking metformin and a history of MI and a hemoglobin A1c of 8.8%?
   A. Sitagliptin
   B. Dulaglutide
   C. Dapagliflozin
   D. Lixisenatide

10. Which statement is correct related to the benefits of adding rivaroxaban to aspirin for patients with stable CAD?
    A. Significantly reduces the composite ischemic outcome and all the individual components of MI, stroke, and CV death
    B. The decrease in ischemic events outweighed the increased risk of bleeding.
    C. There was no significant difference in any bleeding between those treated with rivaroxaban 2.5 mg twice daily compared with those treated with aspirin only.
    D. In young patients (<65 years old) with low ischemic risk, the addition of rivaroxaban 2.5 mg twice daily to aspirin significantly reduces the risk of ischemic events and CV death.
Overcoming Barriers to Influenza Vaccination: Examining Available Vaccines for 2021-2022 and Addressing Hesitancy During the COVID-19 Pandemic

EDUCATIONAL OBJECTIVES

At the completion of this activity, the participant will be able to:

• Examine the epidemiology of the influenza virus and the challenge of increasing influenza vaccination rates during the era of COVID-19
• Determine the patient populations at elevated risk of complications related to influenza and COVID-19 and the need to improve vaccination rates during the pandemic
• Explore the recommendations, safety, and efficacy of the available influenza vaccines for the 2021-2022 influenza season
• Investigate the growing presence of pharmacies as a site of care to improve influenza and COVID-19 vaccination rates especially during the ongoing pandemic and the role of the pharmacist as patient identifier, educator, and vaccine administrator

TARGET AUDIENCE: Pharmacists

ACTIVITY TYPE: Application

RELEASE DATE: December 15, 2021

EXPIRATION DATE: January 15, 2023

ESTIMATED TIME TO COMPLETE ACTIVITY: 2.5 hours

FEE: This lesson is offered for free at www.pharmacytimes.org.

Introduction

In 1918, the influenza A (H1N1), Spanish flu, killed 50 million to 100 million people worldwide, and was called “the mother of all pandemics.”1 Influenza vaccines have been available for more than 80 years with the first-generation live-attenuated vaccine developed in 1933. Due to the predominant use of embryonated chicken eggs for their production and the continuous antigenic changes in the influenza viruses, they had challenges with effectiveness. In 1973, the World Health Organization (WHO) issued annual recommendations for the composition of the vaccine based on surveillance cultures and in 1978, the first trivalent vaccine was produced, resulting in improved responses.2,3

Vaccination is a powerful tool for limiting the progression and dissemination of infectious diseases, as vaccines save lives and are one of the greatest achievements in the history of public health. It is estimated that vaccines save more than 9 million lives per year worldwide.4 Thanks to extensive vaccination, smallpox, a deadly disease, has been eradicated with the WHO proclaiming the disease to be eliminated worldwide in 1980.5 It was an unprecedented achievement in public health. Despite this progress, some diseases that were almost eliminated by vaccines are slowly increasing. For example, cases of measles in the United States have been on the rise even though endemic measles were declared eliminated in 2000. This increase was related to an antivaccination trend that started following a 1997 study suggesting that the measles, mumps, rubella (MMR) vaccine was causing autism; however, this study was disproven and retracted.6,7 As vaccine hesitancy continues to present a challenge, it is imperative that pharmacists address potential misconceptions to increase vaccination rates for all vaccines, including the influenza vaccine.
This is of utmost importance given the continued burden respiratory illnesses impose on the health care system.

In December 2019, a group of patients in Wuhan, China, experienced shortness of breath and fever resulting in isolation of a novel coronavirus, SARS-CoV-2, as the causative agent. In January of the following year, the Centers for Disease Control and Prevention (CDC) confirmed the first laboratory-confirmed case of COVID-19, the illness caused by SARS-CoV-2. The WHO declared the coronavirus outbreak a Public Health Emergency of International Concern at the end of the month, and a COVID-19 pandemic on March 11, 2020, with most US states reporting widespread cases by the next month. Elective surgeries were put on hold and routine health care was delayed, including vaccinations. In 2020, routine vaccination rates declined significantly across all populations in the United States due to fears of contracting COVID-19 and overwhelmed US health care systems. Several COVID-19 vaccines were developed about 10 months later. Unfortunately, due to various reasons including fear, distrust, and confusion, there has been hesitation for people to receive the COVID-19 vaccine, adding to the vaccine hesitancy issue. This article will focus on a review of influenza and its complications and a selection of available influenza vaccines as well as the impact of the COVID-19 pandemic on immunizations, objections to vaccination, and overcoming barriers to improve immunization rates.

### Review of Influenza

Influenza is an acute infection caused by the virus of the Orthomyxoviridae family involving both the type A and type B viruses. As the influenza virus has a high mutation rate, the WHO serologically monitors the yearly changes and recommends the strains that need to be included in next year’s vaccine to the FDA, which makes the final decision. Influenza A viruses are classified by

#### FIGURE 1. PERCENTAGE OF VISITS FOR INFLUENZA-LIKE ILLNESS

Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, 2020-2021 and Selected Previous Seasons

![Graph showing percentage of visits for influenza-like illness by week, with different lines representing various seasons from 2009-10 to 2020-21, with a note that these seasons did not have a week 53, so the Week 53 value is an average of week 52 and week 1.](image_url)

†These seasons did not have a week 53, so the Week 53 value is an average of Week 52 and Week 1.
their envelope glycoproteins, hemagglutinin (HA) and neuraminidase (NA). The 3 major HA subtypes (H1, H2, and H3) and 2 NA subtypes (N1 and N2) are commonly associated with disease in humans. Influenza B viruses have 2 genetic lineages, B/Victoria/2/87-like and B/Yamagata/16/88-like. Minor changes in these viruses are defined as antigenic drifts, while major changes are antigenic shifts. Only influenza A viruses have antigenic shifts, which can result in a pandemic.

In 2019 and 2020, influenza and pneumonia were the ninth most common cause of death in the United States. Fatalities from influenza begin to rise in midlife and are highest in persons with chronic disease. The number of cases fluctuate each year (FIGURE 1) and vary by age (FIGURE 2). Measures available to reduce the incidence of influenza include immunoprophylaxis with inactivated or live influenza vaccine and chemoprophylaxis. Vaccination of people at risk and those likely to transmit influenza to at-risk populations is the most effective measure. In addition, healthy practices of avoiding others who are ill, using proper handwashing, and covering one’s mouth properly when coughing or sneezing will help stop the spread of germs and prevent respiratory illnesses. The impact of these practices reducing influenza can be seen on FIGURE 3 for the 2020-2021 season when the COVID-19 pandemic restrictions were in place.

The influenza vaccine provides protection from influenza and decreases potential complications and health care costs. It is estimated that in the United States, vaccines prevented 1.6 million to 6.7 million illnesses, 790,000 to 3.1 million outpatient medical visits, 39,000 to 87,000 hospitalizations, and 3000 to 10,000 respiratory and circulatory deaths during the influenza seasons between 2010 and 2016. The 2017-2018 season was cited as particularly severe due to elevated influenza activity. Despite a vaccine efficacy of 38%, it was estimated that vaccination prevented 7.1 million illnesses, 3.7 million medical visits, 109,000 hospitalizations, and 8000 deaths.

As of November 3, 2021, approximately 45.6 million cases of COVID-19 had been reported in the United States, including...
approximately 740,000 deaths.16 There were 400,000 influenza-like illness hospitalizations in the 2019-2020 influenza season. Although influenza activity during the 2020-2021 season was low throughout the United States (FIGURE 13), fewer influenza vaccinations did not result in more influenza. Masking, social distancing, increased handwashing, and decreased travel led to a significant reduction in influenza for 2020-2021.17

The timing and intensity of the 2021-2022 influenza season cannot be predicted. Influenza vaccination remains an important tool for the prevention of potentially severe respiratory illness, which might decrease stress on the US health care system during the COVID-19 pandemic.15,17

Healthy People 2030 is a group that continues to promote the movement throughout the United States to increase immunization rates and reduce preventable infectious diseases.18 They also address vaccine hesitancy and continue to have a significant impact on preventing communicable diseases, reducing preventable complications, and improving clinical outcomes. A goal target of 70% was set for individuals to receive the influenza vaccine. They have not met their goal as only 49.2% of persons aged 6 months and older were vaccinated against seasonal influenza for the 2017-2018 season. However, adult vaccination coverage remains low for most routinely recommended vaccines and below the Healthy People 2030 target.19

It is important to note that the effectiveness of the influenza vaccine is dependent on factors such as a patient’s age and health status, circulating strains, and type of vaccine. For this reason, the overall effectiveness varies from season to season ranging from 19% to 60%.4 A key point for patients to remember is that they could still get the flu if vaccinated, but vaccination significantly reduces the incidence and severity of influenza and risk of serious complications, hospitalizations, and death to both themselves and others.4 Influenza vaccine is recommended for all people aged 6 months or older without contraindications.4 This is particularly important to reduce complications during the current COVID-19 pandemic.

Patients need to be reminded that cold, influenza, and COVID-19 symptoms can be similar. Most people understand that COVID-19 has caused many deaths, but they need to understand that infections with influenza can cause mild to severe illness that can also lead to death. Both COVID-19 and flu usually have a sudden onset with symptoms consisting of fever or chills, cough, sore throat, runny or stuffy nose, muscle or body aches, headaches, and fatigue. Change in or loss of taste or smell may occur, but this is more frequent with COVID-19. See TABLE 19,21 for a comparison of symptoms.

Patients need to be assessed and tested to determine which infection is present and provide the proper management. Individuals can be infected with both viruses and have symptoms of both influenza and COVID-19. Both are transmitted through inhalation and surface contact, with COVID-19 being more contagious than influenza. Also, the COVID-19 virus can spread much faster to large numbers of people. COVID-19 mortality rate is higher in the elderly population and in those with preexisting chronic medical conditions.22

Typically, most people who get the flu will recover in 3 to 14 days. Both COVID-19 and flu can result in complications, including pneumonia, respiratory failure, acute respiratory distress syndrome, sepsis, heart attack, inflammation of the heart (myocarditis), encephalitis, myositis, worsening of chronic medical conditions, and multiple-organ failure that could cause a long recovery. Secondary bacterial infections are more common with influenza. These complications can be severe, requiring hospitalization.20

Reye syndrome, a complication that occurs almost exclusively in children, presents with severe vomiting and confusion, which may progress to coma because of swelling of the brain. To decrease this from occurring, infants, children, and teenagers should not be given aspirin for fever reduction or pain relief.5

Zanetti et al examined the effects of influenza vaccination in elderly individuals on COVID-19 mortality. They found that overall, a 10% increase of influenza vaccination rates was associated with a statistically significant 5% average decrease in the COVID-19 death rate. Their findings suggest that influenza vaccination can play a protective role in COVID-19.21 Huang et al reviewed 56 million health records of older adults (>65 years) to determine if influenza vaccine had an impact on COVID-19 infections. Those who had received an influenza vaccination had a 24% decreased risk of getting a COVID-19 infection and a 28% decreased risk of developing a severe COVID-19 illness, compared with others who had not received influenza vaccination. The authors similarly concluded that an influenza vaccination seems to have a protective effect against COVID-19 infection.24 Other studies continue to show the importance of receiving the influenza vaccine during the COVID-19 pandemic.

**STAR**

How do you differentiate influenza from COVID-19?

*S = Stop; T = Think; A = Assess; R = Review

**STAR**

What populations are at a higher risk of developing complications if they contract influenza?
High-Risk Groups

Certain conditions put patients at much higher risk of developing complications if they contract influenza. Older adults and individuals who have severe underlying medical conditions such as heart or lung disease or diabetes seem to be at higher risk for developing more serious complications from COVID-19 illness, so it is important that they receive both the influenza and COVID-19 vaccines. Pharmacist should be aware that some high-risk groups vary according to recommendations from the Advisory Committee on Immunization Practices (ACIP) or the CDC.

People who are at increased risk for influenza-related complications include the following:

- Persons aged 50 years or older (per ACIP) versus persons aged 65 and older (per CDC)
  - The age varies based on the underlying health and comorbidities of the patient
- Children aged 5 through 59 months
- Women who are or will be pregnant during the influenza season (per ACIP) versus women who are pregnant and women up to 2 weeks after the end of pregnancy (per CDC)
- Residents of nursing homes and other long-term care facilities
- Adults and children who have chronic pulmonary (including asthma), cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)
- Persons who are immunocompromised due to any cause (including but not limited to immunosuppression caused by medications or HIV infection)
- Children and adolescents (aged 6 months through 18 years) who are receiving aspirin- or salicylate-containing medications and who might be at risk for experiencing Reye syndrome after influenza infection
- American Indians and Alaska Natives (per ACIP) versus non-Hispanic Black, Hispanic or Latinos, American Indian or Alaska Natives, non-Hispanic Asian or Pacific Islander (per CDC)
- Persons who are extremely obese (body mass index [BMI] ≥40 kg/m² for adults)

Unfortunately, the risk factors putting people at developing complications from influenza are similar to risk factors for contracting severe COVID-19 disease. Age is the strongest risk factor for COVID-19. As of September 2021, the mortality rate for people 65 years or older residing in the United States was 80 times more than the rate of 18- to 29-year-olds. Individuals living in long-term care facilities comprised more than 35% of all COVID-19 deaths. Cancer, cerebrovascular disease, chronic kidney disease, certain chronic lung and liver diseases, diabetes, heart conditions (heart failure, coronary artery disease, or cardio-

<table>
<thead>
<tr>
<th>TABLE 1. COMPARISON OF COLD, INFLUENZA, AND COVID-19 SYMPTOMS²⁰,²¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom onset</strong></td>
</tr>
<tr>
<td>Symptom onset</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Aches</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td>Fatigue, weakness</td>
</tr>
<tr>
<td>Chest discomfort, cough</td>
</tr>
<tr>
<td>Sneezing</td>
</tr>
<tr>
<td>Stuffy nose</td>
</tr>
<tr>
<td>Sore throat</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Change in or loss of taste and smell</td>
</tr>
<tr>
<td>Shortness of breath or difficulty breathing</td>
</tr>
<tr>
<td>Nausea, vomiting, and diarrhea</td>
</tr>
</tbody>
</table>

Uncompromised due to any cause (including but not limited to immunosuppression caused by medications or HIV infection)
- Children and adolescents (aged 6 months through 18 years) who are receiving aspirin- or salicylate-containing medications and who might be at risk for experiencing Reye syndrome after influenza infection
- American Indians and Alaska Natives (per ACIP) versus non-Hispanic Black, Hispanic or Latinos, American Indian or Alaska Natives, non-Hispanic Asian or Pacific Islander (per CDC)
- Persons who are extremely obese (body mass index [BMI] ≥40 kg/m² for adults)
myopathies), depression or schizophrenia, obesity (BMI ≥30 kg/m²), pregnancy or recent pregnancy, smoking (current or former) and tuberculosis are comorbidities with the strongest evidence of causing greater complications with COVID-19 infections. The risk of COVID-19 increases at any age as a person has a higher number of underlying medical conditions. People with disabilities or those who live in a congregate setting or face more barriers to health care have a higher risk of serious COVID-19 disease as well. Black or African American, Hispanic and Latino people are less likely to get the COVID-19 vaccine and more likely to get seriously ill and die from COVID-19 and its complications. People with disabilities or those who live in a congregate setting or face more barriers to health care have a higher risk of serious COVID-19 disease as well. Black or African American, Hispanic and Latino people are less likely to get the COVID-19 vaccine and more likely to get seriously ill and die from COVID-19 and its complications. These individuals may have different economic, social, environmental, and geographic factors that cause challenges to vaccine acceptance and access.

Patients need to understand the value of getting both the influenza vaccine yearly and staying up-to-date with COVID-19 recommendations and the potential consequences if these recommendations are not followed. Vaccination remains the best way to protect against influenza. Pharmacists have a responsibility to instruct patients that while there is still a potential chance they could contract influenza after vaccination, it will be a much less severe case if they receive the influenza vaccine. Educating patients on the potential for life-changing complications due to influenza or COVID-19 infections and the importance of avoiding this burden could help improve immunization rates.

Overview of Influenza Vaccines
Recommendations for the 2021-2022 Season
The ACIP makes yearly recommendations for routine influenza vaccination. Routine annual influenza immunization is recommended for all persons aged 6 months or older who do not have contraindications. The available vaccines include the standard-dose inactivated influenza vaccine, quadrivalent (IIV4); high-dose inactivated influenza vaccine, quadrivalent (HD-IIV4); standard-dose adjuvanted inactivated influenza vaccine, quadrivalent (aIIV4); standard-dose cell-culture-based inactivated influenza vaccine, quadrivalent (ccIIV4); recombinant influenza vaccine, quadrivalent (RIV4); and live-attenuated influenza vaccine quadrivalent (LAIV4). No specific vaccine is preferred in persons for whom more than one formulation is appropriate. Select vaccines will be covered in more detail, with an emphasis on available vaccines indicated specifically for older adults.

There were 6 recommendations made for the 2021-2022 season. The biggest update is that trivalent vaccines are no longer available as all US-licensed influenza vaccines are quadrivalent. This should provide patients with expanded coverage and protection against influenza.

Additionally, while the B strains did not change, the A strains included in the 2021-2022 influenza vaccines available in the United States have been changed from the previous season and include:

- Influenza A
  - H1N1
    - A/Victoria/2570/2019 (H1N1)pdm09-like virus (for egg-based vaccines) OR
    - A/Wisconsin/588/2019 (H1N1)pdm09-like virus (for cell culture–based and recombinant vaccines)
  - H3N2
    - A/Cambodia/e0826360/2020 (H3N2)-like virus

- Influenza B
  - B/Washington/02/2019 (Victoria lineage)-like virus
  - B/Phuket/3073/2013 (Yamagata lineage)-like virus

A third change is the approved age indication for ccIIV4 (Flucelvax) from older than 4 years to older than 2 years. Fourth, providers should use the ACIP and CDC recommendations for guidance and consideration for coadministration of influenza vaccines and COVID-19 vaccines. Pregnant women should ideally receive the influenza vaccination in September or October. However, pregnant women in the third trimester should receive it as soon as the vaccine becomes available (July or August). Children 6 months through 8 years who are flu vaccine naïve or who have not had 2 lifetime total doses should receive their first dose as soon as possible. The second dose should be administered at least 4 weeks later. The remaining population ideally should receive the vaccine by the end of October, avoiding vaccination in July and August unless there is concern that later vaccination is not possible.

There have also been modifications to the contraindications and precautions associated with the use of ccIIV4 (Flucelvax) and RIV4 (Flublok). A precaution to the use of ccIIV4 or RIV4 is a history of a severe allergic reaction to a previous dose of an egg-based vaccine; in these patients, the vaccines should be administered in a medical setting (eg, doctor’s office or clinic) under supervision of a provider who can recognize and manage a severe allergic reaction. Providers may consider an allergist consultation to assist with determining which vaccine component was responsible for the reaction. A contraindication to future use of ccIIV4 includes a history of a severe allergic reaction such as anaphylaxis.
to any ccIIV vaccine or component of ccIIV4. Similarly for RIV4, history of a severe allergic reaction to any RIV vaccine or component of RIV4 is a contraindication.8

### Available Vaccines in the 2021-2022 Season

**TABLE 2. INFLUENZA VACCINES AVAILABLE IN THE UNITED STATES FOR THE 2021-2022 INFLUENZA SEASON**

<table>
<thead>
<tr>
<th>Brand name (manufacturer)</th>
<th>Dose</th>
<th>Recommended age</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inactivated influenza vaccine, quadrivalent (IIV4), standard-dose, egg-based vaccines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afluria Quadrivalent (Seqirus)</td>
<td>0.25 mL, PFS</td>
<td>6 through 35 months</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td>0.5 mL, PFS</td>
<td>≥3 years</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td>0.5 mL, 5 mL MDV*</td>
<td>≥6 months (needle/syringe); 18-64 years (jet injector)</td>
<td>IM</td>
</tr>
<tr>
<td>Fluarix Quadrivalent (GlaxoSmithKline)</td>
<td>0.5 mL, PFS</td>
<td>≥6 months</td>
<td>IM</td>
</tr>
<tr>
<td>Flulaval Quadrivalent (GlaxoSmithKline)</td>
<td>0.5 mL, PFS</td>
<td>≥6 months</td>
<td>IM</td>
</tr>
<tr>
<td>Fluzone Quadrivalent (Sanofi Pasteur)</td>
<td>0.5 mL, PFS</td>
<td>≥6 months</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td>0.5 mL, SDV</td>
<td>≥6 months</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td>0.5 mL, 5 mL MDV*</td>
<td>≥6 months</td>
<td>IM</td>
</tr>
<tr>
<td><strong>High-dose inactivated influenza vaccine, quadrivalent (HD-IIV4), egg-based vaccine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluzone High-dose Quadrivalent (Sanofi Pasteur)</td>
<td>0.7 mL, PFS</td>
<td>≥65 years</td>
<td>IM</td>
</tr>
<tr>
<td><strong>Adjuvanted inactivated influenza vaccine, quadrivalent (aIIV4), standard-dose, egg-based vaccine with MF59 adjuvant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluad Quadrivalent (Seqirus)</td>
<td>0.5 mL, PFS</td>
<td>≥65 years</td>
<td>IM</td>
</tr>
<tr>
<td><strong>Cell-culture-based inactivated influenza vaccine, quadrivalent (ccIIV4), standard-dose vaccine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flucelvax Quadrivalent (Seqirus)</td>
<td>0.5 mL, PFS</td>
<td>≥2 years</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td>0.5 mL, 5 mL MDV*</td>
<td>≥2 years</td>
<td>IM</td>
</tr>
<tr>
<td><strong>Recombinant influenza vaccine, quadrivalent (RIV4)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flublok Quadrivalent (Sanofi Pasteur)</td>
<td>0.5 mL PFS</td>
<td>≥18 years</td>
<td>IM</td>
</tr>
<tr>
<td><strong>Live attenuated influenza vaccine, quadrivalent (LAIV4), egg-based vaccine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FluMist Quadrivalent (AstraZeneca)</td>
<td>0.2 mL prefilled single-use intranasal sprayer</td>
<td>2-49 years</td>
<td>Nasal</td>
</tr>
</tbody>
</table>

*IM, intramuscular; MDV, multidose vial; PFS, prefilled syringe; SDV, single-dose vial.

*MDVs have approximately 25 mcg/0.5 mL mercury (from thimerosal).

Vaccines Specifically for Patients 65 Years and Older

There are 2 influenza vaccines this year, HD-IIV4 (Fluzone High-Dose) and aIIV4 (Fluad), that are indicated for persons 65 years or older. This is because, as patients grow older, their immune system is not as robust so they typically have weaker immunogenic responses (antibody production) to influenza vaccination than younger persons, and their antibody levels may decline more rapidly.20 This leads to decreased vaccine effectiveness.

Recombinant, high-dose, and adjuvanted influenza vaccines result in higher antibody production. Cowling and colleagues immunized community-dwelling adults aged 65 to 82 years residing in Hong Kong, with either recombinant, high-dose, adjuvanted vaccines or standard-dose inactivated influenza vaccine. The patients receiving any of the 3 enhanced vaccines showed greater humoral and cell-mediated immune responses, compared with the standard-dose vaccine subjects.20
During the 2018-2019 influenza season, Pelton et al performed a retrospective cohort study of individuals in the United States who were 65 years or older and vaccinated with either adjuvanted trivalent influenza vaccine (aTIV, Fluad) or trivalent influenza vaccine-high dose (TIV-HD, Fluzone) to assess relative effectiveness. The final unadjusted sample included 561,243 aTIV and 1,672,797 TIV-HD recipients. Influenza-related hospitalization/emergency department visits and associated costs among people aged 65 and older were comparable between the 2 vaccines. The aTIV had a higher relative vaccine effectiveness in preventing influenza-related office visits as compared with TIV-HD. Both vaccines appear to provide comparable clinical and economic benefits in providing protection against influenza and associated complications among the older population. Other studies have shown similar responses but there is need for additional clinical trials comparing the recombinant, adjuvanted, and high-dose vaccines in older adults. Currently there are no studies comparing the new HD-IIV4 and aIIV4 to standard-dose IIV4 due to the recent availability of these formulations.

**High-dose Inactivated Influenza Vaccine**

HD-IIV4 (Fluzone High-dose) contains 4 times the amount of antigen that is included in standard-dose inactivated influenza vaccines. This is the second season that it is a quadrivalent preparation. Several studies in adults 65 years or older have shown a reduced risk of respiratory-related and all-cause hospitalization and death in patients receiving the high-dose inactivated trivalent vaccine compared with standard-dose inactivated trivalent vaccines. In a randomized, double-blind trial of almost 32,000 adults 65 years or older, the high-dose inactivated trivalent vaccine induced significantly greater antibody responses than the standard-dose inactivated trivalent vaccine and was 24% more effective in preventing laboratory-confirmed influenza illness.8,29,32-36

**Adjuvanted Inactivated Influenza Vaccine**

The aIIV4 (Fluad) contains MF59, an oil-in-water emulsion of squalene oil that increases the immune response by recruiting antigen-presenting cells to the injection site and promoting uptake of influenza virus antigens. In a randomized trial in adults 65 years or older, an adjuvanted inactivated trivalent vaccine produced significantly greater antibody responses against all 3 influenza strains than a nonadjuvanted inactivated trivalent vaccine. Other studies have shown that older adults who received an adjuvanted inactivated trivalent vaccine were less likely to develop symptomatic influenza illness or to be hospitalized for influenza or pneumonia compared with those who received a nonadjuvanted inactivated trivalent vaccine.8,34,38 McConeghy et al examined the use of adjuvanted versus nonadjuvanted trivalent influenza vaccine in 823 nursing homes throughout the United States. This cluster-randomized trial supports the use of adjuvanted influenza vaccine over nonadjuvanted, standard-dose, egg-based vaccines to prevent nursing home resident hospitalizations during the influenza season. The adjuvanted trivalent vaccine was more effective in preventing hospitalizations during an A/H3N2-predominant season that exhibited low trivalent influenza vaccine effectiveness.29

**Select Additional Vaccines**

**Recombinant Influenza Vaccine**

RIV4 (Flublok) is produced without the use of influenza virus or chicken eggs. It contains 3 times the amount of antigen compared with the standard-dose inactivated influenza vaccines. It is approved for individuals 18 years or older. The vaccine is made using recombinant DNA technology and a baculovirus expression system that produces virus-like particles. In a randomized, double-blind trial in 8604 adults 50 years or older during the A/H3N2-predominant 2014-2015 season, the recombinant quadrivalent vaccine was 30% more effective than a nonadjuvanted standard-dose inactivated quadrivalent vaccine in preventing laboratory-confirmed influenza illness.8,32

**Live-attenuated Influenza Vaccine**

LAIV4 (Flumist) was developed as a quadrivalent vaccine for individuals aged 2 to 49 years that is administered intranasally.8 It was not recommended to be used from 2015 to 2018 due to its low effectiveness against H1N1 influenza among children during the 2013-2014 and 2015-2016 seasons. The manufacturer subsequently determined that the H1N1 strain had poor replicative fitness during the seasons in which LAIV was poorly effective. Data from the manufacturer indicate that the H1N1 strain used in the newer vaccine has improved replicative fitness and induces higher antibody responses than the earlier strain. Seroconversion rates to the newer strain are comparable with those obtained in response to H1N1 strains used in LAIV during seasons in which the vaccine was observed to be effective against influenza A/H1N1 influenza viruses.5 Because it is a live vaccine, there are several contraindications and precautions that needed to be considered. It should not be given to pregnant women, children and adults who are immunocompromised, those who have a history of severe allergic reaction (eg, anaphylaxis) to any component or to a previous dose of any influenza vaccine, or if one has close contact or are a caretaker of severely immunosuppressed individuals.41-43 It is important to note that influenza antiviral use might interfere with LAIV. Use...
of oseltamivir (Tamiflu) or zanamivir (Relenza) within 48 hours before, peramivir (Rapivab) within 5 days before, or baloxavir marboxil (Xofluza) within 17 days before or if any of these are given within 2 weeks after vaccination could inhibit antibody production and reduce efficacy. If this occurs, patients should be revaccinated with the appropriate IIV or RIV.43

Considerations for Vaccine Selection
While the ACIP provides no preference for vaccine type based on efficacy, patient-specific and vaccine-specific factors such as age or contraindications should be taken into consideration for vaccine selection. Studies have illustrated potential benefits of specific vaccines in different populations such as older adults. If a specific vaccine is unavailable, influenza vaccination should not be delayed.8

There are other scenarios where specific vaccine types should be avoided. Although most influenza vaccines contain trace amounts of egg protein (ovalbumin), numerous studies have demonstrated that patients with an egg allergy are not at increased risk for a reaction to any influenza vaccine.44 The ACIP states that persons with egg allergy of any severity can receive any age-appropriate influenza vaccine. However, patients with a history of a severe egg allergy (angioedema, respiratory distress, lightheadedness, recurrent vomiting, or requiring epinephrine or another emergency medical intervention) who receive an egg-based vaccine should be vaccinated in a medical setting supervised by a clinician experienced in managing severe allergic reactions. The recombinant vaccine and the cell culture-based vaccine do not contain egg protein.8 The Joint Task Force on Practice Parameters comprised of members from the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology state that no special precautions are necessary for patients with egg allergy of any severity.44

Adverse Effects
Injection site pain is the major adverse effect that occurs with inactivated influenza vaccines and other adverse effects are less common. In clinical trials, the incidence of injection site pain with the HD-IIV4 and aIIV4 in participants 65 years and older were 41% and 16%, respectively. The most common systemic reactions with HD-IIV4 were myalgia (22.7%), headache (14.4%), and malaise (13.2%) versus headache (10.8%) and fatigue (10.5%) with aIIV4.37,45

The most common adverse reactions associated with the LAIV are runny nose, nasal congestion, fever, and sore throat. LAIV can increase the risk of wheezing, especially in children younger than 5 years with recurrent wheezing and in persons of any age with asthma. Influenza vaccination has been associated with Guillain-Barré syndrome, but the absolute risk is very low (about 1-2 additional cases per million persons vaccinated).4 Influenza infection itself has also been associated with Guillain-Barré syndrome.46

Patients should remain in a seated position for at least 15 minutes after receiving a vaccine to prevent injury from a syncopal episode. Patients should refrain from taking prophylactic ibuprofen, acetaminophen, or aspirin; these medications are only recommended to be taken post-vaccination to relieve adverse effects.

Use of and physical activity with the arm that received a vaccine has been shown to reduce pain and discomfort following vaccination. Patients should be educated to use their arms throughout the day or use a cool, damp washcloth over the area to minimize arm pain. Sometimes patients feel feverish and will feel better by drinking plenty of fluids and wearing lighter clothing until the fever passes. Fatigue might occur but should only last for up to a few days. The patient should be advised to call the pharmacy if these adverse effects do not go away within 48 hours.

Patients need to be reminded that the vaccine does not cause the flu. They might experience illness shortly after receiving the flu vaccine for several reasons, including illness due to other respiratory viruses, such as rhinoviruses, that cause similar symptoms; exposure to flu viruses shortly before, or during the 2-week period after vaccination; composition of seasonal flu vaccine poorly matched to circulating strains of virus; and variability in the effectiveness of vaccine response among individuals.

Role of the Pharmacist
Pharmacists have a professional responsibility to promote vaccines that will save lives and prevent disease. The COVID-19 pandemic offers an important opportunity for pharmacists to have a continued impact on patient care. Patients need to be reminded not only of the value of influenza and COVID-19 vaccines, but other vaccines such as pneumococcal, zoster, and pertussis. This could possibly assist with managing the impact of COVID-19

STAR
- What are some management strategies for vaccine adverse effects?

STAR
- What are some strategies to address vaccine hesitancy?
on health care systems by reducing morbidity and mortality and associated health complications or hospitalizations due to non-COVID-19 respiratory infections as well as bacterial infections during a COVID-19 infection. This would reduce the resources needed to care for patients without COVID-19.47,49

Pharmacists’ involvement in immunization as educators, facilitators, or administrators of vaccines improves immunization rates.50-52 Pharmacies are an accessible option for patients seeking vaccinations with the most common setting of influenza vaccination for adults in the 2020-2021 season including a pharmacy or store.53 Educating patients regarding the availability of various types of influenza vaccines and nuances in their recommendations is important.

Patel et al examined the national individual immunization data for influenza and pneumococcal immunizations. Five years after

### TABLE 3. DISCUSSION POINTS AND TAKEAWAYS FOR HIGH-RISK PATIENTS25

<table>
<thead>
<tr>
<th>Condition</th>
<th>Suggested Patient Discussion Points</th>
<th>Takeaways for Getting Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>As you grow older, your immune system is not as strong to fight off infections and you are at a higher risk of getting the flu which will put you at risk to develop other medical problems. Between 50% and 70% of flu-related hospitalizations and 70%-85% of flu-related deaths occur in people 65 years and older.</td>
<td>Although immune responses may be lower in older people, studies have shown that the flu vaccine reduces medical visits, hospitalizations, and deaths associated with flu.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Your diabetes puts you at a big risk for developing serious flu complications including sinus and ear infections, pneumonia, bronchitis, and death. The flu can also make it harder for you to control your blood glucose.</td>
<td>Getting the influenza vaccine can significantly decrease your risk of getting the flu and being admitted to the hospital. It can also decrease the risk of worsening of your diabetes and having other complications.</td>
</tr>
<tr>
<td>Heart disease and stroke (excludes isolated hypertension)</td>
<td>Cardiovascular disease (CVD) puts you at a higher risk for developing serious flu complications. If you get the flu, you have an increased risk of a stroke or heart attack.</td>
<td>Getting the influenza vaccine can significantly decrease your risk of getting the flu and being admitted to the hospital. It can also decrease the risk of worsening your current health. Vaccination can reduce the risk of major cardiac events among adults with existing CVD.</td>
</tr>
<tr>
<td>Patients with cancer, chronic kidney disease, dialysis, HIV, or transplant</td>
<td>You have a weaker immune response, due to your condition, which can make the immune system less able to fight infections. This puts you at a much higher risk of getting the flu, which can result in worsening of your current illness, hospitalization, and even death.</td>
<td>Receiving the influenza vaccine can significantly decrease your risk of getting the flu and being admitted to the hospital.</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Pregnant women are more susceptible to the flu and are more likely to have more severe cases compared to non-pregnant women. Fever, a common symptom of flu, may be associated with negative outcomes for a fetus.</td>
<td>Getting the influenza vaccine can reduce your risk of getting the flu, being admitted to the hospital, and protect your baby from flu illness. Get the inactivated vaccine ideally in September or October. Earlier vaccination can be considered for women in their third trimester.</td>
</tr>
<tr>
<td>Respiratory disease (asthma and chronic obstructive pulmonary disease [COPD])</td>
<td>Respiratory disease puts you at a higher risk for developing serious flu complications. The flu can cause inflammation of the airways and trigger an asthma attack or COPD exacerbation. The flu can also lead to pneumonia and other respiratory complications. People with respiratory disease are more likely to develop pneumonia if they get the flu than people who do not.</td>
<td>Getting the influenza vaccine can decrease your risk of getting the flu and prevent having an asthma attack, COPD exacerbation, or getting bacterial pneumonia. Influenza vaccination has been associated with reduced hospitalizations for adults with chronic lung disease.</td>
</tr>
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national implementation, they estimated that 6.2 million additional influenza immunizations and 3.5 million additional pneumococcal immunizations were attributable to pharmacy-delivered immunization services. Pharmacists have played a key role in COVID-19 vaccine administration through their involvement with the Federal Retail Pharmacy Program for COVID-19 vaccination. As of October 2021, more than 141 million doses were administered by retail pharmacies across the United States, including 8 million doses administered at long-term care facilities, which highlights the potential reach of pharmacists.

Pharmacists need to take advantage of every patient encounter to increase vaccination rates. Data from the 2020-2021 influenza season in the United States demonstrate that influenza vaccination coverage among adults aged 65 years or older was higher (75.2%) than coverage among adults aged 18 to 49 years (37.7%) and 50 to 64 years (54.2%), although there is room for improvement in all age groups. There are even lower immunization rates in the socioeconomically disadvantaged and various ethnicities.

Patients can be reminded about the importance of obtaining an annual influenza vaccine at multiple encounters. Video or audio recordings while patients are waiting in the pharmacy or on the phone are great ways to inform patients. Providing immunization histories periodically and keeping these updated in the patient profile system both for inpatients and outpatients in the hospital, clinic, or pharmacy are key. Reminders should be sent to patients through postcards or text messages. Many pharmacies are using automated phone or computer systems to allow patients to schedule their COVID-19 vaccine appointments; this strategy can be used for influenza vaccines and other vaccines as well. Patient vaccine screening questionnaires at the time of vaccination should contain questions to determine if a patient qualifies for other vaccines as well. Patient vaccine screening questionnaires at the time of vaccination should contain questions to determine if a patient qualifies for other vaccines as well. When vaccines are needed, patients should be educated on their value and be immunized. Combining multiple strategies across different settings and addressing patient barriers may offer the best approach to optimize vaccine administration.

While nearly all individuals would be appropriate candidates for the influenza vaccine, it is especially important to promote vaccination in individuals who are at high risk, such as older adults. Table 3 includes some key education and talking points for patients at high risk for influenza-associated complications who also have a higher risk of COVID-19 infection. Furthermore, pharmacists should educate high-risk patients to call their physician immediately if they start to have flu symptoms so antiviral therapy can be initiated, which could help reduce the severity and duration of influenza regardless of their vaccination status.

Influenza vaccination has been associated with reduced hospitalizations for adults (including those >65 years) with diabetes and chronic lung disease. Vaccination reduced the risk of major cardiac events among adults with existing CVD. Additionally, among adults hospitalized with the flu, intensive care unit (ICU) admissions decreased, and fewer days were spent in the ICU.

**Addressing Vaccine Hesitancy**

Despite the proven value and promotion of vaccination, vaccine hesitancy, the belief that a vaccine may be unnecessary, ineffective, or unsafe, is a growing problem. In 2019, the WHO named vaccine hesitancy as one of the 10 threats to global health. The first international systematic endeavor that examined this problem was a working group of a WHO advisory body, the Strategic Advisory Group of Experts on Immunization (SAGE). The SAGE Working Group on Vaccine Hesitancy defined vaccine hesitancy as the delay in acceptance or refusal of vaccination despite availability of vaccination services.

The SAGE group created “3 Cs” model to describe and understand vaccine hesitancy. It included the following factors:

- **Confidence:** lack of trust in safety and effectiveness of vaccines
  - This includes the reliability and competence of health care professionals, health services, and/or the motivation of policy makers who make decisions about vaccines.

- **Complacency:** not perceiving diseases as high risk and vaccination as necessary
  - Low perceived risk of vaccine-preventable diseases, leading to an assumption that vaccines are not needed. It is affected by many factors, including other life/health responsibilities that seem more important at that point in time.

- **Convenience:** practical barriers
  - The ability to access, understand (language and health literacy), and afford the vaccination services as well as quality of the service (real and/or perceived).

Vaccine hesitancy reduces vaccine uptake, compromises herd immunity, and undermines the effectiveness and success of immunization programs. When herd immunity is compromised, disease outbreaks among the unvaccinated population are likely. Vaccine hesitancy represents a threat that can seriously jeopardize success of past vaccination campaigns as well as the control of the COVID-19 pandemic and implementation of new vaccines in the future. These factors are context specific and multidimensional; they overlap and interact. While high levels of hesitancy lead to low vaccine demand, low levels of hesitancy do not necessarily
mean high vaccine demand. Hesitancy describes a continuum between complete acceptance and complete refusal. 64

Others have expanded on the 3C model as they feel additional factors play a role in vaccine hesitancy. Betsch and colleagues developed the 5C scale to include psychological factors of vaccination. They replaced convenience with constraints, and added calculation and collective responsibility for the 5C model 65:

- **Confidence**: having trust in safety and effectiveness of vaccines and the health care team and services who deliver them
- **Complacency**: not perceiving diseases as high risk and vaccination is not necessary as a preventive action
- **Constraints**: structural (ability to access, afford, geographical factors) and psychological barriers (language and health literacy issues)
- **Calculation**: engagement in extensive information searching
  - Related to perceived vaccination and disease risks
- **Collective responsibility**: willingness to protect others by getting vaccinated and promoting herd immunity

Pharmacists should be aware of the various factors that can affect vaccination behavior and assess the relative importance of psychological factors and previous experiences. These could assist in a patient’s decision to be vaccinated.

**Communication Strategies**

Pharmacists have opportunities to provide advice and recommendations to vaccine-hesitant persons. To adequately address vaccine hesitancy, it is important for pharmacists to understand the factors that contribute to vaccine hesitancy and how to support patients in their decision-making process to guide them toward vaccine acceptance. Potential reasons why people are vaccine hesitant involve lack of understanding or information, concern about adverse effects, effect of psychological factors, and previous experiences. These could assist in a patient’s decision to be vaccinated.

When talking to patients, motivational interviewing has been shown to be an effective means of reversing vaccine hesitancy. Motivational interviewing is a counseling method that helps people resolve ambivalent feelings and insecurities to find the internal motivation they need to change their behavior. There are 4 principles in motivational interviewing: open-ended questions, affirmations, reflective listening, and summary (OARS). 66,67 Pharmacists should use this method along with the key talking points discussed to try to improve patients’ perceptions on vaccinations.

**Educational Points for Vaccines During COVID-19**

Pharmacists and other healthcare professionals have challenges ahead to dispel negative beliefs in promoting immunization with the influenza vaccine, as well as the COVID-19 vaccine. The COVID-19 vaccines were developed quickly and there are ongoing changes that pharmacists need to educate patients about. As the qualified age for administration expands, new opportuni-
**SIDEBAR. DISPELLING MISCONCEPTIONS ABOUT VACCINES**

**“I’ve gotten the flu when I got the flu shot.”**
It takes about 2 weeks for antibodies to develop after vaccination, so any exposure to the flu during this time or shortly before could lead to illness. Further, the flu presents like many other respiratory viruses including rhinoviruses (common cold), which the flu shot does not protect against. The flu vaccine covers 4 types of flu strain virus based on predictions. Sometimes these predictions are not accurate, leaving the public susceptible to these viruses.

**“It’s better to get the flu and build up my immune system than get the flu shot.”**
In some cases, catching a disease and becoming ill (natural immunity) results in a stronger immunity to the disease than a vaccination. However, the dangers of this approach far outweigh the benefits. If infected with the flu, health complications, hospitalizations, or death are more likely to occur in young or older adults and those with chronic health conditions but can also happen in healthy children and adults.

**“I’m healthy and have never gotten the flu so I don’t need the flu shot.”**
Although young children, elderly persons, and people with certain chronic diseases are particularly vulnerable to the flu, even otherwise healthy people can have serious complications, hospitalizations, and death. Also, when a majority of people get vaccinated, herd immunity occurs, which provides protection against infection to a non-vaccinated person. This is important because there will always be a portion of the population who cannot receive vaccines for medical reasons. So, the benefits of getting vaccinated outweigh the risks.

It remains important to receive an influenza vaccination to reduce the risk of a co-infection of influenza and COVID-19. Because influenza and COVID-19 present with similar symptomatology and occupy the same medical resources, the influenza vaccine is crucial in reducing the number of patients with severe influenza to free up resources that may be necessary to handle another wave of patients with COVID-19. Maximizing the number of people immunized, especially older adults and/or adults at risk, with seasonal influenza vaccination for these individuals should take multiple factors into consideration, including the degree of influenza circulation in the community and the patient’s underlying risk of complications.

The WHO, CDC, and other organizations have identified common misconceptions of vaccinations that pharmacists should be prepared to address. Some of these myths and educational points to discuss with patients are listed in the **SIDEBAR**. Pharmacists can assist with addressing common questions, clarify any confusion surrounding vaccines, and direct patients to additional educational resources for information about vaccines if needed.

**Conclusion**

It takes about 2 weeks for antibodies to develop after vaccination, so any exposure to the flu during this time or shortly before could lead to illness. Further, the flu presents like many other respiratory viruses including rhinoviruses (common cold), which the flu shot does not protect against. The flu vaccine covers 4 types of flu strain virus based on predictions. Sometimes these predictions are not accurate, leaving the public susceptible to these viruses.

Although young children, elderly persons, and people with certain chronic diseases are particularly vulnerable to the flu, even otherwise healthy people can have serious complications, hospitalizations, and death. Also, when a majority of people get vaccinated, herd immunity occurs, which provides protection against infection to a non-vaccinated person. This is important because there will always be a portion of the population who cannot receive vaccines for medical reasons. So, the benefits of getting vaccinated outweigh the risks.

It remains important to receive an influenza vaccination to reduce the risk of a co-infection of influenza and COVID-19. Because influenza and COVID-19 present with similar symptomatology and occupy the same medical resources, the influenza vaccine is crucial in reducing the number of patients with severe influenza to free up resources that may be necessary to handle another wave of patients with COVID-19. Maximizing the number of people immunized, especially older adults and/or adults at risk, with seasonal influenza and other vaccines can reduce the burden of the targeted diseases, but also prevent a proportion of COVID-19 morbidity and mortality.

There are many ways that pharmacists can promote vaccination; one of the most important contributions is by administering vaccines. Pharmacists can assess patients and vaccination records to help identify high-risk patients to be immunized and provide recommendations to patients. Using the appropriate motivational interviewing, pharmacists can inform patients of their risk of infection when delaying or refusing vaccination, address concerns about vaccine safety and efficacy, and encourage vaccination. When counseling a patient, it is important to ask about any concerns they may have to identify any opportunities to address vaccine hesitancy by correcting misinformation and providing statistical facts demonstrating the benefits of vaccination.

Pharmacists need to advocate for patients to receive the influenza vaccine as well as other required vaccines. Pharmacists are essential members of the health care team and are key to improving health care through promotion and delivery of immunization to patients during the current COVID-19 pandemic.
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POSTTEST QUESTIONS

1. Which statement is correct regarding the influenza vaccine for 2021-2022?
   A. If a patient has received the influenza vaccine last flu season, they can skip receiving one this flu season.
   B. The influenza vaccines in the United States are trivalent and quadrivalent.
   C. Adjuvanted inactivated influenza vaccine, quadrivalent (Fluad) is an influenza vaccine approved for patients 65 years and older.
   D. The Advisory Committee on Immunization Practices (ACIP) strongly recommends patients receive the recombinant influenza vaccine as it produces the highest antibody response.

2. According to the Centers for Disease Control and Prevention, which patient is considered the highest risk for complications related to influenza and COVID-19?
   A. A 60-year-old patient with no comorbidities
   B. A 62-year-old patient with hypertension
   C. A 68-year-old patient with diabetes
   D. A 55-year-old patient with osteoarthritis

3. Jake is an 18-year-old college student who presents to your pharmacy. He has no underlying diseases, takes no medication, and has an egg allergy (rash). He received his second COVID-19 vaccine 7 days ago because he needed it to attend college; he does not like needles and almost passed out when he got the COVID-19 vaccine. He also tells you that his sister underwent a bone marrow transplant 1 month ago and he is going home to see her this weekend. Based on this information, what action should you take?
   A. Jake should be scheduled to be immunized with the recombinant influenza vaccine in a medical setting this week.
   B. Jake should wait another week to get the inactivated influenza vaccine (IIV4) because he received the COVID-19 vaccine just 7 days ago.
   C. Jake should receive the LAIV4 intranasal spray today because he does not like needles.
   D. Jake should receive any of the inactivated influenza vaccine (IIV4), standard dose today.

4. Which statement is correct regarding influenza and the COVID-19 pandemic?
   A. COVID-19 infections increased the number of influenza cases seen in 2020-2021.
   B. In 2020-2021, routine vaccination rates increased significantly across all populations in the United States due to fears of getting COVID-19.
   C. Studies in the elderly population have concluded that an influenza vaccination seems to have a protective effect against COVID-19 infection.
   D. There were fewer influenza vaccinations given in 2020-2021 resulting in a higher rate of influenza.

5. Which of the following is an example of how pharmacists can improve influenza and COVID-19 vaccination rates?
   A. Tell the patient to receive the influenza and COVID-19 vaccines 2 weeks apart to minimize adverse effects.
   B. Tell patients who were hospitalized for influenza that they have antibodies and will not need the flu vaccine this year.
   C. Clearly communicate evidence and advice in a tailored message.
   D. Avoid discussing adverse drug effects so you do not scare the patient.
Sambucol Black Elderberry
Manufactured by: Sambucol
As the original bestselling elderberry brand, Sambucol Black Elderberry offers consumers a natural solution to help stay healthy. The range of products includes a variety of ways to provide natural immune system support, including the original syrup; kids syrup and gummies; throat lozenges; infant drops; high-potency gummies; immune drink powder; effervescent tablets; capsules; and sugar-free. All formulations are scientifically tested to support immunity with high antioxidant levels, and Sambucol is the No. 1 pharmacist-recommended homeopathic cough product, according to the Pharmacy Times® 2020-2021 OTC Guide.

FOR MORE INFORMATION:
sambucolusa.com

Cold-Eeze Plus Defense
Manufactured by: Mylan
For patients looking to shorten the duration of a cold, Cold-Eeze Plus Defense can promote immune health and help with fatigue. Available as lozenges and chewable gels, the cold remedy includes proprietary zinc gluconate to shorten the duration of a cold and homeopathic active ingredients to promote immune health. According to researchers, the oral release of zinc ions can inhibit the cold virus and its ability to replicate, shortening the duration of the common cold. New sizes also include more doses, with a 25-count lozenge package.

FOR MORE INFORMATION:
coldeeze.com

NyQuil and DayQuil
Manufactured by: Vicks
Because 8 of 10 patients suffer at least 4 cold symptoms concurrently in the first days of their illness, NyQuil and DayQuil attack multiple symptoms simultaneously, including nasal congestion, runny nose, sore throat, sneezing, headache, and cough. According to the results of a study, nasal congestion was the predominant symptom, peaking on day 2, with more than 90% of cold episodes characterized by the presence of congestion throughout the day for the first 5 days. When 3 concurrent symptoms were examined, the presence of secretory symptoms, pain or feverish symptoms, and nasal congestion represented the highest symptom burden, with 77% of cold episodes characterized by these 3 symptoms for the first 3 days. All symptoms, however, significantly decreased by day 7 among participants taking DayQuil and NyQuil.

FOR MORE INFORMATION:
vicks.com
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