Let’s Celebrate Pharmacy Professionals and Their Invaluable Work

MIKE HENNESSY JR
President & CEO
MJH Life Sciences

OCTOBER IS A BIG MONTH in the pharmacy profession—a time to acknowledge the powerful impact pharmacists and pharmacy technicians make on patients and communities. Not only is it American Pharmacists Month, but we also celebrate Women Pharmacist Day on October 12, 2022, and Pharmacy Technician Day on October 18, 2022.

Pharmacy Times® will be saluting pharmacists throughout the month to recognize their contributions to health care. Check out our coverage at PharmacyTimes.com.

One pharmacist who stands out is Matthew Pruitt, PharmD, site director of microfulfillment for Walgreens in Phoenix, Arizona. He is featured in this issue and on the cover and is the winner of the Parata Systems and Pharmacy Times® Next-Generation Pharmacist® of the Year award.

Pruitt said his greatest achievements include his “work with the first COVID-19 mass vaccination site in Arizona, [which] is one of the most fulfilling projects I have had the opportunity to help a team through and display how vital pharmacists are to the health care ecosystem. Additionally, my advocacy work to drive health equity along with helping mentor hundreds of student pharmacists and seeing them succeed and change the profession is high on the list.”

Since 2010, the Next-Generation Pharmacist® program has honored pharmacists, technicians, students, and industry advocates who are defining the future of pharmacy in 10 categories. The winners, all featured in this issue, are a group of exceptional pharmacy professionals who have gone above and beyond in caring for patients and advancing the profession. Please join me in congratulating them for their extraordinary efforts to improve patient care.

In this month’s issue, Suzanne Soliman, PharmD, BCMAS, chief academic officer at the Accreditation Council for Medical Affairs and founder of the Pharmacist Moms Group, the largest group of female pharmacists in the United States with more than 35,000 members, writes about Women Pharmacist Day and the significant achievements that women have made in the profession.

In addition, the October issue features articles on myriad topics, including the cover feature by Kathleen Kenny, PharmD, RPh, called “Know the COVID-19 Vaccine, Treatment Options,” which presents the latest information on helping patients stay healthy amid a continuously changing landscape.

We also hope you find the October technician supplement useful; it focuses on the contributions of these essential members of the pharmacy team.

Thanks for reading.
October is American Pharmacists Month

which celebrates the profession of pharmacy and generates recognition for pharmacists and community.

Join Pharmacy Times® on Twitter, Facebook, Instagram, and LinkedIn with #ThankAPharmacist and to show our appreciation for your profession, celebrate a pharmacist’s achievements, or share what you do to positively impact patient health.

#Thank A Pharmacist

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Use #APharmacistIs on social media or email submissions to Aislinn Antrim at aantrim@pharmacytimes.com.
CVS ANNOUNCED ITS ACQUISITION OF Signify Health on September 5, 2022, cementing the company as no longer just a pharmacy chain but as a health care sector conglomerate in the home-provided services business. Notably, nowhere in the CVS Health-issued statement is there any mention of “Aetna” or “pharmacy.” CVS Health cited a desire to solidify capabilities in value-based care delivery as the motivating force behind the purchase.

Walmart Floats Trial Balloon With UnitedHealth Group
Walmart announced a partnership with UnitedHealth Group (UHG) on September 7, 2022, to provide analytics and other support from UHG’s Optum suite of capabilities to assist with Walmart Health deployments. This partnership is the first major integration with a health plan since Walmart’s teaming with Humana on Medicare enrollments. Notably, “pharmacy” is not mentioned in the statement by UHG, but the rationale for the partnership is to offer better and more integrated plan provider value-based care delivery.

Amazon Gets Into Primary Care, for Real This Time
Amazon announced the purchase of One Medical in July 2022; such a bricks-and-mortar acquisition has not occurred since it bought Whole Foods in 2017. Yet One Medical has qualities with which Amazon is familiar: analytics, data collection, and devices, plus a subscription model, for which customers pay $199 per year to access same-day in-person or virtual visits. Notably, “pharmacy” is mentioned in the Amazon/One Medical media coverage, with PillPack as a supporting offering.

Better Late Than Never, Rite Aid Makes Its Medical Care Play
In May 2022, Rite Aid and Homeward announced a partnership to focus on the accessibility of medical care in rural pharmacy locations (in the parking lot to start with). This follows already-in-place medical integration efforts by CVS-HealthHUB-MinuteClinic; Kroger-The Little Clinic; VillageMD-Walgreens; and Walmart Health. Notably, the news release mentioned the importance of pharmacies in communities.
Buy vs Partner: Regardless, Owning Patient Journey Is the Future

Some have the cash to spend billions to buy, whereas others choose to partner or start piloting first. Regardless, the prevailing motivation behind these acquisitions and partnerships is to own the patient journey. Much like Apple’s ecosystem, everything from form to function is designed to keep customers in that system. From content procurement to devices and software on down to the charging method, the goal is to keep customers buying the same family of products. The entry points into the health care system are home health, the pharmacy, and primary care. All 3 are being put together en masse based on a bet that patients will prefer a more accessible system and that value-based care, at its core, is keeping patients away from hospitals and specialists, also known as health systems. There is a tectonic battle between the old guard of providers and the better-funded new guard of Wall Street providers.

Chatter Abounds About Collaborative Practice Agreements

The question remains, what does all this have to do with community pharmacy practice and pharmacists? I was heartened to hear recently that at least one pharmacy group and likely another are working to grant credentials to pharmacists and creating collaborative practices agreements between integrated primary care providers and pharmacists. Let’s hope this leads to using pharmacists as valuable health care providers in an opportunity-based health care services delivery setting.

We Have Been Saying Delivery of Professional Services Is the Future for More Than 3 Decades

It turns out this was right in the end, but the timing was not. It did not happen in the 1990s, 2000s, or 2010s. It will occur in the 2020s and be precipitated by 2 factors: a pandemic that fundamentally changed patient and purchaser perceptions about pharmacists and pharmacies; and value-based care delivery leading to consumers, employers, and taxpayers becoming fed up and asking for sane, economical options that provide tangible outcomes. They say that it is darkest right before the dawn. Maybe the dawn is on the horizon.

REFERENCES

Study Results Suggest Acupuncture Reduces Anxiety in Patients With Parkinson Disease

REAL ACUPUNCTURE (RA) MAY HELP treat anxiety in patients with Parkinson disease (PD), according to research results published in JAMA Open Network.

The study data demonstrated that RA had higher clinical improvement for anxiety than sham acupuncture (SA). Patients who had RA also experienced a noticeable improvement in quality of life (QOL), along with positive effects on their overall condition.

“This study’s results suggest that acupuncture with clinical monitoring may alleviate anxiety of patients with [PD],” the study authors wrote. Anxiety affects nearly one-third of all patients with PD.

The study objective was to explore effective anxiety treatments for PD with minimal adverse effects. Investigators evaluated the efficacy of acupuncture treatment, which was previously determined to be as effective as certain behavioral therapies. This study is the first randomized clinical trial (NCT04729010) to assess acupuncture for the treatment of anxiety in patients with PD.

The team performed a double-blind, 8-week, randomized clinical trial to compare the efficacies of RA and SA in 70 patients enrolled in the PD clinic of a Chinese hospital. The study was conducted between June 20, 2021, and February 26, 2022, with 64 patients participating in the April 15, 2022, follow-up.

The primary outcome was scored on the Hamilton Anxiety Rating Scale (HAM-A), which evaluates degree of anxiety. From the baseline, the mean reduction of the HAM-A score dropped 4.38 points among patients who had RA. The mean reduction in HAM-A score was even greater at the follow-up, at 7.03 points lower than patients who had SA.

Secondary outcomes were based on the scores of the Unified Parkinson’s Disease Rating Scale and the 39-item Parkinson’s Disease Questionnaire. These tests measure QOL, which can be worsened by anxiety.—Erin Hunter

Sandoz’s Denosumab Meets Primary End Points in Phase 3 Trial

SANDOZ, A DIVISION OF NOVARTIS, announced the release of positive results from the integrated phase 3 clinical trial (NCT03974100) of denosumab, which is the biosimilar for Prolia from Amgen.

Denosumab is a human monoclonal antibody that binds to the RANKL protein, which is an activator of osteoclasts. This decreases the production and activity of osteoclasts, resulting in reduced bone loss and likelihood of fractures or other serious bone conditions.

“Biosimilars have the opportunity to create a substantial positive impact on patient access and health care systems sustainability,” Florian Bieber, global head of development at Sandoz Biopharmaceuticals, said in a statement. “Therefore, this important milestone means that we are one step closer to giving individuals living with osteoporosis access to a more affordable, biosimilar version of this critical medicine, which may help to change the course of their disease.”

Denosumab is indicated to treat a variety of conditions, including osteoporosis in postmenopausal women, increased risk of fractures in men, treatment-induced bone loss, prevention of skeletal-related complications in cancer that has spread to the bone, and giant cell tumors on the bone.

Study results showed that the biosimilar matches the reference medication in efficacy, immunogenicity, pharmacodynamics, pharmacokinetics, and safety. It also showed that the drug contributed to the demonstration of similarity, which is the basis for use in all indications.—Ashley Gallagher

Multivitamin Mineral Supplements Show Potential for Improving Cognition

COCOA EXTRACT DOES NOT BENEFIT COGNITION; however, multivitamin minerals (MVM) have potential to improve cognition in older adults, according to results of the COSMOS-Mind (NCT03035201) study published in Alzheimer’s & Dementia.

COSMOS-Mind is a large, randomized, 2-by-2, factorial, 3-year trial that assessed daily administration of cocoa extract of 500 mg/d compared to placebo and commercial MVM. Individuals were enrolled in COSMOS-Mind from August 2, 2016, to August 17, 2017.

Out of 2262 individuals, investigators found that cocoa extract had no effect on cognition. However, they found that daily MVM resulted in a statistically significant benefit for global cognition vs the placebo.

Investigators said the effect was highest in individuals with a history of cardiovascular disease (CVD).

The subgroup with CVD history included more men, tended to be older, had higher body mass index, more hypertension, used statins more, were more depressed, and had less physical activity.

However, investigators found that when this subgroup was removed from the analysis, the main MVM findings remained unchanged, showing that daily MVM continued to have a statistically significant benefit on global cognition.

Additionally, in the prespecified subgroups, investigators said cocoa extract effects suggested that response could vary with baseline body mass index. The MVM benefits in the prespecified groups were also observed in memory and executive function.

Investigators assessed cognition by phone at baseline as well as annually. Approximately 92% of individuals completed baseline assessment and at least 1 annual assessment.

Investigators found that those who missed at least 1 assessment were more likely to be from an underrepresented racial or ethnic group, reported less physical activity and more chocolate intake, more smoking, tended to have lower education, and a higher prevalence of type 2 diabetes.—Ashley Gallagher
George Rafferty, president of corporate partnerships at AmerisourceBergen, shares his love of golfing, running, and above all else, chasing his grandchildren around the yard in his free time.

TO WATCH: https://bit.ly/3BjbSGg

Rebekah Bernard, MD, a physician wellness speaker, talks about the differences between professional burnout and physicians' lack of satisfaction in their practice. She also discusses self-care strategies to help physicians avoid the burnout and help them maintain job satisfaction so they want to stay in the field.

TO WATCH: https://bit.ly/3QmqpFe

Jonathan Miller and Eric Wang, both from the US Hemp Roundtable, discuss the regulatory issues surrounding cannabinoids and their sale.

TO WATCH: https://bit.ly/3KShiLA

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Know the COVID-19 Vaccine, Treatment Options

Latest Information Is Key to Helping Patients Stay Healthy Amid Continuously Changing Landscape

By KATHLEEN KENNY, PHARMD, RPH

With fall having arrived, it is important for pharmacists to be sure they are up-to-date with information on COVID-19 vaccines and options for treatment. Because of their role as a resource in keeping patients healthy, pharmacists have a special responsibility in sharing the latest information and statistics surrounding the pandemic.
Approximately 96 million individuals in the United States have had some version of the COVID-19 virus; of that number, 1.05 million have died, according to the CDC. Most individuals who experience severe illness from COVID-19 are older than 50 years (though not always) and have underlying medical conditions such as chronic kidney disease, chronic obstructive pulmonary disease, diabetes, heart disease, or obesity.

CONTROL EFFORTS
Due to the rising number of COVID-19 cases and lack of knowledge about the disease at the beginning of 2020, efforts to prevent spread of the virus were extreme. These included banning large gatherings, closing public places and schools, and encouraging work from home. Many individuals were required to wear masks outside their homes.

These measures slowed the spread of COVID-19 but also hurt the economy, forcing many small businesses to close. Many individuals were scared, creating a defensive, tense environment. Children forced to stay home from school often fell behind in their studies and developed anxiety disorders.

In hindsight, perhaps these efforts were too extreme for individuals not at high risk for developing severe disease, but because little was known about COVID-19 at the time, it was a decision based on protecting the population.

VACCINATION
Operation Warp Speed (OWS), a partnership between the US Departments of Defense and Health & Human Services, was designed to speed development of a COVID-19 vaccine. The US Government Accountability Office determined that vaccine makers and OWS adopted strategies for quickly developing vaccines while mitigating risk.

The 3 vaccines resulting from OWS were from Johnson & Johnson, Moderna, and Pfizer/BioNTech. These fast-tracked vaccines started to be available in January 2021. Since then, more than 262 million individuals or 79% of the US population have received at least 1 dose. Overall, more than 224 million individuals or 68% of the population are considered fully vaccinated. Additionally, more than 108 million individuals or 33% of the population have received a booster dose.

On August 31, 2022, the FDA authorized using bivalent formulations of the vaccines as single booster doses at least 2 months after primary or booster vaccination. These bivalent vaccines consist of 2 messenger RNA (mRNA) components of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), according to an FDA news release. The first component is from the original strain of SARS-CoV-2, for broad protection against COVID-19. The other is a component in common between the Omicron variant’s BA.4 and BA.5 lineages, which are causing most US cases of COVID-19 and are expected to circulate from now through the winter, according to the FDA release. In June 2022, the FDA’s Vaccines and Related Biological Products Advisory Committee voted to include an Omicron component in COVID-19 booster vaccines.

For each bivalent COVID-19 vaccine, the FDA considered available evidence. According to the FDA news release, this included effectiveness and safety data for each monovalent mRNA COVID-19 vaccine; immunogenicity and safety data from a study of a bivalent COVID-19 vaccine containing mRNA from Omicron variant BA.1 lineage that is similar to each vaccine being authorized; and nonclinical data obtained using a bivalent COVID-19 vaccine with mRNA of the original strain and mRNA in common between Omicron’s BA.4 and BA.5 lineages.

Based on data supporting these authorizations, the bivalent COVID-19 vaccines should provide increased protection against Omicron, according to the FDA news release. Individuals getting a bivalent COVID-19 vaccine may experience adverse effects (AEs) common among those getting monovalent mRNA COVID-19 vaccines. The monovalent mRNA COVID-19 vaccines are no longer authorized as booster doses for individuals 12 years and older, according to the FDA, which said it will evaluate data and submissions to support authorization of bivalent COVID-19 boosters for more age groups. The bivalent Moderna COVID-19 vaccine is authorized for use as a single booster dose in individuals 18 years and older, provided it has been at least 2 months since they completed primary vaccination or got their most recent booster dose of any authorized monovalent COVID-19 vaccine. Similarly, the bivalent Pfizer-BioNTech COVID-19 vaccine is authorized for use as a single booster dose in individuals 12 years and older, according to the FDA release.

COVID-19 TREATMENT
The FDA has authorized certain antiviral medications...
Pharmacists who counsel patients this fall and winter should realize that COVID-19 presents a constantly changing landscape.

and monoclonal antibodies to treat mild to moderate COVID-19 in individuals more likely to experience severe illness, according to the CDC. Antiviral treatments target specific parts of the virus to stop it from multiplying in the body, helping prevent severe illness and death. Monoclonal antibodies help the immune system recognize the virus and do a better job of fighting it. According to the CDC, these treatments include the following:

**Bebtelovimab.** This monoclonal antibody is indicated in adults and children 12 years and older. Given as a single intravenous (IV) injection, it should be started within 7 days of symptom onset.

**Nirmatrelvir with ritonavir (Paxlovid; Pfizer).** This antiviral treatment is indicated in adults and children 12 years and older. This is an oral dosage taken at home that should be started within 5 days of symptom onset.

**Remdesivir (Veklury; Gilead).** This antiviral treatment is indicated in children and adults. This is an IV infusion given at a health care facility for 3 consecutive days and should begin within 7 days of symptom onset.

**PATIENT PEARLS**

Some treatments might have AEs or interact with other medications, according to the CDC. Patients should ask physicians about the medications; those without health care providers can visit Test to Treat locations or contact a local community health center or health department. Hospitalized patients might receive other types of treatments, depending on the extent of illness. These could include medications to treat the virus, reduce an overactive immune response, or treat COVID-19 complications, according to the CDC. Many individuals with COVID-19 experience mild illness and can recover at home by using OTC medicines such as acetaminophen or ibuprofen, the CDC said.

Pharmacists who counsel patients this fall and winter should understand that COVID-19 presents a constantly changing landscape. Patients may look to pharmacists as an important community resource and as a way of keeping informed about the latest developments regarding the coronavirus. It is crucial that pharmacists stay informed about COVID-19.

**REFERENCES**

THE SIGNIFICANCE OF ORAL HEALTH and hygiene often is overlooked until an issue arises. Research has established that oral health is critical to general health and well-being.

Poor oral health and hygiene may lead to infections and pain, which may result in eating and speaking problems and affect overall quality of life, including self-esteem and social interactions, according to the CDC.¹

The 3 most common oral conditions affecting overall health and quality of life are cavities, severe periodontal disease, and severe tooth loss (meaning having 8 or fewer teeth), according to the CDC.¹ Recent statistics show that an estimated 26% of adults in the United States have untreated tooth decay; approximately 46% of all US adults 30 years or older exhibit signs of periodontal disease, with 9% having severe periodontal disease.² Moreover, about 68% of adults 65 years or older experience some degree of periodontal disease.²

Periodontal diseases are common but largely preventable and treatable if detected early. They may present with varying degrees of severity and are primarily the result of infections and inflammation of the bones that support and surround teeth, as well as the gums.³ Gingivitis is the early stage of periodontal disease, affecting only the gums, and is characterized by gingival bleeding, redness, and swelling.³ The most common cause of gingivitis is poor oral hygiene, which promotes the accumulation of plaque.³ By contrast, periodontitis, the most severe form of periodontal disease, is characterized by gingival inflammation, accompanied by loss of supportive connective tissues around the teeth. Comparable to gingivitis, periodontal disease is most often caused by poor oral hygiene.³ Certain chronic conditions and/or factors augment the risk for periodontal disease, including diabetes, genetic factors, having a compromised immune system, and poor oral hygiene.³ Moreover, use of tobacco products is an important risk factor for development of periodontal disease. In advanced stages, periodontal disease can lead to bleeding and sore gums, painful chewing problems, and tooth extraction and/or loss.³ Hormonal changes during pregnancy, metabolic diseases, and the use of certain medications such as antihypertensive agents and immunosuppressants may also affect the gums.³

NEWS AND CLINICAL STUDIES

Investigators at Tufts University School of Dental Medicine in Boston, Massachusetts, discovered that targeting *Fusobacterium nucleatum*, which often thrives in periodontal disease, could slow development of Alzheimer disease (AD). However, more research is warranted.¹

Although the correlation between AD and periodontal disease is not new, the association with this bacterium is. Investigators indicated that this is the first study to discover that *F nucleatum* can produce systemic inflammation and even infiltrate nervous system tissues, exacerbating the signs and symptoms of AD.³

Prevent, Identify Periodontal Disease for Overall Patient Health

*Integrating an Oral Hygiene Regimen Into Patients’ Daily Routines Is Essential to Overall Well-being*

By YVETTE C. TERRIE, BSPHARM, RPH

YVETTE C. TERRIE, BSPHARM, RPH, is a consulting pharmacist and medical writer in Haymarket, Virginia.
In a recent publication, the American Heart Association indicated that more than 100 diseases can show symptoms in the oral cavity. For example, periodontal disease commonly occurs in those with diabetes; cases tend to be more severe, particularly in individuals with poorly controlled diabetes and those with higher HbA1c values, and diabetes-related complications are exacerbated and increased.

Research results indicate that the presence of periodontal disease has been correlated with several cardiovascular diseases, including carotid atherosclerosis, hypertension, and myocardial infarction. A 2020 systematic review indicates that periodontitis may boost the risk of developing rheumatoid arthritis.

Finally, research suggests connections between periodontitis and respiratory diseases such as asthma, chronic obstructive pulmonary disease, and pneumonia, probably because of inflammatory processes and aspiration of microorganisms from the periodontal pocket. Pharmacists can help to identify medical conditions and/or medications that contribute to or exacerbate oral health issues, making recommendations based on individual situations. They can also educate patients about and promote proper use of the various oral hygiene products, as well as expand awareness of the importance of oral health and its impact on overall health and well-being. During counseling, pharmacists should remind patients that routine oral health, including professional dental care, is essential to maintaining good overall health. In general, the goals of oral hygiene are to decrease the incidence of halitosis and xerostomia; eliminate or thwart the formation and buildup of plaque and tartar; prevent dental caries, periodontal disease, and tooth loss; and reduce dentin hypersensitivity.

Pharmacists can also remind patients about the recommended proper brushing and flossing technique from the American Dental Association (ADA) and other helpful tips about oral health, such as the following:

• Brush teeth at least twice daily with a soft-bristled brush. The shape and size of the brush should allow accessibility to all areas of the mouth.

• Floss after brushing.

• Limit consumption of sugary beverages and snacks.

• Replace the toothbrush every 3 or 4 months, or sooner if the bristles are frayed. A worn toothbrush does not clean teeth properly.

• Use an ADA-accepted fluoride toothpaste (see https://www.mouthhealthy.org/en/ada-seal-products).

• Visit a dentist at least twice a year.

For more information, visit the ADA's Mouth Healthy website (https://www.mouthhealthy.org/en/az-topics/b/brushing-your-teeth).

REFERENCES


Hydrating Makeup Removing Plant-Based Wipes
Manufactured by CeraVe
CeraVe now offers Hydrating Makeup Removing Plant-Based Wipes, a gentle facial cleaner formulated to remove makeup, including waterproof mascara. The wipes lock in hydration without disrupting the skin’s protective moisture barrier and without leaving a greasy or sticky feeling. The formula, developed by dermatologists, has glycerin and 3 essential ceramides, which help hydrate and protect the skin’s natural barrier. The wipes are suitable for all skin types, including sensitive. The wipes are biodegradable in a home compost.

FOR MORE INFORMATION:
cerave.com

Daily Immune Support, Sleep + Immune Support Gummies
Manufactured by Zicam
Zicam now offers 2 new gummy supplements. Daily Immune Support gummies come in bottles of 23 servings. Each serving has 100% of the daily value of ascorbic acid (vitamin C) and cholecalciferol (vitamin D), as well as zinc. The natural citrus and strawberry gummies can be taken every day; adults should take 3 gummies daily. Sleep + Immune Support gummies include 100% of the daily values of vitamins C and D, as well as zinc and 3 mg of melatonin per serving. The blackberry-flavored and lavender-flavored gummies should be taken at bedtime for sleep support.

FOR MORE INFORMATION:
zicam.com

Eye Allergy Itch Relief
Manufactured by Clear Eyes
Clear Eyes now offers once-daily Eye Allergy Itch Relief drops. The product contains olopatadine hydrochloride and is intended for relief from indoor and outdoor allergens, including grass, pet dander, pollen, and ragweed. Clear Eyes states on its website that the drops are original prescription strength and work within minutes. The product is intended to be used once a day for all-day relief. Individuals 2 years and older should use 1 drop in the affected eye daily but not more than once per day. If other ophthalmic products are being used, the individual should wait 5 minutes between each product.

FOR MORE INFORMATION:
cleareyes.com

Rapid Relief With Lidocaine Hemorrhoidal Spray
Manufactured by Preparation H
Preparation H now offers Rapid Relief With Lidocaine Hemorrhoidal Spray. It is intended to reduce swelling and numb painful burning, itching, and swelling on contact. The spray comes in the highest lidocaine strength available. To apply, individuals should cleanse the affected area and then gently pat dry with a soft cloth or tissue before applying the product. The spray can be used on the irritated area up to 4 times a day, according to Preparation H’s website.

FOR MORE INFORMATION:
preparationh.com
Menopause

By RUPAL MANSUKHANI, PHARM.D, FAPHA, CTTS; AND AMMIE PATEL, PHARM.D, BCACP

CASE 1: Hot Flashes

MK is a woman aged 52 years whose menstrual periods have gradually stopped, with none during the past year. Her most common symptoms of menopause were hot flashes, which presented as a sudden feeling of warmth, especially on her chest, face, and neck. MK said the hot flashes sometimes caused her to sweat. They have occurred overnight and caused sleep disturbances. MK has had trouble functioning at work and at home. However, she does not wish to take medication and asks about lifestyle modifications to help her overcome these symptoms. What information should the pharmacist provide?

MK’s vasomotor symptoms are the most common signs of menopause and are mediated by thermoregulatory dysfunction occurring in the hypothalamus because of estrogen withdrawal. The warmth she feels is the result of peripheral vasodilation, which increases blood flow to the skin. Shortly after having a hot flash, MK may even experience shivering as her body attempts to restore the core temperature.

The pharmacist should advise her to dress in layers that are easy to remove and keep indoor temperature cool with air conditioning and fans. MK should avoid triggers leading to hot flashes, including spicy foods and stressful situations. At the onset of a hot flash, she should practice deep, slow breathing. Risk factors for hot flashes include drinking alcohol and caffeine, being sedentary, obesity, and smoking. Other ways of managing hot flashes include meditation, tai chi, and yoga.

CASE 2: Vaginal Dryness

SN is a woman aged 57 years. She is experiencing vaginal dryness, along with cessation of menstruation and some mild hot flashes. She is seeking nonpharmacologic treatment options. What should the pharmacist advise?

Vaginal dryness is a symptom of vaginal atrophy secondary to menopause. As such, a pelvic examination is recommended for women experiencing dyspareunia, sexual dysfunction, or vaginal dryness to assess the etiology and rule out cancer and infections. If SN’s medical provider recommends first-line nonhormonal vaginal lubricants and moisturizers, the pharmacist can advise OTC products.

Although vaginal lubricants and moisturizers may provide symptomatic relief, SN may still need a prescription hormonal treatment.

The pharmacist should counsel SN about the difference between lubricants and moisturizers. Lubricants have a base of oil, silicone, or water, and should only be used during sexual activity. Some commercially available brands include Astroglide, Elegance Woman’s Lubricant, ID Millennium, K-Y Jelly, and Pjur. Inform SN that oil-based lubricants can cause a breakdown of latex condoms. Moisturizers are made with hyaluronic acid and should be used routinely, about 2 to 3 days per week. Some commercially available moisturizer products include K-Y Liquibeads, Replens, and Vagisil moisturizer.
CASE 3: Black Cohosh

**Q**

MA is a woman aged 53 years who has questions about herbal supplements. She has been experiencing hot flashes and has not found relief. MA has read that black cohosh (*Actaea racemosa*) may be a natural remedy for menopausal hot flashes. What information should the pharmacist share with MA?

**A**

Black cohosh is derived from a root and is commercially available as Remifemin. Black cohosh extract is usually taken as 40 mg in 1 or 2 doses per day. The exact mechanism of action is unknown, and there have been mixed reports of efficacy in mitigating menopausal hot flashes. It is known that black cohosh does not have estrogen-like properties. The American College of Obstetrics and Gynecologists guidelines report the evidence is not sufficient to support natural products for menopause. Large randomized clinical studies are needed to provide additional information regarding efficacy.²,³

Black cohosh has an overall good safety profile, with minor adverse effects including gastrointestinal complaints, headaches, rashes, and weight gain. There have been some case reports of hepatitis after using black cohosh, but no causal relationship has been established. Because of a lack of long-term safety data on black cohosh, use beyond 6 months is not recommended.⁴-⁶

CASE 4: Evening Primrose Oil

**Q**

KN is a woman aged 54 years who asks about evening primrose oil (*Oenothera biennis*), because her friends have been using this supplement for relief from hot flashes. What information should the pharmacist share?

**A**

Evening primrose oil is widely used by women to treat menopausal hot flashes. Evening primrose oil is rich in ω-6 fatty acids, including linolenic acid. It is considered effective because of its anti-inflammatory processes. Two to 4 g of evening primrose oil per day is given as a capsule or liquid by mouth. Although well tolerated, evening primrose oil can cause adverse effects such as abdominal pain, diarrhea, headaches, or nausea. Additionally, individuals taking anticonvulsant medications should avoid evening primrose oil, because it has been associated with seizures.⁷,⁸
HEART FAILURE (HF) REQUIRES MULTIDRUG therapy as patients progress from early to later stages that include refractory and structural disease. Consequently, the guidelines are onerous and consider the likelihood of atherosclerotic disease, comorbid hypertension, diabetes, metabolic syndrome, and obesity. They also look at concurrent use of cardiotoxins and each patient’s genetic risk for cardiomyopathy. With new guidelines issued in 2022, it is critical to note some changes within them and some that are too new to be included.1

UP-AND-COMERS
Sodium-glucose cotransporter-2 inhibitors, initially considered anti-diabetic drugs, have significant antihypertensive and cardiovascular (CV) benefits in patients with or without diabetes who have congestive HF (CHF). These drugs now lead the list of take-home points in the new guidelines.1 By blocking glucose reabsorption, these medications lead to weight loss and lower blood pressure and reduce abdominal and total body fat and CV complications. The new guidelines recommend their use in HF with reduced ejection fraction (HFrEF) and HF with mildly reduced ejection fraction. These medications’ most common adverse effects (AEs) include hypoglycemia, renal dysfunction, and volume depletion.1

<table>
<thead>
<tr>
<th>TABLE 1. Approaches to Overcoming Diuretic Resistance1-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Add acetazolamide. Although not included in the 2022 guidelines, acetazolamide improves natriuresis; adding acetazolamide 250 mg to furosemide 40 mg increased diuresis similar to that achieved by doubling the furosemide dose.</td>
</tr>
<tr>
<td>• Add a sodium-glucose cotransporter-2 inhibitor, which causes glycosuria resulting in osmotic diuresis and decreased sodium and water reabsorption at the proximal renal tubule.</td>
</tr>
<tr>
<td>• Change the route of administration from oral to intravenous.</td>
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<tr>
<td>• This bypasses the gastrointestinal tract and overcomes delayed absorption.</td>
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<tr>
<td>• Intravenous furosemide increases the risk of ototoxicity in patients currently receiving other ototoxic drugs, such as aminoglycosides; administer doses of 80 mg or more slowly.</td>
</tr>
<tr>
<td>• Change the timing of drug administration.</td>
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<tr>
<td>• Increase diuretic dose; patients with renal failure will not respond to increased doses of furosemide.</td>
</tr>
<tr>
<td>• Reduce sodium intake.</td>
</tr>
<tr>
<td>• Use thiazide-like drugs, such as chlorothiazide, indapamide, and metolazone, in combination with loop diuretics.</td>
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</tbody>
</table>
LOOP DIURETIC RESISTANCE

Patients with HF rely on diuretics to manage or stabilize fluid retention. The associated treatment goal is to reach euvolemia, in which the circulatory system has sufficient blood. Unfortunately, patients can develop diuretic resistance (DR), which is the failure to achieve relief of congestion using an appropriate diuretic dose.\(^2\),\(^3\) DR is more common in moderate to severe CHF than in mild HF with preserved renal function (HFpRF). Proposed mechanisms include chronic or excessive use of diuretics, delayed gut absorption, and inhibited prostaglandin synthesis and diminished renal blood secondary to use of nonsteroidal anti-inflammatory drugs.\(^2\),\(^3\) \n
Table 1\(^1\)-\(^5\) describes approaches to overcoming DR. A critical note for pharmacists is that before making a diagnosis of DR, the team should assess the patient’s adherence.

LOOP DIURETICS VS SACUBITRIL/VALSARTAN

In HFrEF, clinicians have traditionally used loop diuretics to reduce volume overload leading to congestion.\(^6\)-\(^8\) Of concern with loop diuretics are electrolyte disturbances and neurohormonal activation associated with arrhythmias, progressing HF, and death, especially as the dose increases. Participants in pivotal trials for sacubitril/valsartan (Entresto) were less likely to need larger doses of loop diuretics, raising the possibility that sacubitril/valsartan may improve HF outcomes and increase kidney sensitivity to diuretics better than angiotensin-converting enzyme inhibitors or angiotensin receptor blockers alone in HFrEF. The results of several studies showed that the combination of sacubitril/valsartan does just that, a finding that has led investigators to dub this combination “diuretic sparing.” They suggest that improved dilation of the vas afferents and augmented natriuretic peptides might explain this effect.\(^6\)-\(^8\)

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiac disorder. It gradually progresses to include dyspnea and exercise intolerance. Patients with HCM and HFpRF have responded unpredictably to available medications. Mavacamten (Camzyos) is a first-in-class oral molecule approved for this condition. This small molecule modulates β-cardiac myosin and reduces hypercontractility, a key mechanism in HCM’s pathogenesis.\(^9\),\(^10\) Phase 2 and phase 3 trial results showed that mavacamten improved physiologic and symptomatic metrics for symptomatic patients with HCM with few AEs.

Mavacamten capsules are available in 2.5-mg, 5-mg, 10-mg, and 15-mg doses. Patients usually start with 5 mg once daily, with titration at weeks 4, 8, and 12, to a maximum dose of 15 mg daily, if necessary. Target plasma concentration for mavacamten ranges from 350 to 700 ng/mL. Reaching steady-state levels and therapeutic effects can take weeks. Clinicians must assess the patient’s clinical status, left ventricular ejection fraction (LVEF), and left ventricular outflow tract gradient regularly and before dose titration. This medication requires that a medication guide be given at each prescription fill.\(^11\)

Mavacamten might worsen HF or cause a complete block of ventricular function. A decrease of up to 10% in LVEF has been reported. Mavacamten’s most common AEs are dizziness and syncope. \n
Table 2\(^11\) lists less likely potential AEs.

CONCLUSION

Knowledge about HF has expanded in recent years, and the HF guidelines have been updated. Numerous studies are underway that, if successful, may identify medications and medication combinations that decrease hospitalization rates and improve outcomes.

<table>
<thead>
<tr>
<th>TABLE 2. Mavacamten’s Potential AEs(^11)</th>
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<tbody>
<tr>
<td>Acute stress cardiomyopathy</td>
</tr>
<tr>
<td>Angina pectoris</td>
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<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Chest pain</td>
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<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Fatigue</td>
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<tr>
<td>Headaches</td>
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<tr>
<td>Leg edema</td>
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<tr>
<td>Palpitations</td>
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<tr>
<td>Ventricular tachycardia</td>
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</tbody>
</table>

AEs, adverse effects.
A PRESCRIPTION FOR ALIROCUMAB (PRALUENT; Regeneron) 150 mg/mL prefilled pen with the directions “Inject 1 mL under the skin every 2 weeks” was dispensed with the directions “Inject 1 mg under the skin every 2 weeks.”

Alirocumab is a PCSK9 inhibitor dispensed by retail and specialty pharmacies and used for homozygous familial hypercholesterolemia, primary hyperlipidemia, or secondary prevention of cardiovascular events. The product is available as a single-use prefilled pen device, and the entire contents of the pen should be administered for a dose (1 mL total). The pen does not have dose markings or a mechanism to select a specific mg dose. It would be impossible to accurately measure 1 mg. In this case, a pharmacy technician inadvertently typed mg instead of mL as the dosing unit, and the error was not caught during preverification by the pharmacist or during final verification by a second pharmacist. When the error was discovered, the pharmacist corrected the directions and called the patient, who confirmed that he was taking the medication correctly.

The specialty pharmacy that reported this case does not have a standardized process for typing directions for prefilled pens. The pharmacy writes the directions as close to what the doctor ordered, rather than changing them to be standardized and clearer for the patient.

For example, although the doctor wrote “inject 1 mL,” clearer and more instructive directions based on the design of the pen device would have been “inject the contents of 1 pen under the skin every 2 weeks.”

Pharmacies and prescribers should consider implementing a standardized sig code or directions for injectable products, making sure the directions match up with how the drug device is designed and how the prescribed dose is delivered. This can help reduce confusion at the pharmacy and for patients. Before new products are added to the inventory and available for dispensing, proactively assess for risks with dispensing, including possible confusion or opportunities to standardize the directions. Educate staff
members about the risk for sig errors and provide a reference tool indicating how directions and dosages should be relayed to the patient on the label, such as mg, mL, or pen. Teach patients how to use pens. If this teaching is conducted in person or via videoconferencing technology, employ the teach-back method and have patients demonstrate how they will use the pen devices. If education is provided via telephone, have the patient verbalize how they will use the pen devices.

**POOR FAX QUALITY LEADS TO ERROR**

A specialty pharmacy received a new prescription for a somatropin pen injector for a patient with growth hormone deficiency. The prescription had a lower dose than what had been dispensed previously, and the patient’s parent was not aware of the dose reduction. While confirming the new dose, the pharmacist realized that the previous prescription had been dispensed incorrectly. The previous prescription had been faxed to the pharmacy, but the quality of the fax was poor with significant fax noise. The intended dose of 0.6 mg had been misread and dispensed as 0.8 mg. The start date was entered incorrectly as 12/8 instead of 12/6. The Figure shows how the numeral 6 in the sig field and start date field looks like the numeral 8. Thankfully, the incorrect dose of 0.8 mg daily did not harm the patient because it still fell within an acceptable dose range based on the patient’s weight.

Fax noise, or the random marks and streaks on faxes, is an inherent problem with this technology, and it may be more common in old or poorly maintained fax machines. The ISMP has received many reports of errors related to the presence of extraneous interference, lines, or markings on prescriptions caused by old or poorly maintained equipment. Carefully review faxed prescriptions for fax noise.

If the transmission has fax noise in the area of the prescribed medication and directions for use, call the prescriber to confirm the prescription. Check the faxed order against the original, if available. Maintain fax machines, printers, and scanners according to manufacturer recommendations to ensure clear prescription images. Schedule regular maintenance of sending and receiving fax machines. If maintenance fails to improve fax quality, replace the machine. Notify prescribers if their equipment is contributing to poor fax quality.

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**FIGURE.**

The numeral 6 in the sig field and start date field, indicated by the red arrows, was misinterpreted as the numeral 8 due to the poor quality of the faxed prescription.
Ustekinumab (Stelara)
Manufactured by Johnson and Johnson
The FDA has approved ustekinumab (Stelara; Janssen Pharmaceutical Companies of Johnson and Johnson) for the treatment of children aged 6 years or older with active psoriatic arthritis (PsA). Ustekinumab is the first biologic that targets cytokines IL-12 and IL-23, which are thought to affect overreacting inflammatory response in several autoimmune diseases. The drug is administered subcutaneously 4 times a year following 2 started doses for patients with active PsA. The approval is based on pharmacokinetic data and extrapolation of the established efficacy and safety profile of ustekinumab in several phase 3 trials. The trials included CADMUS (NCT01090427), CADMUS Jr (NCT02698475), PSTELLAR (NCT01550744), PSUMMIT/PSUMMIT II (NCT01009086).

FOR MORE INFORMATION: jnj.com

Upadacitinib (Rinvoq)
Manufactured by AbbVie
AbbVie has submitted upadacitinib (Rinvoq) for a new indication, which will include the treatment of individuals with moderately to severely active Crohn disease, to the European Medicines Agency and the FDA. The application is supported by 3 phase 3 clinical trials, including 2 induction studies, U-EXCEED (NCT03345836) and U-EXCEL (NCT03345849), and 1 maintenance study, U-ENDURE (NCT03345823). Individuals were given upadacitinib 45 mg once daily as an induction therapy and upadacitinib at either 15 or 35 mg once daily as a maintenance therapy. Across all 3 studies, investigators found that a significantly higher number of individuals treated with the drug achieved the coprimary end points of clinical remission and endoscopic response. Additionally, they found that more individuals had a clinical remission measured by the Crohn Disease Activity Index by patient-reported symptoms of abdominal pain and stool frequency. The safety results across all 3 studies were generally consistent with the known safety profile of upadacitinib, and no new safety signals were observed.

FOR MORE INFORMATION: abbvie.com

Coagulation Factor IX (Recombinant) GlycoPEGylated (Rebinyn)
Manufactured by: Novo Nordisk
The FDA has approved coagulation factor IX (recombinant) GlycoPEGylated (Rebinyn; Novo Nordisk) for routine prophylaxis in adults and children to prevent hemophilia B–related bleeding. In 2017, coagulation factor IX (recombinant) GlycoPEGylated was approved as an extended half-life treatment used to replace clotting factor IX for on-demand treatment and control of bleeding episodes. The new indication is for prevention of bleeding and to reduce the risk of bleeding. Study results showed that adults and adolescents who were previously treated and taking coagulation factor IX (recombinant) GlycoPEGylated 40 IU/kg once weekly for 1 year experienced an overall median annualized bleeding rate of 1.04, with zero observed inhibitors or thrombotic episodes.

FOR MORE INFORMATION: novonordisk-us.com

Zonisamide Oral Suspension (Zonisade)
Manufactured by Azurity Pharmaceuticals and Eton Pharmaceuticals, Inc
The FDA approved zonisamide oral suspension (Zonisade; Azurity Pharmaceuticals and Eton Pharmaceuticals, Inc) as an adjunctive therapy for individuals with epilepsy 16 years or older who suffer from partial seizures. It is the first FDA-approved oral liquid formation of zonisamide in the 100 mg/5 mL dosage, which helps individuals with epilepsy who have difficulty swallowing tablets. The drug was approved following 3 double-blind, multicenter, placebo-controlled trials, which found it to be effective and tolerated by patients. It was approved to be prescribed at 1 to 2 doses daily.

FOR MORE INFORMATION: etonpharma.com
MUCINEX INSTASOOTHE™

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✓ Relieves Sore Throat Pain
✓ Fast Acting

Alpine Herbs & Fresh Mint flavor
Hexylresorcinol 2.0 mg | Oral Pain Reliever & Dextromethorphan HBr 5.0 mg | Cough Suppressant
Sore Throat + Cough Relief
3 in 1 formula
✓ Quiets Cough
✓ Cooling Comfort
✓ Fast Acting

Elderberry & Wild Cherry flavor
Hexylresorcinol 2.0 mg | Oral Pain Reliever
Sore Throat + Pain Relief
3 in 1 formula
✓ Relieves Sore Throat Irritation
✓ Maximum Strength Pain Relief
✓ Fast Acting
THE FDA HAS APPROVED TIRZEPATIDE INJECTION (Mounjaro; Eli Lilly and Company) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2D). The approval carries the limitations that Mounjaro has not been studied in patients with a history of pancreatitis and is not indicated for use in patients with type 1 diabetes.1

PHARMACOLOGY AND PHARMACOKINETICS
Mounjaro is a glucose-dependent insulinotropic polypeptide receptor and glucagon-like peptide-1 receptor agonist. It enhances first-phase and second-phase insulin secretion and reduces glucagon levels, both in a glucose-dependent manner. Steady-state plasma concentrations are achieved after 4 weeks of once-weekly administration. Mounjaro reaches maximum plasma concentration 8 to 72 hours after subcutaneous administration and has an elimination half-life of approximately 5 days.1

DOSAGE AND ADMINISTRATION
The recommended starting dose of Mounjaro is 2.5 mg subcutaneously once weekly. After 4 weeks, the dose should be increased to 5 mg subcutaneously once weekly. If additional glycemic control is required, the dose may be increased in 2.5-mg increments after at least 4 weeks of the current dose. The maximum dose is 15 mg subcutaneously once weekly. Mounjaro should be injected subcutaneously in the abdomen, thigh, or upper arm with rotation of the injection sites. The weekly dose may be administered at any time of day without regard to meals.1

CLINICAL TRIALS
The effectiveness of Mounjaro as an adjunct to diet and exercise to improve glycemic control in adults with T2D was determined in 5 trials. It was evaluated as monotherapy (SURPASS-1 [NCT03954834]); as an add-on to metformin, sodium-glucose cotransporter 2 inhibitors, and/or sulfonylureas (SURPASS-2 [NCT03987919], SURPASS-3 [NCT03882970], and SURPASS-4 [NCT03730662], respectively); and in combination with basal insulin, with or without metformin (SURPASS-5 [NCT04039503]). The trials compared Mounjaro 5 mg, 10 mg, and 15 mg subcutaneously once weekly to insulin degludec, insulin glargine, a placebo, and/or semaglutide 1 mg. The results of all 5 trials showed that treatment with Mounjaro resulted in a statistically significant reduction from the baseline in hemoglobin A1c compared with an active comparator or a placebo.1,2

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS
Mounjaro carries a boxed warning stating that the medication causes thyroid C-cell tumors in rats, and it is not known whether Mounjaro causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. The warning also states that treatment with Mounjaro is contraindicated in patients with a family or personal history of MTC or in patients with multiple endocrine neoplasia syndrome type 2, and that patients should be counseled about the potential risk of MTC and the symptoms of thyroid tumors. Mounjaro is contraindicated in patients with a known serious hypersensitivity to the medication or any of the excipients. Pancreatitis has been reported in patients using Mounjaro, and if this is suspected, the medication should be promptly discontinued. Concomitant use with insulin or an insulin secretagogue may increase the risk of hypoglycemia, including severe hypoglycemia, and may require a dose reduction of insulin or the insulin secretagogue. Hypersensitivity reactions have been reported. Patients with renal impairment who report severe adverse gastrointestinal (GI) reactions should have their renal function monitored. Treatment with Mounjaro may be associated with GI adverse reactions, sometimes severe, and is not recommended in patients with severe GI disease. Mounjaro has not been studied in patients with diabetic macular edema, nonproliferative diabetic retinopathy requiring acute therapy, or proliferative diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for progression. Acute gallbladder disease has occurred during treatment, and if suspected, clinical follow-up and gallbladder studies are indicated. Mounjaro may cause fetal harm. Women using oral contraceptives should switch to a nonoral contraceptive method or add a barrier method of contraception for 4 weeks after initiation of treatment with Mounjaro and for 4 weeks after each Mounjaro dose increase. The most common adverse reactions are abdominal pain, constipation, decreased appetite, diarrhea, dyspepsia, nausea, and vomiting.1

FOR REFERENCES, GO TO PHARMACYTIMES.COM/PUBLICATIONS.

AUTHOR BIO
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Marketed by Cipla
Compare To: Revlimid
The FDA approved Cipla’s abbreviated new drug application for lenalidomide capsules in 4 dosages: 5 mg, 10 mg, 15 mg, and 25 mg. The capsules are the generic version of Revlimid (Bristol Myers Squibb). The immunomodulatory prescription drug can be used as monotherapy for adults with hematological malignancies and can be combined with first-line or maintenance treatment or in the relapsed setting. Lenalidomide is indicated to treat cancer types such as follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, and myelodysplastic syndrome. Lenalidomide should not be prescribed to children or pregnant women, and cannot be used in treating patients with chronic lymphocytic leukemia.

FOR MORE INFORMATION:
cipla.com

Diclofenac Sodium Topical Solution USP 2%
Marketed by Lupin
Compare To: Pennsaid Topical Solution 2%
The FDA has approved Lupin’s abbreviated new drug application for diclofenac sodium topical solution USP 2%, which is the generic equivalent of Pennsaid topical solution 2% from Horizon Therapeutics. Pennsaid is a nonsteroidal anti-inflammatory drug indicated for the treatment of signs and symptoms of osteoarthritis in the knees, according to the FDA. The most common adverse reaction investigators saw for Pennsaid was application site reaction. The generic version of the drug has estimated annual sales of $484 million in the United States, according to the company.

FOR MORE INFORMATION:
lupin.com
Rifaximin 200-mg Tablets
Marketed by Norwich Pharmaceuticals
Compare To: Xifaxan
Rifaximin 200-mg tablets, indicated to treat travelers' diarrhea, has received tentative approval from the FDA. Rifaximin is not expected to hit US markets until July 2029, because a patent for the reference product, Xifaxan from Bausch Health Cos, does not expire until then. Alvogen’s Norwich Pharmaceuticals, which filed for an abbreviated new drug application from the FDA for the generic diarrhea tablets, is not expected to market the product until the original patent expires.

FOR MORE INFORMATION:
alvogen.com

Adapalene and benzoyl peroxide topical gel 0.3%/2.5%
Marketed by Alembic Pharmaceuticals
Compare To: Epiduo Forte
The FDA approved a new drug application for adapalene and benzoyl peroxide topical gel 0.3%/2.5%. The topical treatment is indicated to treat acne vulgaris in patients 12 years and older. The reference product is Epiduo Forte topical gel, which was developed by Galderma Laboratories. Adapalene and benzoyl peroxide topical gel 0.3%/2.5% had an estimated market size of $211 million in March 2022, according to Alembic Pharmaceuticals.

FOR MORE INFORMATION:
alembicpharmaceuticals.com
FDA Approves Lucentis Biosimilar, Cimerli, for Commercial Launch

**THE FDA APPROVED COHERUS** BioSciences’ Cimerli (ranibizumab-eqrn), a biosimilar of Genentech’s Lucentis (ranibizumab injection). Developed by bioeq, the joint venture of Polpharma Biologics and Formycon, Coherus will launch Cimerli in 0.3-mg and 0.5-mg doses in the United States in October 2022. Ranibizumab-eqrn will be used to treat all 5 indications for ranibizumab injection including age-related neovascular (wet) macular degeneration and other serious retinal diseases such as diabetic macular edema, diabetic retinopathy, macular edema following retinal vein occlusion, and myopic choroidal neovascularization.

“As the impact of serious retinal diseases continues to rise in the United States, it is critical that treatment options are efficacious and affordable. Advanced biosimilars to ranibizumab injection can change patients’ lives while also minimizing the financial impact of the cost of treatment on health care systems,” Michael Soldan, CEO of Polpharma Biologics Group, said in a statement.

Cimerli is a member of the antivascular endothelial growth factor therapy class of biologics. It works by inhibiting vascular endothelial growth factor that causes excessive blood vessels to form in the retina, leading to impaired vision.

“Polpharma Biologics is proud to have collaborated with Formycon and Bioeq on the development of ranibizumab biosimilar, and we are excited about our contribution to this valuable treatment option that we expect to positively impact many patients’ lives,” Soldan said.

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Online Pharmacy Offers Imatinib for Leukemia

**THE MARK CUBAN COST** Plus Drug Company is offering imatinib mesylate, used to treat leukemia and other cancers, at a price at least $2000 lower than what other pharmacies charge.1 "The markup on potentially lifesaving drugs that [individuals] depend on is a problem that can’t be ignored," Alex Oshmyansky, MD, PhD, CEO and founder of Cuban’s online pharmacy, said in a statement. "It is imperative that we take action and help expand access to these medications for those who need them most." 1

The company will sidestep pharmacy benefit managers, which negotiate prices among drug manufacturers, employers, and health insurers.2 Generic drugs are typically 80% to 85% cheaper than brand-name equivalents, according to the FDA, and Cuban said his company is trying to manufacture its own generic drugs.2

A September 2021 poll from Gallup and West Health estimated that 10 million Americans could not afford 1 or more doctor-prescribed medications.

“The Mark Cuban Cost Plus Drug Company will negotiate prices with the drug manufacturers directly1 and offers more than 800 generic drugs to treat many diseases, such as cancer, diabetes, and heart conditions.1

Long Grove Pharmaceuticals Introduces Drug to Treat Multiple Types of Arthritis

**LONG GROVE PHARMACEUTICALS’ FDA-APPROVED** triamcinolone acetonide injectable suspension, USP, is now available to treat several types of arthritis and other intramuscular and intra-articular conditions.1 This single-dose and multidose suspension is an AB-rated generic for Bristol Myers Squibb’s Kenalog-40. It is Trade Agreements Act–compliant and made in the European Union.1

Established in 2019, Long Grove Pharmaceuticals of Rosemont, Illinois, focuses on complex generics, such as injectables and topical products. The new triamcinolone acetonide injectable suspension, USP, is the first in a yearlong series of launches from Long Grove.1

Triamcinolone acetonide injectable suspension, USP, is a synthetic glucocorticoid corticosteroid anti-inflammatory.2 Study results have shown that single 60-mg to 100-mg doses can cause adrenal suppression that returns to normal, according to the FDA.2 The recommended dose is 60 mg in the gluteal muscle.2

“We are excited about the launch of triamcinolone acetonide," Dan Robins, PhD, president and CEO of Long Grove, said in a statement. "This successful launch required hard work from the entire team here at Long Grove. We are proud of this significant accomplishment and look forward to further expanding our portfolio.”1

Brand, Generic Amphetamine/Dextroamphetamine Face Shortages in Drug Stores

**AMPHETAMINE/DEXTROAMPHETAMIN, THE GENERIC FORM** of Adderall, a popular stimulant prescribed for attention-deficit/hyperactivity disorder, is facing a potential shortage in the supply chain, which may not ease in US markets until October 2022, according to an article on the BestLife website. Drug shortages commonly occur, because of delays, discontinuation, or manufacturing issues, according to the article.

The COVID-19 pandemic exacerbated many supply chain issues. Although amphetamine/dextroamphetamine is not on the FDA’s shortage list yet, that could occur if the supply chain does not normalize, according to the article.

Brand-name and generic forms of Adderall were prescribed to almost 41 million individuals in 2021, according to the article.
ISSUE OF THE CASE
When a group medical practice applies to the state board of pharmacy to open and operate an in-office pharmacy to serve patients and that application is denied by the regulatory board, may the group practice successfully challenge that denial in court?

FACTS OF THE CASE
A group of 4 physicians operating a hematology and oncology practice in a mid-Atlantic state applied for a pharmacy permit to establish a “closed-door clinic pharmacy.” This would be within the practice location and would serve only patients treated by the physician members of the group.

The state board of pharmacy considered the application, resulting in a vote to deny the request to establish and operate an in-office pharmacy. The basis for the decision was documented in a 7-page explanation.

While reviewing the application, the board focused on the first argument advanced by the applicants: whether a state statute that prohibits physicians from referring patients to sources of health care services owned by them would bar the business initiative. That statute included several exceptions regarding application of the law to specific situations. One such exception identified by the applicants stated that “the restrictions on referral of patients...shall not apply to...medical treatment or a procedure that is provided at the practitioner’s medical office.” The attorney for the medical practice members argued that pharmacies do provide medical treatment.

The applicants also argued that the state board of pharmacy had acted beyond its authority, because the legislature, when enacting the statute, had assigned enforcement responsibility to the state board of medical examiners. Thus, in the view of the physicians, the board of pharmacy was acting outside its authorized scope of enforcement. A third argument made by counsel for the applicants was that the board’s decision to deny the application amounted to “impermissible anticompetitive conduct.”

THE RULING
The appellate court rejected all the arguments advanced by the attorneys...
for the medical group practice members and upheld the state board of pharmacy’s decision to deny the application.

THE COURT’S REASONING
The court began its published opinion by reviewing the role of a court of appeals when reviewing a decision made by an administrative agency. The court acknowledged that “agencies have expertise and superior knowledge...in their specialized fields,” so an agency’s decision should be upheld “unless there is a clear showing that it is arbitrary, capricious, or unreasonable, or that it lacks fair support in the record.”

Further, appellate courts “accord deference to the agency’s interpretation of a statute it is charged with enforcing.” Finally, “deference to agency interpretation of a statute is appropriate as long as that interpretation is reasonable and does not conflict with the express or implied intent of the legislature.”

The court affirmed the conclusion of the professional regulatory board that pharmacies do not provide medical treatment. The court pointed to the different scopes of practice and educational backgrounds of pharmacists and physicians, concluding that “physicians provide medical care, while pharmacists provide pharmaceutical care.” Based on that distinction, the court concluded that the “in-office” exception to application of the statutory prohibition was inapplicable.

The court then turned to the argument that the professional licensure board had exceeded the scope of its authority by “interpreting, applying, and enforcing” the relevant state statute. The argument made by the attorney for the medical group practice was that the state’s pharmacy practice act only empowered the board to regulate the practice of pharmacy. That boundary, the argument ran, meant the board had no authority to regulate physicians; that authority existed with the medical board.

The pharmacy practice act identified the board’s responsibilities and powers as including action to “deny...the permit of any pharmacy practice site” if the board finds “that any conduct of the...applicant is violative of any federal, state, or local laws or regulations relating to the practice of pharmacy.” In the view of the judges overseeing this case, that grant of authority covered the board of pharmacy’s action here in enforcing the relevant state statute.

The next argument advanced by the medical group was that the pharmacy board engaged in anti-competitive conduct, because the members of the board are “active market participants” (ie, practicing pharmacists). The group inferred that the board’s vote to deny the application was motivated by a desire “to protect its members’ financial interests by prohibiting nonpharmacists from competing against them in the free market.”

The judges pointed out that the medical group’s attorney had presented no evidence of improper activity by the board members. Rather, the court was asked to “infer that the board acted with an anticompetitive motive.”

The court rejected that argument, because the state government had taken proactive steps in reviewing the decision, involving experienced state employees outside the board of pharmacy to review the decision prior to implementation.

The concluding sentence of the court’s opinion is a highly appropriate summation: “In sum, petitioner fails to convincingly show the board acted with an improper motive or arbitrarily, capriciously, or unreasonably.”

The judges noted that the medical group’s attorney had presented no evidence of improper activity by the board members.
HEALTH EQUITY IS A GOAL for all health care providers. Inaccessibility to appropriate health care services, because of cost or proximity, is a leading indicator of poor health outcomes. If patients cannot receive necessary care, their health can deteriorate until medical costs and intervention become much more severe than they would have been initially. As part of achieving health equity, health care facilities must be easily accessible to the surrounding population and must provide access to appropriate resources that meet all patient needs.

Originally, Project Extension for Community Healthcare Outcomes was implemented in 2003 at The University of New Mexico. The goal was to expand accessibility and care for patients with hepatitis C virus in rural and underserved areas of New Mexico by using teleconferencing technology to connect specialist providers, known as the hubs, with primary care providers, known as the spokes.

The Expanding Capacity for Health Outcomes (ECHO) Act of 2016 required that the secretary of the US Department of Health and Human Services examine and compile a report on “technology-enabled collaborative learning and capacity building models.” These findings were presented to Congress, which found that the evidence, although modest, consistently showed positive effects; Congress recommended expanding the evidence base, including directly funding technical assistance and evaluation.

The ECHO Act of 2019 built upon previous findings and was implemented to further increase accessibility to health care services for rural and underserved populations in need. The ECHO Act acknowledges that rural areas within the United States face many challenges when it comes to health care services, including limited access to general and specialty practices. Approximately 15% of all Americans live in rural areas, where there are often higher rates of poverty, a lack of insurance, and less health care access. These areas also experience increased rates of chronic illness, such as heart disease, and higher rates of potentially preventable deaths as a result.

**Federal ECHO Act Helps Goal of Health Equity**

*Expanding Capacity of Health Care Outcomes Statutes Aims to Link Specialists With General Practices*

By HANNAH S. MERCADO; AND JOSEPH L. FINK III, JD, DSC (HON), BSPHARM, FAPHA

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As of January 2017, unintentional injury deaths, largely because of accidental opioid overdoses and motor vehicle collisions, were approximately 50% higher in rural than in urban areas. Furthermore, rural areas are often not close to academic medical centers or other facilities with more extensive resources to adequately treat severe medical emergencies, so access to specialized treatments often may be delayed. This can lead to less successful treatment and mortality outcomes for patients in these areas, due to lack of timely access and proximity to appropriate care. The ECHO Act of 2019 increased accessibility to health care grants, services, and technological assistance to establish support for health care facilities and providers in the areas deemed medically at need.

The ECHO Act has meant considerable progress for patient care accessibility and telehealth expansion for individuals without resources. The hub-and-spoke telemonitoring network facilitates connection of primary care providers to specialist teams, easing consultation and improving the standard of care for patients who are medically at need.

Prior to the ECHO Act, these patients would have had to travel far outside their local areas to larger medical practice centers if they were able or else would not have had access to this scope of specialized care. This is an example of using technology to enhance delivery of health services. Because many in society, as well as within health care, have become more comfortable with advanced technologically facilitated communication, patients have seen many benefits. This is a crucial step toward addressing misdistribution of health care practitioners to serve patients in rural areas. The telecommunication link can also be used as part of an innovative continuing professional education project to allow rural practitioners greater flexibility in keeping abreast of developments with less time committed to travel, as well as to facilitate interprofessional collaboration.

Congress overwhelmingly supported the implementation of all ECHO Act provisions in 2019, which focused a national spotlight on the issues associated with inaccessibility to appropriate medical care for many Americans. Increased accessibility to health care may have a drastic, positive impact on quality of life in these areas. By expanding health care services in these areas, preventable disease rates could fall due to increased education and early treatment. The passing and implementation of the ECHO Act is a step toward health equity for all, as well as a brighter, healthier future for Americans regardless of where they live.

REFERENCES


WHEN LALEH FORD, PHARMD, MSC, RPH, started working at CDM Drugs in Corona del Mar, California, in 2015, it was a traditional pharmacy that did not offer compounding, immunization, or medication therapy management (MTM). But as a research scientist who specialized in formulating skin care compounds, she knew a pharmacy could do more than fill prescriptions. Pharmacies also can provide personalized care for patients to ensure that they receive the best medications for their conditions.

The key is communication between pharmacists and physicians, Ford said in an interview. “A lot of medical error happen[s] because of the miscommunication between doctors and pharmacy, and that’s really big out there...When I was studying, I was seeing [that] it was something they always alert us about,” she said. “I always ask [patients] what condition they have to make sure the medication is correctly prescribed to begin with and [to determine whether] I feel something is a better option or is not, as part of the MTM.”

Pharmacists have more frequent contact with patients than physicians do, so it would make sense for them to deal more directly with patients’ therapy management beyond filling prescriptions, Ford said. “I see all the patient’s medications on the file. The [doctors usually] see it too, but we as pharmacists know about drugs better; they know better about diagnostic,” Ford said. “If I see something can be a better choice for the patient...I usually have a template [on which] I write why and what it is and then refax to the doctor, because you cannot [reach] them on the phone.”

Although this is extra work, it is worth it when patients get the best medication for their conditions, Ford said, adding that physicians are usually so busy that sometimes when they prescribe medications, they do not consider all the possibilities. Pharmacists are better versed in medication compounding than physicians are, she said. As an example, Ford said that if a steroid is prescribed for an infant, she might suggest another option to the physician. “[I might say] instead of using a steroid, we should use [this because] it helps for this skin condition. This is a mixture of this compound, and these are all vitamins, or [this is] all good stuff, rather than give the patient a steroid, and [physicians] really appreciate this,” she said.

Additionally, pharmacists can help evaluate potential medication adverse events (AEs) and recommend to a physician that a patient should switch to a different drug. This can occur, for example, with patients who have AEs because of taking a generic antidepressant. In that case, Ford would reach out to the physician and ask about switching medications or whether the physician wants to talk directly with the patient about the medication.

Ford has made personalized compounds for patients and has several patented formulations. “What I do with a lot of dermatology offices, basically they send me pictures and they ask, ‘Is [there] something you can do beside[s] a steroid for this patient with psoriasis?’ [And we] come up with this formulation [that is more] beneficial for [the] patient” with fewer AEs, she said. Many patients have seen significant positive changes to their skin conditions because of her formulations, Ford said.

CDM Drugs recently received the newly created Innovation Award from Health Mart at McKesson ideaShare 2022, recognizing a pharmacy that offers innovative, unique strategies for going above and beyond the standard of care. Ford appreciates the award, adding that patients depend on pharmacies, because that is their point of contact after they see physicians.

“So as a pharmacist, you’re there to...ensure they get the best option and look out for their interests,” she said.
Senior Sections in Pharmacies Can Improve Drug Safety

Redesigning Stores With Special OTC Areas for Older Patients Can Enhance Communication, Education

By JENNIFER GERSHMAN, PHARMD, CPH, PACS

OTC medication safety is especially important for patients 65 years and older. In fact, older adults account for 30% of OTC medication use in the United States.1 Approximately 25% of older adults take a combination of 10 or more OTC and prescription medications.1 This can result in problems including adverse drug reactions (ADRs) and drug interactions. Redesigning pharmacies with specific OTC senior sections for older patients can improve medication safety. Pharmacists can play a critical role in this process to ensure that older patients are educated about appropriate OTC medication use and product selection.

Pharmacists can educate older patients about OTC medications that should be avoided or used cautiously because of the risk of ADRs and drug interactions. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Motrin) should be avoided, especially long term.2 These medications can increase the risk of bleeding and stomach ulcers.2 Additionally, they can raise blood pressure and cause renal dysfunction. Patients taking anticoagulants such as apixaban (Eliquis) or warfarin (Coumadin) have a higher risk of bleeding, especially when taking them with NSAIDs.2

FIGURE. Senior Section Advantages

MTM, medication therapy management.

AUTHOR BIO
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In an interview, Michelle Chui, PharmD, PhD, professor and director of the Sonderegger Research Center for Improved Medication Outcomes at the University of Wisconsin-Madison School of Pharmacy, discussed her study regarding senior sections for OTC medications in pharmacies.1 The pilot study examined implementing senior sections in 4 Midwest pharmacies that included the following 4 medication classes: allergy, cold and cough, pain, and sleep.4 Certain high-risk products for older adults, such as aspirin when used for pain and diphenhydramine and cold and cough combination products, were excluded from the senior sections.4 The main OTC aisle also included signage identifying high-risk medications and encouraging older individuals to visit the senior sections and ask pharmacists questions about products.4 The study found that the senior sections provided more effective, efficient, and frequent engagements between patients and pharmacy staff members (Figure).4

“[Individuals] want the ability to select their own product on their own time; to support that, we need to design pharmacies to facilitate not only safety but also patient autonomy. We redesigned the OTC section of pharmacies with signage and tools to help patients make appropriate selections, in proximity to the pharmacy counter,” Chui said.

“With pharmacists at close range, patients could easily reach out with questions, or pharmacists could come over and see whether they needed help choosing the safest OTC option for them. Our redesign provided an effective, sustainable long-term solution in that it builds a system that draws [individuals] to do the right thing,” Chui said. “Importantly, it improved medication safety without increasing pharmacist or technician workload.”

In a separate interview, Nikki Chilson, PharmD, pharmacy manager at Heart of Florida Health Center in Ocala, discussed OTC product education for older individuals. She incorporates her retail pharmacy experience into her MTM consultations.

Implementing senior sections at pharmacies would benefit pharmacists and patients, Chilson said.

“The proximity encourages patients to ask questions and helps staff to more easily notice shoppers who need assistance. Saving time is beneficial to both patients and pharmacy staff, so that’s a win-win,” Chilson said.

The OTC products she most often educates patients about are constipation medications, low-dose aspirin, and multivitamins. “I find myself recommending multivitamins to patients who are taking lots of supplements and who say the physician has never mentioned a vitamin deficiency. Once-daily vitamins help to streamline therapy and increase adherence in this population,” Chilson said. “Many of these individuals are looking for energy or to replace a vitamin that may be missing from their diet.”

Chilson counsels patients about constipation products and checks what they have taken previously that has worked to help with selecting an appropriate product. The most common medication-related problem she encounters is patients taking aspirin but unsure of the indication for which they are using it, she said.

“With these individuals, I take the time to counsel on signs of bleeding, benefits of coated aspirin, and supplements to avoid. I also ask probing questions to help bring out the root cause of the aspirin use,” Chilson said.

“When completing a personalized medication list, I also ask which physician recommended the aspirin. I believe it is important to document provider recommendations, so patients can look back and remember which OTCs they decided to take on their own,” she said.
ONE IN 3 AMERICAN ADULTS LIVES with prediabetes, but 25% of individuals who have the condition are undiagnosed.1 Prediabetes, as defined by the American Diabetes Association (ADA), is abnormal carbohydrate metabolism not yet at the level of type 2 diabetes (T2D). Diagnoses include elevated hemoglobin A1c, impaired fasting glucose (IFG), and impaired glucose tolerance (IGT).1 IFG is an elevated fasting plasma glucose (FPG) level after an 8-hour fasting period. IGT is an elevated 2-hour plasma glucose level during an oral glucose tolerance test.1

Table 1 compares diagnostic test cutoffs when diabetes is a concern. The ADA associated A1c between 5.5% and 6% and 6% and 6.5% with a 5-year risk of developing T2D between 9% and 25% and 25% and 50%, respectively. Those in the 6% to 6.5% range have 20 times' higher risk than those with A1c levels of 5%.2

Risk factors for prediabetes and diabetes include the following1,2:
- Elevated body mass index (BMI)
- First-degree relative with diabetes
- High-density lipoprotein cholesterol level below 35 mg/dL and/or a triglyceride level above 250 mg/dL
- High-risk ethnicity or race, including American Indian, Asian American, Black, Hispanic, or Pacific Islander
- History of cardiovascular disease (CVD)
- History of gestational diabetes
- Hypertension (≥ 140/90 mm Hg or on antihypertensive therapy)
- Other clinical conditions associated with insulin resistance
  - Acanthosis nigricans
  - Small-for-gestational-age birth weight
  - Stein-Leventhal syndrome, also known as polycystic ovary syndrome
- Sedentary lifestyle

Because prediabetes is often asymptomatic, patients can have the condition for years without knowing it. Insulin resistance is primarily because of excess weight, particularly with a higher percentage of body fat in the abdominal area.1

**DIABETES TESTING**

A1c levels average the patient’s glycemic concentration over 3 months. Table 2 estimates the average glucose over 3 months based on A1c levels.
results. Health care providers should begin testing patients for prediabetes if they meet 1 or more of the following criteria:

- Aged 35 years or older
- BMI 25 kg/m² or higher, or 23 kg/m² or higher in Asian Americans, and 1 or more risk factors
- History of gestational diabetes
- HIV diagnosis

A\textsubscript{1C} readings have little variability. However, discrepancies occur with abnormal changes in red blood cell count, such as anemia, end-stage renal disease, glucose-6-phosphate dehydrogenase deficiency, pregnancy, recent blood transfusion(s), and use of erythropoietic-stimulating agent(s). For patients on the verge of needing therapy change or initiation, providers should double check readings with a blood glucose monitor or 14-day continuous glucose monitor.

### DIET AND EXERCISE

Among the 7.4% US adults with prediabetes, 80% are overweight and 50% have attempted to lose weight. The National Diabetes Prevention Program provides lifestyle change initiatives through counseling, motivational events, and “restart” opportunities. It focuses on caloric deficits, healthy lifestyles, managing everyday challenges, physical activity, and self-monitoring.

The CDC recommends 5% to 7% weight loss in patients with prediabetes to prevent T2D. Exercise improves insulin sensitivity and reduces abdominal fat. Physical activity alone reduced the risk of T2D by 58% to 71%. A minimum of 150 minutes of moderate-intensity physical activity, equivalent to brisk walking, is recommended, broken up into at least 3 sessions per week and at least 10 minutes per session. Patients may include up to 75 minutes of strength training toward their 150-minute goal.

### MEDICATIONS AND FOLLOW-UP

Metformin is a staple first-line treatment for patients with prediabetes. The ADA recommends metformin for patients with prediabetes aged 25 to 59 years, A\textsubscript{1C} of 6% or more, a BMI of 35 kg/m² or higher, FPG of 110 mg/dL or more, and/or or prior gestational diabetes. Metformin improves A\textsubscript{1C} levels, CVD, and weight. Metformin may cause bloating, diarrhea, and gastrointestinal discomfort. It is contraindicated in patients with an estimated glomerular filtration rate of less than 30 mL/min/1.73 m². In instances of metformin overdose or renal failure, patients may present with rare but serious lactic acidosis.

In patients with prediabetes and elevated CVD risk, the American Association of Clinical Endocrinology (AACE) recommends angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for CVD and renal benefits. Alternatively, thiazolidinediones may provide cardioprotective effects. The results of 1 study showed that pioglitazone and rosiglitazone decreased CVD by 72% and 62% after 2 to 3 years, respectively.

A separate meta-analysis recommended against prophylactic statin therapy in prediabetes for cardiovascular protection because of a 20% increased relative risk of T2D. However, in patients with prediabetes and dyslipidemia, the AACE recommends maximally tolerated statins for CVD prevention.

Patients with new-onset prediabetes without medication therapy should seek testing annually. Exceptions include patients with:

- Maintenance therapy and within glycemic goals; providers recommend following up with a health care provider for testing at least every 6 months.
- A prior history of gestational diabetes; testing includes lifelong follow-up with the provider for a minimum of every 3 years.
- Unmet glycemic goals and/or starting a new therapy; providers recommend following up for testing within 3 months.

Otherwise, providers should evaluate patients at elevated risk for prediabetes for a minimum of every 3 years, with more frequent testing depending on results.

### CONCLUSION

Prediabetes can be daunting because of extensive recommendations, including lifestyle modifications, medication therapy, and monitoring. Patients with new-onset prediabetes often have concerns or questions for health care providers to better understand the disease.
**Eye Conditions Watch**

**Investigators Suggest Conjunctivitis May Transmit Monkeypox**

**FERNANDO LY-YANG, MD,** and investigators from the Ophthalmology Service, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos in Madrid, Spain, found that conjunctivitis may be associated with monkeypox, after observing that a man, aged 42 years, who had monkeypox also had conjunctivitis and HIV. The research team suggests that patients who are immunocompromised with HIV may be more likely to have conjunctival inflammation from monkeypox.

The patient’s eye had conjunctival lesions and thickening, mucoid discharge, and ulcerations on the margins of his eyelid. He also experienced photophobia in his left eye.

The patient was treated with intravenous acyclovir 1 g every 8 hours, tecovirimat 600 mg every 12 hours, and topical zinc (for skin lesions) every 8 hours. His topical conjunctivitis treatment regime included chlorhexidine 0.2%, ganciclovir 0.15%, povidone-iodine 1%, and moxifloxacin drops 5 times per day.

The investigators said 23% of monkeypox cases result in conjunctivitis, although these cases generally happen in boys younger than 10 years. Monkeypox is not confirmed to spread through tears during conjunctivitis, but smallpox is. Investigators noted that the similarity between the 2 diseases might indicate that conjunctivitis can spread monkeypox.

**Help Prevent Spread of Pink Eye**

**CONJUNCTIVITIS, ALSO CALLED PINK EYE,** is the most common eye problem among children. It is a highly contagious disease, with more than 3 million cases occurring every year in the United States.

School is a common setting where the illness spreads, according to a University of Kentucky (UK) associate professor of ophthalmology, Seema Capoor, MD, who is also a UK HealthCare ophthalmologist. Children tend to touch their eyes, and can infect other children by sharing toys and equipment.

Symptoms of pink eye include eyelash or eyelid burning, crusting, irritation, itching, or swelling; pink or red in the whites of the eye; respiratory symptoms; sensitivity to bright lights; and tenderness in the lymph nodes, according to Capoor. Most conjunctivitis cases are allergic, bacterial, or viral. Depending on the type, pink eye can be treated by a medical practitioner using antibiotic drops or ointment, antihistamine medication, or cold compresses.

Ways of preventing infection include changing sheets and towels and washing clothes in hot water daily. Additionally, patients should avoid touching their eyes and faces, clean glasses regularly, and discard eye makeup upon diagnosis. Capoor suggested seeking treatment if a child is showing signs of pink eye.

**Aldeyra Therapeutics Plans Submission for Dry Eye Disease Treatment by End of 2022**

**ALDEYRA THERAPEUTICS PLANS TO** submit a new drug application (NDA) for the novel dry eye disease treatment reproxalap by the end of 2022. Reproxalap has shown significant clinical results for multiple indications.

Aldeyra conducted 5 clinical trials to evaluate reproxalap in more than 2000 patients, none of whom had severe adverse events. In the NDA efficacy package, it is noted that the treatment can be administered short term, or that patients can undergo up to 12 weeks of effective, safe treatment.

“We believe that we have aligned with the FDA on the content of the regulatory package that will support what we expect to be a uniquely comprehensive NDA submission for the treatment of dry eye disease, encompassing data demonstrating improvement that may occur within minutes of drug administration in symptoms and 3 different objective signs,” Todd C. Brady, MD, PhD, Aldeyra’s president and chief executive officer, said in a statement.

Reproxalap is a novel reactive aldehyde species (RASP) modulator. RASP is found at elevated levels in ocular and systemic inflammatory disease. RASP can cause eye redness, change lipid tear composition, decrease the production of tears, and increase ocular inflammation.

Dry eye disease affects more than 39 million US adults each year. Symptoms are characterized by discomfort, dryness, inflammation, irritation, lower quality of life, and pain. Severe cases have led to permanent vision impairment.
Women Pharmacist Day Focuses on Achievements in the Profession
Woman Pharmacist of the Year Awards Honor 4 in Community, Health System, Independent, and Nontraditional Categories
By SUZANNE SOLIMAN, PHARMD, BCMAS

Women Pharmacist Day will bring together women in the profession to celebrate their achievements, past and present.

The fifth Women Pharmacist Day will be observed on October 12, 2022. October is also National Pharmacist Month. October 12 was chosen to honor Elizabeth Gooding Greenleaf, an apothecary during Colonial times who is regarded as the nation’s first female pharmacist; she had 12 children. As recently as the 1960s, only 8% of all US pharmacists were women; they now represent almost 70% of the pharmacy workforce.

In addition, 4 pharmacists will be chosen as Woman Pharmacist of the Year in the categories of community, health system, independent, and nontraditional pharmacy, based on their impact in the profession. The winners will be announced live during a program held by the Pharmacist Moms Group on Facebook and broadcast on its Facebook, Instagram, and LinkedIn pages. There will also be nearly 500 giveaway items for event participants, from such brands as CeraVe, La Roche-Posay, and Vichy.

The organization wishes to thank those sponsors, as well as L’Oreal. Gratitude also is extended to Dynavax Technologies, as immunizing is a key role for pharmacists and hepatitis B is a key area of focus.

PREVIOUS AWARD WINNERS
• 2021, Community Pharmacy: Bled Tanoe, PharmD, vice president of pharmacy advocacy for RPhAlly and inpatient pharmacist and founder of #PizzaIsNotWorking
• 2021, Health System Pharmacy: Nicole Bookstaver, PharmD, BCACP, ambulatory care pharmacist at Prisma Health, University of South Carolina College of Pharmacy,
• 2021, Independent Pharmacy: DeAnna “Dixie” Leikach, MBA, RPh, PRS, FACA, vice president at YOUR Community Pharmacy; president and CEO at Pharmacy Ethics, Education and Resources; and managing network facilitator at CPESN MD
• 2021, Nontraditional Pharmacy: Seena Haines, PharmD, professor and chair of the Department of Pharmacy Practice and director of professional well-being and belonging, University of Mississippi School of Pharmacy, Jackson
• 2020: Jennifer Shannon, PharmD, BCPS, clinical pharmacist at and owner of Lily’s Pharmacy and Wellness Center, Johns Creek, Georgia
• 2020: Krista Capehart, PharmD, BCACP, clinical associate professor and director of the Wigner Institute for Advanced Pharmacy Practice, Education, and Research, West Virginia University School of Pharmacy, Morgantown
• 2019: Jesica Mills, PharmD, MBA, RPh, owner of Owensboro Family Pharmacy, Owensboro, Kentucky

WHAT IS NEXT?
The Pharmacist Moms Group recently relaunched its website with a new overall look and feel. In addition, Coffee With Suzy launched this year and is held every Friday at 9:30 AM eastern time. The group will host networking and professional development events across the country. Those interested in getting involved by joining the community, sponsoring an event, or writing should feel free to reach out.
Pharmacy Technicians are recognized for playing a vital part in pharmacies, helping both patients and pharmacists. Pharmacy Times celebrates all Pharmacy Technicians for their dedicated service and assistance with helping to provide their patients with top-tier health and safety service in their community.

Learn more about resources for Pharmacy Technicians:
Pet Peeves

Missed Call
When the pharmacy calls a patient and leaves a voicemail message about a prescription, and the patient calls back and says they did not listen to the message and asks what the call was about.

Getting Carded
Patients who show up to get COVID-19 boosters and leave their CDC cards at home. They get reminders to have the cards but still say, “Oh, I didn’t know I’d need to bring that.”

Positively Dreadful
Patients who test positive for COVID-19 and then arrive without a mask on to pick up their Rx.

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

What’s Bothersing 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

**CASE 1**

RK is a man aged 58 years who was recently given a diagnosis of small cell lung cancer (SCLC). His medical history includes chronic obstructive pulmonary disease, insomnia, and type 2 diabetes. He is a smoker with a 30 pack-year history and presented to the emergency department with declining respiratory function and severe dyspnea. Two weeks earlier, he tested positive for COVID-19; he assumed the latest symptoms were related to that diagnosis. However, a staging work-up revealed extensive-stage SCLC. His oncologist recommends the following initial chemotherapy regimen: carboplatin area under the concentration time curve (AUC) 5 intravenous (IV) daily on day 1, etoposide 100 mg/m² IV once daily on days 1 to 3, and durvalumab (Infinzi) 1500 mg IV on day 1, repeated every 21 days for 4 cycles.

**Calculate the appropriate doses of carboplatin and etoposide.**

**CASE 2**

LK is a Black woman aged 60 years who was recently given a diagnosis of nonresectable EGFR-mutant non–small cell lung cancer. She has asthma, eczema, and hypertension. LK is a retired construction worker who has never smoked. One month ago, her oncologist started her on osimertinib (Tagrisso) 80 mg orally daily as monotherapy. LK had a follow-up with her oncologist this week. Although her Eastern Cooperative Oncology Group performance status is 0, she has been experiencing mild grade 1 diarrhea and a rash resembling acne on her chest and face for approximately 3 weeks. LK describes her symptoms as “embarrassing and hideous” and is seeking help.

**What interventions should the pharmacist suggest to alleviate her symptoms?**

**AUTHOR BIOS**

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**Answers**

**FOR REFERENCES, GO TO PHARMACYTIMES.COM/PUBLICATIONS**
Fun Facts

Q: Do gummy multivitamins work?
A: For many children, and some adults, nothing screams multivitamin more than gummies, those candylike, colorful, pillowy-soft confections. But gummy candy...er, gummy vitamins, often are so sweet because they are laden with sugar.\(^1\)

The American Heart Association suggests limiting sugar consumption to 25 grams per day for women and 36 grams per day for men. But gummies can average between 2 and 8 grams of sugar per serving. This could consequently account for up to one-third of the daily recommended sugar intake.\(^1\) Children should steer clear of gummies, and try pills or chewable vitamins instead.\(^1\)

In addition, nutritional value might not be high in gummy vitamins.\(^1\) To keep them, well, gummy, gummies are not as stable as chewables and dried pills. This results in their efficacy waning before users can get the full dosage indicated on the label.\(^1\)

Although supplements and vitamins reportedly are a $30-billion-a-year market in the United States, research results published in *BMJ Open* suggest that the benefits of multivitamins may be a placebo effect.\(^2\)

Extracting data from the 2012 National Health Interview Survey, investigators looked at 21,000 multivitamin users and nonusers in the United States. “Multivitamin users self-reported better overall health, despite no apparent differences in clinically measurable health outcomes,” according to the study.\(^2\)

Although new research points to the benefit of certain mineral and vitamin supplements in specific circumstances, most evidence suggests that healthy individuals will not benefit from multivitamins.\(^2\)

Q: What alcohol-drug combo was used to treat plague victims in the 1600s?
A: Laudanum.
Paracelsus, born Philippus Aureolus Theophrastus Bombastus von Hohenheim, was a Swiss philosopher and physician credited as a pioneer of the medical revolution during the Renaissance and a father of toxicology. Paracelsus is also credited with opium use increasing during the 16th century. The physician referred to the drug as the “stone of immortality,” which may have been the impetus for his fine-tuning it to develop laudanum.\(^3\)

Laudanum—coming from “laudare” in Latin, which means “to praise”—was named by Paracelsus in view of his strong feelings toward the drug. Paracelsus said laudanum was “superior to all other heroic remedies.”
Be on the lookout for the 2023 OTC Guide
Continuing the Conversation: Seeing Improvements in the Management of Age-Related Macular Degeneration and Diabetic Macular Edema With Pharmacist Involvement

**EDUCATIONAL OBJECTIVES**

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

- Identify commonly asked questions regarding the management of age-related macular degeneration (AMD), diabetic macular edema (DME), and individualized care
- Analyze safety, efficacy data, and clinical evidence for the use of current and emerging therapies in the management of AMD and DME
- Illustrate best practices for the pharmacist in the management of AMD and DME

**TARGET AUDIENCE:** Health-system, retail, and specialty pharmacists

**ACTIVITY TYPE:** Application

**RELEASE DATE:** October 1, 2022

**EXPIRATION DATE:** October 1, 2023

**ESTIMATED TIME TO COMPLETE ACTIVITY:** 2.0 hours

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

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**Introduction**

Neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) are disorders affecting the choroidal and retinal vasculatures, respectively.¹ Vision loss related to these diseases is associated with a substantial socioeconomic impact and contributes to profound reductions in quality of life for patients and burden for their caregivers.²,³

**Age-Related Macular Degeneration**

AMD is a disorder primarily occurring in older adults, with 10% to 13% of patients older than 65 years affected in North America, Europe, Australia, and Asia (Figure 1).⁴ Prevalence of AMD increases with age and is expected to continue to increase as the population ages. Global projections made in 2004 estimated a prevalence of 196 million people affected by 2020, further rising to 288 million by 2040. In the United States alone, the prevalence of AMD is expected to reach 22 million by 2050.⁶

When compared with other races, AMD is prevalent in White individuals (Figure 1). Differences in the prevalence of AMD among racial/ethnic groups have been attributed to dissimilarities in the frequency and impact of genetic markers (e.g., age-related maculopathy susceptibility 2, complement factor H).⁷ Whereas nAMD, also known as exudative or wet AMD, only makes up about 10% to 15% of cases of AMD, and non-nAMD, also known as non-exudative or dry AMD, makes up the remainder. Non-AMD makes up more than 80% of all AMD cases that result in severe visual acuity (VA) loss or blindness.⁸

**Diabetic Macular Edema**

A major driver of the incidence and prevalence of DME is the increasing occurrence of diabetes in the United States and worldwide. The Centers for Disease Control and Prevention’s 2020 National Diabetes...
Statistic Report estimated that, in 2018, 13.0% of US adults 18 years or older and 26.8% of US adults 65 years or older experienced adult-onset (type 2) diabetes.9 Further, the prevalence of diabetes in US adults 18 years and older has increased by approximately 26% between the years 1999 and 2016 (from 9.5% to 12.0%).9 The prevalence rates of DME vary between type 1 and 2 diabetes. Estimates of DME in patients with type 1 diabetes range from 14.0% to 20.1%, while the estimates for individuals with type 2 diabetes vary from 6.0% to 25.4%.10

**Pathophysiology of Age-Related Macular Degeneration**

Besides age, several other elements and cellular processes (eg, inflammation, lipofuscinogenesis, neovascularization, drusogenesis) play essential roles in the development and progression of AMD.11 The role of inflammation in AMD, an increasingly common suspect in many disease states, may also be linked via the complement cascade and drusogenesis, which is the process of developing drusen (lipid deposits).12 Lipofuscinogenesis refers to the process of accumulating lipofuscin, a pigment generated by cellular metabolism that accumulates in lysosomes.13 The pathogenesis of nAMD involves the recruitment of immune cells to the damaged macula and secretion of proinflammatory and proangiogenic cytokines, particularly vascular endothelial growth factor (VEGF).14 VEGF stimulates endothelial cell proliferation and migration and consequently leads to angiogenesis and increased vascular permeability.15,16 The newly growing blood vessels leak fluid, disrupting and damaging the layer of photoreceptors and impairing vision. Although the abnormal vessels of wet AMD typically arise from the choroidal circulation, neovascularization and leakage also can emerge from the retinal vasculature.17

**Pathophysiology of Diabetic Macular Edema**

DME can be defined by the amount of retinal thickening (≥250 μm) that manifests from several pathophysiologic processes that damage the retinal endothelium, thus impairing the blood-retinal barrier.18 The hyperglycemia of diabetes drives metabolic changes that lead to the disruption of the blood-retinal barrier, and VEGF plays a major role in this process (FIGURE 19).20 Because 15% to 20% of DME cases are refractory to anti-VEGF therapies, the intricate etiology of DME may be split into vasogenic and inflammatory.20,21

The availability of anti-VEGF therapies has advanced the management of both nAMD and DME.22,23 However, the outcomes achieved in these diseases are often suboptimal.24,25 One potential reason for these shortcomings is the significant burden of frequent treatment and monitoring that contributes to poor adherence to recommended dosing strategies.24,25 Fortunately, novel agents are emerging to address these limitations by enhancing the durability of treatment response to decrease treatment burden in both nAMD and DME.22,26 Moreover, home monitoring strategies offer additional methods to decrease the overall burden of disease monitoring on patients and health care systems while improving personalized care.27 Given the plethora of practice-altering developments that are rapidly materializing, pharmacists—who are pivotal members of the health care team serving these patient populations—require a necessary and up-to-date educational initiative that details the latest advances in the fields of both nAMD and DME.

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**STAR**

How do new treatments for both nAMD and DME compare with traditional agents? What are the advantages associated with these new therapies?

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

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**Clinical Data of Current and Emerging Therapies in nAMD and DME**

Insights into the pathophysiology of nAMD and DME have been the driving force for developing therapeutic options.
Prior to the introduction of anti-VEGF agents, the predominant treatments for nAMD and DME focused on photodynamic therapy, which has the ability to only reduce the rate of vision loss. In contrast, anti-VEGF therapies can achieve vision restoration and are estimated to decrease legal blindness due to nAMD by approximately 72% (95% CI, 70%-74%).

Traditional Anti-Vascular Endothelial Growth Factor Therapies

Clinical treatment guidelines for both nAMD and DME recommend the use of anti-VEGF agents aflibercept, ranibizumab, or off-label bevacizumab as first-line therapy to improve VA and prevent disease progression. TABLE 1 lists these 3 therapies in addition to brolucizumab. However, there do appear to be some differences in efficacy among these agents, such as the number of letter improvements, retinal drying effect seen on optical coherence tomography, effect on VA based on baseline characteristics, or the duration of action between injections.

For instance, when patients do not respond to off-label bevacizumab, they are often switched to aflibercept or ranibizumab in hopes of a better retinal drying effect or longer treatment interval. Protocol T from the Diabetic Retinopathy Clinical Research Network compared these 3 anti-VEGF therapies in eyes with vision loss due to center-involved DME and found that when vision loss was mild at baseline, all 3 agents had similar VA improvement, although aflibercept had a better drying effect. When the VA loss was greater at baseline, aflibercept was superior in achieving greater VA improvement compared with bevacizumab after 2 years of treatment. In another comparison trial involving DME, aflibercept, bevacizumab, and ranibizumab had similar efficacy when VA was better than 20/50 (approximately +8 letters at 1 year), but when the baseline VA was 20/50 or worse, aflibercept improved VA more than the other 2 therapies (+19 vs +12 letters with bevacizumab and +19 vs +14 letters with ranibizumab). There was no difference in improvement in VA between ranibizumab and bevacizumab. The median number of intravitreal injections was similar among the 3 treatments (9, 10, and 10 in the aflibercept, bevacizumab, and ranibizumab groups, respectively). Rates of adverse effects (AEs)
were generally low and similar among the 3 groups. \(^{37}\)

Ranibizumab is a recombinant humanized monoclonal antibody fragment that binds to and inhibits VEGF-A. The efficacy of a ranibizumab injection for nAMD was established in both the MARINA and ANCHOR trials. In the MARINA trial at the 24-month end point, 92.0% of patients receiving 0.3 mg of ranibizumab and 90.0% of individuals receiving 0.5 mg of ranibizumab lost fewer than 15 letters from baseline VA compared with 52.9% of those in the sham injection group \((P < .001\) for both treatment groups compared with the sham group). \(^{40}\) The ANCHOR trial compared ranibizumab with an active control, verteporfin photodynamic therapy. \(^{41}\) Greater percentages of trial participants treated with 0.3 mg or 0.5 mg of ranibizumab lost fewer than 15 letters of VA (90.0% and 89.9%, respectively) at the 24-month end point compared with 65.7% of patients in the control group. \(^{41}\) In a retrospective analysis that compared 3-year outcomes of ranibizumab versus aflibercept in DME, a total of 534 eyes of 402 patients were included. \(^{42}\) The real-world observational study demonstrated that the longitudinal adjusted VA change over the 3-year period between ranibizumab and aflibercept using all eyes differed significantly \((P < .001)\). \(^{42}\) However, the adjusted mean changes in the central subfield thickness remained significantly different \((P < .01)\) throughout the 3-year period in favor of aflibercept. \(^{42}\) Findings also showed that when patients had moderate baseline visual impairment (VA: ≤68 Early Treatment Diabetic Retinopathy Study letters), the vision improved faster in eyes treated with aflibercept up until 18 months of treatment compared with eyes treated with ranibizumab, which then stayed similar until 36 months of treatment. \(^{42}\)

Aflibercept is a recombinant fusion protein with the soluble receptor domains of VEGF receptors 1 and 2 linked to the core molecule of a human immunoglobulin G1 fragment. \(^{34}\) This agent binds to VEGF-A and placental growth factor and inhibits binding and activation of endothelial cell receptors, thereby suppressing neovascularization and slowing vision loss. \(^{34}\) The efficacy and safety of this agent for the treatment of nAMD were assessed in the VIEW 1 and 2 clinical trials using ranibizumab as the active control. \(^{43}\) Aflibercept was studied at 3 dosing regimens—0.5 mg every 4 weeks, 2 mg every 4 weeks, and 2 mg every 8 weeks—while ranibizumab was used at the recommended dosing regimen of 0.5 mg every 4 weeks. \(^{43}\) Testing of the extended dosing interval of 8 weeks sought to reduce the burden and risk of monthly injections. \(^{43}\) With an active control arm, the primary end point of the VIEW 1 and 2 studies was noninferiority of aflibercept compared with ranibizumab with respect to the percentage of patients maintaining VA (<15 letters from baseline) at 52 weeks, and all 3 aflibercept dosing regimens achieved the primary end point. \(^{43}\) In both studies, 94.4% of ranibizumab (0.5 mg every 4 weeks) maintained VA, while the results for aflibercept were (VIEW 1 and 2 data, respectively) 95.9% and 96.3% for 0.5 mg every 4 weeks; 95.1% and 95.6% for 2 mg every 4 weeks; and 95.1% and 95.6% for 2 mg every 8 weeks. \(^{43}\) AEs were similar across treatment groups. \(^{43}\)

Brolucizumab is a humanized single-chain antibody fragment that inhibits the VEGF-1 and -2 receptors by binding to VEGF-A isoforms. \(^{38}\) Efficacy of brolucizumab for the treatment of nAMD was established in the HAWK and HARRIER clinical trials, which used aflibercept as an active control. \(^{44}\)

### TABLE 1. TRADITIONAL THERAPIES FOR NAMD AND DME\(^{33-38}\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication (nAMD/DME)</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept injection</td>
<td>nAMD/DME</td>
<td>nAMD: 2 mg DME: 2 mg</td>
<td>nAMD: 2 mg every 4 weeks x 3 months, followed by 2 mg every 8 weeks DME: 2 mg every 4 weeks x 5 injections, followed by 2 mg every 8 weeks</td>
</tr>
<tr>
<td>Bevacizumab injection</td>
<td>Off label</td>
<td>nAMD: 1.25 mg DME: 1.25 mg</td>
<td>nAMD: 1.25 mg monthly x 3 months, then may be given scheduled (monthly) or as needed based on monthly ophthalmologic assessment DME: 1.25 mg initially; repeat every 4 weeks depending on ophthalmologic response</td>
</tr>
<tr>
<td>Brolucizumab injection</td>
<td>nAMD/DME</td>
<td>nAMD: 6 mg DME: 6 mg</td>
<td>nAMD: 6 mg monthly x 3 doses, followed by 6 mg every 8-12 weeks DME: 6 mg every 6 weeks x 5 doses, followed by 6 mg once every 8-12 weeks</td>
</tr>
<tr>
<td>Ranibizumab injection</td>
<td>nAMD/DME</td>
<td>nAMD: 0.5 mg DME: 0.3 mg</td>
<td>nAMD: monthly DME: monthly</td>
</tr>
</tbody>
</table>

DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration.
studied at 3-mg (HAWK only) and 6-mg doses using loading doses of 3 monthly injections followed by every 12-week dosing that was modified to every 8 weeks if researchers observed disease progression in patients, while the active control arm received 2 mg of aflibercept every 8 weeks. The studies concluded that brolucizumab was noninferior compared with aflibercept at 48 weeks with respect to the mean best-corrected visual acuity (BCVA) change from baseline as follows: HAWK (+6.8 letters for aflibercept, +6.1 letters for brolucizumab 3 mg, +6.6 letters for brolucizumab 6 mg) and HARRIER (+7.6 letters for aflibercept, +6.9 letters for brolucizumab 6 mg [P <.001 for all comparisons with active control]). In a report that assessed long-term outcomes from HAWK and HARRIER, visual outcomes continued to demonstrate the effectiveness of brolucizumab compared with aflibercept at 96 weeks.

Limitations of Current Treatment Options

While anti-VEGF therapies have advanced care in both nAMD and DME, several limitations exist with these agents (eg, ranibizumab, aflibercept, brolucizumab). The encouraging findings of the clinical trials used to approve VEGF inhibitors (eg, ranibizumab, aflibercept, brolucizumab) are not consistently reproduced in real-world data. The treatment burden associated with frequent injections, physician visits, insurance status, co-pays, and AEs serve as factors for patients receiving significantly fewer injections in practice than in clinical trials. Patients with nAMD and DME in the real-world setting receive substantially fewer injections than those participating in clinical trials. As a consequence, VA outcomes are inferior to those seen in clinical trials.

Formulation and administration challenges have also been identified with intravitreal injections. Bevacizumab is manufactured in 25-mg/mL vials appropriate for use in its FDA-approved indications for treatment of various solid tumors but must be split into single-use syringes by compounding pharmacies or hospital pharmacies for intravitreal administration. Inappropriate and/or unsanitary compounding practices have led to clusters of inflammation and infectious endophthalmitis. Aflibercept and ranibizumab are available as prefilled syringes. Prefilled syringes are preferred over vial formulations, as they require less manipulation by clinical staff and help to lower incidence of vision loss related to endophthalmitis after administration. Unfortunately, prefilled syringes do not eliminate inflammation risk, as clusters of sterile ocular inflammation have been linked to aflibercept. Syringes also pose a risk of injection of silicone droplets that create floaters large enough to obstruct vision.

New and Emerging Therapies

Fortunately, therapies with novel mechanisms of action and drug delivery systems are being developed to overcome some of these barriers (TABLE 2).

Faricimab, approved by the FDA in January 2022, is the first bispecific monoclonal antibody designed for the treatment of nAMD and DME. The bispecific design binds and neutralizes
both VEGF and angiopoietin-2, important mediators of these disorders (FIGURE 3).\textsuperscript{54} This dual-targeted approach leads to improved durability, as treatment intervals can be extended up to once every 4 months without loss of efficacy.\textsuperscript{57}

The phase 3, randomized, double-masked, active comparator-controlled trials, TENAYA and LUCERNE, compared intravitreal injections of faricimab with aflibercept in 1329 treatment-naïve patients with nAMD. Patients received either faricimab 6 mg given up to every 16 weeks or aflibercept 2 mg every 8 weeks after monthly loading doses. The primary end point was mean change in BCVA from baseline. In both trials, faricimab demonstrated noninferiority to aflibercept. In the TENAYA trial, mean gains in BCVA were 5.8 and 5.1 letters in the faricimab and aflibercept groups, respectively. Mean gains in BCVA in the LUCERNE trial were 6.6 in both the faricimab and aflibercept groups. The incidence of AEs was comparable between faricimab and aflibercept.\textsuperscript{58}

In new, 2-year findings from the TENAYA and LUCERNE trials that were recently presented at the American Society of Retina Specialists (ASRS) 2022 annual meeting, more than 60% of faricimab-treated patients were able to be treated every 4 months while achieving comparable vision gains compared with every-other-month aflibercept treatment. This is an increase of over 15% since the 1-year primary analysis, while nearly 80% of those receiving faricimab were able to be treated every 3 months or longer.\textsuperscript{59}

TRUCKEE is an ongoing real-world trial aiming to assess outcomes in faricimab-treated patients with nAMD. Preliminary data from this trial were recently presented at the ASRS 2022 annual meeting. This trial comprised 421 eyes of 377 patients for a total of 770 intravitreal injections. Researchers looked at follow-up of the study participants who had 20/400 vision or better, and most patients (almost two-thirds) received aflibercept as their last anti-VEGF injection prior to switching to faricimab. Follow-up data from 236 eyes were available for analysis; vision was considered stable in these patients. They received their faricimab dose and returned for a follow-up visit. The trial eyes had a mean of 63.3 Early Treatment Diabetic Retinopathy Study letters at follow-up, a mean improvement of 0.5 letters from baseline (from 62.8 letters). Improvements were observed in central subfield thickness and pigment epithelium detachment height, and visual and anatomical improvements were similar in patients who switched from any anti-VEGF treatment. Faricimab has demonstrated encouraging safety-related findings.\textsuperscript{60}

Phase 3, randomized, double-masked, active comparator-controlled trials, YOSEMITE and RHINE, compared faricimab at 2 dosing frequencies with aflibercept in 1891 patients with treatment-naïve DME. Patients received faricimab 6 mg every 8 weeks, faricimab 6 mg based on a personalized treatment interval (PTI) algorithm, or aflibercept 2 mg every 8 weeks. The primary end point was mean change in BCVA from baseline, and faricimab demonstrated noninferiority to aflibercept in both arms. Faricimab met the primary end point of noninferior BCVA change over 1 year versus aflibercept in both trials. In the YOSEMITE trial, mean BCVA change for the faricimab every 8-week, faricimab PTI, and aflibercept groups was 10.7, 11.6, and 10.9 letters, respectively. Meanwhile, the average BCVA change in the RHINE trial for the faricimab every 8-week, faricimab PTI, and aflibercept groups was 11.8, 10.8, and 10.3 letters, respectively. Incidence of ocular AEs was comparable among all 3 treatment groups.\textsuperscript{61}

The ranibizumab port delivery system (PDS) is an innovative drug delivery mechanism for anti-VEGF therapy designed to decrease the frequency of intravitreal injections, thus addressing treatment burden. The refillable implant is inserted surgically into the eye in the operating room and then is refilled in the office every 6 months. It has been shown to provide a continuous release of ranibizumab, thus having the potential to

![FIGURE 3. MECHANISM OF ACTION OF FARICIMAB\textsuperscript{54}]

Ang-2, angiopoietin-2; ICAM-1, intercellular adhesion molecule-1; TNF-α, tumor necrosis factor-alpha; VCAM-1, vascular cellular adhesion molecule; VEGF, vascular endothelial growth factor.

drastically reduce the treatment visit burden. The PDS delivers a serum concentration of ranibizumab within the same maximum and minimum range experienced with monthly injections. The concentration within the implant decreases with a half-life of about 25 weeks.53

The ranibizumab PDS, approved by the FDA in October 2021, is indicated for the treatment of patients with nAMD who previously responded to at least 2 intravitreal injections of a VEGF inhibitor. The approval was based on the results of the ARCHWAY trial.53 This phase 3, open-label, randomized trial compared ranibizumab PDS refilled at 24-week intervals with monthly intravitreal ranibizumab injections.62 The primary end point was change in BCVA, and it demonstrated noninferiority and equivalence of the PDS to monthly injections.62 Mean change in BCVA was 0.2 and 0.5 letters in the ranibizumab PDS and intravitreal injection treatment arms, respectively.52

Common AEs with the PDS included conjunctival hemorrhage or hyperemia, iritis, and eye pain. In the PDS cohort, most AEs occurred within 1 month of implantation. Furthermore, 16 of 248 (6.5%) patients receiving the PDS experienced conjunctival bleb or conjunctival filtering bleb leak. Events were considered not serious, but 1 case did require surgical resection. The incidence of vitreous hemorrhage was significantly reduced with changes in the operation protocol. There were 4 cases of endophthalmitis in the PDS group compared with none in the monthly ranibizumab injection group.62

Investigators evaluated treatment satisfaction for ranibizumab delivered via PDS versus intravitreal injections in addition to patient preference among those assigned to PDS. Researchers used the PDS Patient Preference Questionnaire to measure patient preference in the PDS arm of the ARCHWAY trial at week 40 over previous intravitreal injections. Treatment satisfaction was measured using the Macular Disease Treatment Satisfaction Questionnaire in the PDS and intravitreal injection arms at week 40. In the PDS arm, almost all patients preferred treatment via the PDS (93.2%) versus previous intravitreal injections (1.3%), including 73.5% with a very strong preference for the ranibizumab PDS.63

Research on this delivery system in patients with diabetic retinopathy (DR) and DME is ongoing. Extension of the PDS refill-exchange interval to 36 weeks is being investigated in the phase 3 VELODROME trial, though results are not expected until late 2023.64 Moreover, the phase 3 PORTAL extension trial is designed to evaluate long-term safety and tolerability of the ranibizumab PDS in patients who completed a previous trial with the implant.65

OPT-302 is an investigational decoy receptor targeting VEGF-C/D isoforms, intended for use in combination with standard anti-VEGF-A therapies.66 Concurrent phase 3, double-masked, sham-controlled trials, SHORE and COAST, are currently underway in patients with nAMD.57,68 They will evaluate the efficacy and safety of OPT-302 intravitreal injections in combination with standard anti-VEGF therapies versus anti-VEGF alone. The SHORE trial uses ranibizumab as a comparator, whereas the COAST trial uses aflibercept. If approved, OPT-302 will represent an expansion of treatment to include VEGF subtypes beyond the VEGF-A isoforms targeted by current therapies. OPT-302 is also being evaluated in patients with DME, having completed a phase 1/2, dose-escalation/expansion trial of OPT-302 in combination with aflibercept compared with aflibercept alone.69

Biosimilars are also an area of interest, with FDA-approved biosimilars currently available for aflibercept, bevacizumab, and ranibizumab. Of these products, only the ranibizumab biosimilar is FDA approved currently for use as an intravitreal injection for the treatment of nAMD. The biosimilars for aflibercept and bevacizumab are currently only approved for oncologic indications.70-73 Bevacizumab-vikg is the first ophthalmic formulation of bevacizumab and may soon gain FDA approval for an ophthalmic indication. Recently, a completed phase 3 trial, NORSE TWO, for nAMD compared bevacizumab-vikg monthly injections with ranibizumab injections dosed per package labeling. The trial met its primary end point, with 41% of patients receiving bevacizumab-vikg demonstrating a minimum 15-letter increase in BCVA compared with 23% with ranibizumab (P = .0052).74 Compared with the reference product, the expectation of reduced cost with a biosimilar may still drive future treatment selection as more biosimilars come to market.75

Gene therapy is another exciting treatment modality being investigated for nAMD and DME. Multiple early phase trials are ongoing to evaluate the effectiveness of these therapies in which a genetic vector that encodes a monoclonal antibody fragment is injected into the eye, either in the operating room or in the office. These agents would theoretically be a one-time injection for diseases with a historically high treatment burden.76 Preliminary information has been presented on the phase 2 ALTITUDE and AA VIATE trials evaluating RGX-314, which encodes a soluble anti-VEGF protein related to ranibizumab.77,78 The 2 trials compare a single treatment of RGX-314 with monthly ranibizumab injections in patients with DME and nAMD, respectively. Both trials are still ongoing, but early reports indicate that RGX-314 has generally been well-tolerated.76,79,80
Another gene therapy, ADVM-022, has had more mixed results. This therapy encodes aflibercept and is intended for use as a single, intravitreal injection in the office. The OPTIC trial is evaluating various doses of ADVM-022 for the treatment of nAMD. Preliminary findings indicate a favorable safety profile with mostly mild, treatable inflammation and over 80% of patients not requiring supplemental anti-VEGF injections at follow-up of up to 92 weeks. The INFINITY trial, evaluating ADVM-022 in patients with DME, was halted after some patients developed severe, progressive vision loss from hypotony.

KSI-301 is an investigational anti-VEGF therapy that is unique in structure. It is composed of a humanized immunoglobulin G1 antibody linked to a biopolymer designed to increase intraocular durability. KSI-301 has a strong affinity for VEGF-A and has demonstrated a half-life of 10.5 days in the retina and 12.5 days in the choroid in animal models, around twice the length of the half-lives of other anti-VEGF targeted therapies. Early phase clinical trials are ongoing.

D-4517.2 is a subcutaneous anti-VEGF agent used in an auto-injector form that allows patients with DME or nAMD to self-administer the medication at home as opposed to having to go to a clinic. In a phase 1 study, data demonstrated that D-4517.2 was safe and well-tolerated in healthy subjects. If approved in the future, the role of pharmacists managing these patient populations will be heightened given the need for counseling regarding administration of therapy.

**STAR**

Why do pharmacists play such a pivotal role in the treatment of both nAMD and DME? What are their responsibilities while managing patients with either disease? What can they do to optimize care for these burdened patients?

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**Pharmacist Considerations**

With an adequate comprehension of current and emerging therapeutics, pharmacists can have the ability to positively impact care in patients with nAMD or DME. They are an essential component of the multidisciplinary team when managing these patient populations.

**Patient-Centered Therapy Selection**

Patients under treatment for nAMD and DME may benefit from a patient-centered approach to therapy selection. This model shifts the paradigm of the clinician-patient relationship from a paternalistic approach to a holistic modality, as the patient becomes the focus or reference point with the clinician empowering the patient with shared decision making. Experts propose that a high-quality, patient-centered model should consist of the following elements in an ophthalmology setting:

- Extensive patient education
- Patient-centered communication techniques during counseling sessions
- Personal disease records
- Education programs for caregivers
- On-site ocular care

Incorporating patient-centered practices, including therapy selection, can improve several health-related outcomes (eg, mitigating the severity of AEs). The wide array of current and emerging pharmacologic options for nAMD and DME provide an opportunity for pharmacists to implement patient-centered care into clinical practice, particularly considering the burdens harbored by patients and caregivers regarding clinic visits for appointments.

Low-vision rehabilitation may increase visual function and help with mobility, reading, and driving, thereby optimizing quality of life and independence with activities of daily living for those with AMD. Because early referral can increase outcomes, patients should be referred to a low-vision practice as soon as possible. Additionally, many organizations provide services for patients with AMD and accompanying visual impairment, including the American Foundation for the Blind, National Federation of the Blind, and the Lighthouse Guild. Pharmacists are key clinicians in terms of providing such information.

**Lifestyle Recommendations**

One of the most important actions that patients with nAMD can take to reduce their risk of disease progression is to adopt a diet that includes specific foods and nutrients known to help support ocular health. Two large studies—1 of which spanned a 21-year period—found that patients with AMD who were adherent to a Mediterranean diet (ie, a diet rich in fruits, vegetables, fish, legumes) were 41% less likely to develop advanced AMD.

Similarly, a Mediterranean diet has also been shown to be associated with favorable outcomes in patients with DR (ie, the precursor to DME). In a meta-analysis of 31 studies, researchers evaluated the association between dietary intake and DR. Results demonstrated that greater consumption of dietary fiber and oily fish, in addition to a Mediterranean diet, was protective against DR, whereas high caloric intake was linked to an...
elevated risk of this disease.94

In addition to prioritizing a healthy diet, exercising daily can also help reduce the risk of AMD progression. Implementing aerobic activity can increase available antioxidant levels in the eye, as well as boost the overall emotional state of patients.95,96 Pharmacists should also encourage patients with nAMD to use protective eyewear, especially when they spend time outdoors. Unprotected exposure to the sun’s UV rays can permanently damage structures in the eye and speed the progression of AMD.97 It is recommended that individuals with AMD wear sunglasses with lenses that filter 90% to 100% of both UV-A and UV-B light.97,99 As clinicians who are well placed to provide both advice on the correct use of smoking cessation products and behavioral support to aid with quitting, pharmacists have a monumental role in this aspect of nAMD management. Patients who smoke have up to 4 times the risk of developing AMD compared with nonsmokers, and smoking may decrease the effectiveness of some therapies that treat nAMD.100

Patient Education and Improvement of Adherence

As previously mentioned, patient adherence to traditional anti-VEGF agents is often suboptimal.101,102 Pharmacists can apply a wide range of strategies to help enhance patient education and improve adherence to treatment.

The ongoing COVID-19 pandemic has underscored the need for telemonitoring options to decrease patient-clinician (eg, pharmacist) contact time and travel.103 Telemonitoring has been studied in patients with AMD and DR, offering an alternative to in-person screening examinations and potentially increasing patient participation.27 In 2010, the FDA approved the use of a home monitoring system for early detection of progression from intermediate AMD to nAMD. The ForseeHOME monitoring system uses preferential hyperacuity perimetry testing that detects changing distortions in patients’ relative spatial perception. Real-world analysis of this system demonstrated increased early detection rates, allowing treatment to be initiated before significant VA decline.104 It is also cost-effective in patients at high risk of developing nAMD compared with scheduled examination alone, with an incremental cost-effectiveness ratio of $35,663 per quality-adjusted life-year gained.105

Smartphones are now a valuable tool in the home monitoring arsenal, as an application has been developed for patients to download and conduct self-testing under the supervision of their clinician (eg, pharmacist). A trial evaluated 417 patients who received the offer to use a Home Vision Monitor smartphone app to monitor their vision in a single vision center in the United Kingdom. The investigators found that adherence was associated with a diagnosis of nAMD, White British ethnicity, and baseline VA. The uptake of the system decreased as age increased and adherence was higher in patients who expressed higher comfort with the use of modern technologies. The age-related nature of this disease presents an obvious barrier to the use of these systems, but the application did offer increased reassurance for patients who were able to use it properly.106 This tool may allow pharmacists to track patient adherence in nAMD and DME.

Additionally, pharmacists can play a big role in the treatment of DME by encouraging prompt screening. Many individuals with diabetes do not receive regular eye care examinations.107 The onset of DR-related complications is typically insidious, and patients remain generally asymptomatic and unaware of the disease during the early stages when treatment and medical management are most effective.108 The asymptomatic presentation of DR emphasizes the importance of early retinal examination to detect and evaluate disease severity and identify patients at risk for vision loss.109

After identifying at-risk patients, pharmacists can advise patients to schedule routine eye examinations (particularly important for individuals with diabetes). Counseling and patient education are important components of the pharmacist’s duties, as these activities often constitute a substantial portion of a pharmacist’s workday.110 Once a therapeutic option is determined, pharmacists must continue to monitor therapy for safety and efficacy and encourage patients to adhere to treatment, especially in light of data demonstrating that longer treatment intervals (≥12 weeks) are associated with reduced treatment persistence in nAMD.111 As newer, longer-lasting therapies (eg, faricimab) become increasingly integrated into nAMD and DME treatment paradigms, reemphasizing the need for ongoing and persistent treatment will serve as a pivotal counseling point for patients.

Further, pharmacists should discuss how to use an Amsler grid with a patient with nAMD, as this tool is a marker for larger change in vision and gives the patient some part of their own care.112

Financial Considerations

The high costs of nAMD and DME treatments directly impact patients, including Medicare and Medicaid beneficiaries.113 On the individual side of the equation, patients will likely continue to see options to lower out-of-pocket expenses. Patient assistance programs include those directly from biopharmaceutical manufacturers as well as programs from...
independent organizations, many of which are nonprofits that may receive some funding from biopharmaceutical manufacturers. The Foundation of the ASRS provides a list of patient assistance programs applicable for persons with nAMD or DME. Patients can also feel the financial impact when Medicare drug costs rise via increased out-of-pocket expenses. Furthermore, because the VEGF inhibitors are administered by a physician, they are generally covered under Medicare Part B, where patient co-payments are typically 20% of the drug cost plus the cost of physician services.

On the payer/formulary side of the drug pricing equation, the average wholesale prices (AWPs) of anti-VEGF therapies are good starting points to consider. According to the Micromedex Red Book, the per-dose AWP for FDA-approved anti-VEGF drugs are as follows: $2220 per 2 mg/0.05 mL of aflibercept, $2220 per 6 mg/0.05 mL of brolucizumab, $2437 per 0.5 mg/0.05 mL of ranibizumab injection, and $9600 per unit of ranibizumab PDS. Aflibercept and ranibizumab are 2 of the highest-cost medications in Medicare Part B, accounting for more than $4 billion in 2020. Utilizing new therapies (eg, faricimab) may lead to reduced costs while simultaneously decreasing the treatment burden in patients. Meanwhile, the off-label use of bevacizumab for nAMD and DME has an AWP of just $50 to $75 per 1.25-mg dose. A recent change to Medicare policies may also impact payer/formulary considerations as well as patient costs and outcomes. Starting in January 2019, the Centers for Medicare & Medicaid Services granted Medicare Advantage plans the ability to implement step therapy for Part B drugs, such as anti-VEGF agents. This change in policy, which was seemingly incorporated to lower drug costs, raised concerns among clinicians that implementing step therapy requirements could negatively impact patients by delaying optimal therapy.

Although VEGF inhibitors are typically administered in the office setting, payers may utilize specialty pharmacies to provide the injections to providers rather than allowing the process of buy-and-bill to occur at the provider level. If prior authorizations (PAs) are required by payers for certain therapies, optimal strategies may be utilized to streamline and improve the process. Toward that end, an Academy of Managed Care Pharmacy forum drafted recommendations to improve PA policies and procedures. The forum included stakeholders from a range of perspectives including academia, health plans, integrated delivery systems, pharmacy benefit managers, employers, federal government agencies, national health care provider organizations, and patient advocacy organizations. The recommendations of the forum participants are summarized in 9 categories:

- Patient safety and appropriate medication use
- Clinical decision making
- Evidence-based review criteria
- Automated decision support
- Transparency and advanced notice
- Emergency access
- Provider collaboration
- Need for timeliness and avoiding disruptions in therapy
- Cost-effectiveness and value

A group of industry and professional organizations similarly gathered to suggest areas of improvement in the PA process. They identified 5 such areas: selective application of PA, PA program review and volume adjustment, transparency and communication regarding PA, continuity of patient care, and automation to improve transparency and efficiency.

Pharmacists and other clinicians should continue to navigate the PA process. Managing PAs can consume extensive amounts of resources in time, personnel, and other costs. Case studies suggest that pharmacy professionals can provide significant benefits when managing PAs. In a published case focusing on the role of specialty pharmacy, researchers demonstrated that pharmacists can significantly reduce the PA decision time and the time to first fill. When managed by the specialty pharmacy, the mean PA time (1.9 days) and the mean time to first prescription fill (6.6 days) were significantly shorter when compared with the times when managed by a specialist’s office (mean PA time of 20.9 days [P < .001]; mean time to first prescription fill of 16.2 days [P < .001]).

**STAR**

What questions do patients with either nAMD or DME typically ask their pharmacists? What are the most important aspects that pharmacists need to be cognizant of to optimally care for these patients and attend to their needs?

**Commonly Asked Questions**

Considering that pharmacists are often the first point of contact due to their accessibility and credibility, they are expected to provide valuable information and answer questions from concerned or burdened patients, including those living with nAMD and DME. Individuals possessing either nAMD or DME may ask their pharmacists a plethora of questions, including:

- Does my condition require long-term treatment with medications? Current data demonstrate desirable outcomes
with early and repeated VEGF injections to treat nAMD and DME. However, long-term data are needed to determine whether treatments should be lifelong in patients.

- **Besides injections, are there any other medication-related options to treat my disorder?** A PDS is the only other option currently available to treat nAMD. For DME, only injections are indicated to treat the disorder.

- **Are there options with longer duration between injections?** The faricimab and ranibizumab PDS are 2 currently available agents that have extended durability compared with traditional injectable therapies.

- **What happens if my disease is not treated?** Untreated nAMD will typically lead to severe central visual impairment and, ultimately, legal blindness. Similarly, DME is the most common cause of vision loss in individuals with DR.

- **How fast does my disorder progress?** On average, it takes about 10 years for nAMD to progress to legal blindness from initial diagnosis. In DME, approximately half of patients living with this disease will lose greater than or equal to 2 lines of VA within a 2-year period.

- **What are some lifestyle recommendations that I can implement to help manage my disease?** Exercise has been shown to be beneficial in those with DR, which is a precursor to DME. Similarly, exercise may reduce the risk of AMD progression. Incorporating a Mediterranean diet (ie, a diet rich in fruits, vegetables, fish, legumes) is associated with favorable outcomes in patients with DME as well as those with AMD. Smoking is a major risk factor for AMD, thus smoking cessation is strongly encouraged. Additionally, patients with AMD should wear sunglasses with lenses that filter 90% to 100% of both UV-A and UV-B light to prevent damage of the eyes and slow the progression of AMD. Finally, omega-3 fatty acids (ie, docosahexaenoic acid) have been shown to achieve better sustained improvement of DME-related outcomes when combined with intravitreal medications compared with monotherapy with intravitreal therapies.

**Conclusion**

nAMD and DME are 2 of the leading causes of blindness worldwide. Vision loss severely compromises activities of daily living and leads to numerous comorbidities that drive the socioeconomic burden of these diseases far beyond the basic cost of treatment. Anti-VEGF therapies with intravitreal injections have been the mainstay of therapy over the past 15 years, but real-world data show poor adherence leading to suboptimal results compared with clinical trials. Emerging therapies aim to improve adherence and clinical outcomes by increasing the durability of response and decreasing the frequency of intraocular injections. These treatments include agents directed at new therapeutic targets, innovative drug delivery systems, single-dose gene therapy, and cost-saving biosimilars. Pharmacists, who are at the forefront of patient care, need to have an adequate understanding of the benefits and limitations of current and emerging therapies to develop comprehensive treatment plans that decrease overall disease burden and focus on sight preservation.

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**ADDITIONAL RESOURCES**


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POSTTEST QUESTIONS

1. Which is approved by the FDA for both age-related macular degeneration (AMD) and diabetic macular edema (DME)?
   A. Bevacizumab
   B. Brolucizumab
   C. Dexamethasone
   D. Fluocinolone acetonide

2. Which is a limitation associated with the use of traditional anti-vascular endothelial growth factor (VEGF) agents that are used to treat both AMD and DME?
   A. Discouraging data often reported in clinical trials that led to approval of these agents
   B. Cognitive-related toxicities that are often associated with these therapies
   C. Cardiovascular-related toxicities that are often associated with these therapies
   D. Suboptimal treatment adherence due to frequent injections with these agents

3. Faricimab targets which of the following pathways to treat both AMD and DME?
   A. VEGF-A and platelet-derived growth factor
   B. Angiopoietin-2 and VEGF-A
   C. Angiopoietin-2 and platelet-derived growth factor
   D. VEGF-A and interleukin 5

4. Which is true regarding initial clinical trial findings surrounding faricimab?
   A. Faricimab was associated with increased drowsiness and shorter injection intervals compared with aflibercept.
   B. Faricimab was superior to aflibercept for patients with neovascular AMD (nAMD) in the TENAYA and LUCERNE trials.
   C. Faricimab yielded no greater safety signals and a longer injection interval compared with aflibercept.
   D. An equal proportion of patients gained 10 or more letters from baseline in the faricimab and aflibercept groups.

5. LA is a 72-year-old woman with DME who comes into the pharmacy. She states that she is having difficulty getting a ride every month to receive her intravitreal injection, as this frequent dosing schedule places a substantial burden on both LA and her caregiver. Which is an appropriate counseling point for LA?
   A. Educate LA on new treatments that have extended dosing durations that allow for longer time intervals between injections.
   B. Tell LA that she should be going back every 3 weeks for her intravitreal injections to maintain proper adherence.
   C. Counsel LA on taking a “drug holiday” for 6 months and reassessing her vision afterwards to determine whether she needs to continue her injections.
   D. Counsel LA that the benefits outweigh the cons because monthly intravitreal injections have shown to be the most clinically effective long-term therapies versus injections with extended dosing.

6. Which is available in a port delivery system formulation to treat AMD?
   A. Aflibercept
   B. Bevacizumab
   C. Faricimab
   D. Ranibizumab

7. Which pharmacist-focused strategy has been shown to improve outcomes for patients with either AMD or DME?
   A. Utilizing a patient-centered care model
   B. Urging patients to consult only with their physician with questions regarding AMD and DME therapies
   C. Recommending traditional anti-VEGF agents to treat both AMD and DME
   D. Encouraging patients with a family history of AMD or DME to take preventive anti-VEGF therapies.

8. The Academy of Managed Care Pharmacy forum drafted recommendations to improve prior authorization policies and procedures. Which is a category regarding the recommendations of the forum participants?
   A. Less emphasis placed on patient assistance programs
   B. Greater need for increased use of lower-cost therapies without a consideration for efficacy or safety
   C. More involvement of nurses compared with pharmacists
   D. Patient safety and appropriate medication use
POSTTEST QUESTIONS (continued)

9. What is the FDA-approved dosing interval of ranibizumab port delivery system for the treatment of nAMD?
   A. Every 4 weeks
   B. Every 12 weeks
   C. Every 24 weeks
   D. Every 52 weeks

10. MC is a 66-year-old man who was recently diagnosed with nAMD. He comes into the pharmacy and asks the pharmacist if there are any lifestyle interventions that he can implement to help manage his condition. Which would be the most appropriate option for the pharmacist to recommend for MC?
   A. Use computers or television over printed materials to prevent eye strain
   B. Eat a diet full of red meat to give his eyes proper nutrition
   C. Smoking cessation
   D. Use sunglasses only when eyes feel irritated outside

INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.
Go to www.pharmacytimes.org/AMD-DME 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 successful completion of the 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.

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HIV Therapy: Addressing Unanswered Questions to Optimize Care

**EDUCATIONAL OBJECTIVES**

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

- Explain initiation and monitoring of antiretroviral therapy for both treatment-experienced and treatment-naïve people living with HIV
- Examine potential reasons to switch HIV treatment in the setting of virologic suppression
- Investigate the impact of implicit racial bias, weight gain, and tolerability as barriers to care
- Demonstrate best practices for inclusive HIV care

**TARGET AUDIENCE:** Community pharmacists

**ACTIVITY TYPE:** Application

**RELEASE DATE:** October 5, 2022

**EXPIRATION DATE:** October 5, 2023

**ESTIMATED TIME TO COMPLETE ACTIVITY:** 2.5 hours

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

**INTRODUCTION AND OVERVIEW OF HIV**

**Background**

The human immunodeficiency virus (HIV) is a lentivirus within the Retroviridae family. It is otherwise known as a retrovirus that could be transmitted in sexual fluids or breast milk but is primarily transmitted via contact with HIV-infected blood. Acquired immunodeficiency syndrome (AIDS) will occur in people living with HIV, especially in those with a very weakened immune system (CD4+ T lymphocyte cells [CD4] count <200 cells/mm³) or who have an AIDS-defining condition (eg, opportunistic infections and/or malignancies). The 2 types of HIV are HIV-1 and HIV-2. The HIV-1 type is more widespread globally and pathogenic (disease causing) than HIV-2, which is a less pathogenic variant and mainly localized in West African countries. For the purpose of this activity, discussion will be focused on the HIV-1 type.

The most common route of HIV transmission accounting for approximately 80% of all documented new HIV diagnoses is having condomless sexual intercourse with a person who has a detectable HIV viral load. In terms of sexual risk factors for acquiring HIV, the individual having receptive anal intercourse (“the receiver”) is the most vulnerable, followed by male-to-female vaginal transmission, and then female-to-male penile transmission. HIV transmission can also occur from injectable drug use if users share needles, from receipt of contaminated blood products, and from perinatal transmission in utero or during delivery through breastfeeding. HIV cannot be transmitted through saliva, sweat, or urine. Upon initial disease presentation, an acute phase occurs before HIV progresses to chronicity in the individual. Viral replication and an inflammatory host response induce the destruction of CD4 cells early in acute HIV disease and over time. The natural course of HIV varies among individuals. Some may remain...
healthy with stable CD4 counts from 10 to 15 years after HIV transmission, whereas other individuals may progress to symptomatic disease within a few years after seroconversion.\(^7,8\) The variation is influenced by a range of host and viral factors, such as modulators of the host immune response and tropism of the virus strain, respectively.

**Prevalence and Statistics**

In 2021, an estimated 38.4 million people were living with HIV worldwide, including 36.7 million adults and 1.7 million children younger than 15 years. Furthermore, there were an estimated 1.5 million people newly diagnosed with HIV.\(^9\) Approximately 1.2 million people are living with HIV in the United States.\(^4\) Regarding the types of HIV transmission, an estimated 58% acquired HIV through male-to-male sexual contact, 26% from heterosexual contact, 11% via injection drug use, and 5% had combined risk factors for male-to-male sexual contact and injection drug use.\(^10\) The CDC estimates 77.8% of those living with HIV are male and 22.2% are female; at the time of surveillance data analysis, HIV prevalence data did not include transgender persons.\(^10\)

The HIV epidemic has disproportionately affected Black or African American individuals, perhaps stemming from racism, stigma, health disparities, and access barriers to HIV care and prevention. Approximately 40.3% of people living with HIV are Black or African American, 28.5% are White, and 24.7% are Hispanic or Latino.\(^10\) Among people living with HIV, nearly 60% are 45 years or older, with those older than 55 years accounting for the largest portion followed by those aged 45 to 54 years.\(^4\) Fortunately, there has been an approximately 9% decline in HIV diagnoses from 2015 to 2019, where an estimated 36,940 persons were diagnosed with HIV in 2019.\(^10\) The decline is likely attributed to the available potent antiretrovirals (ARVs) and preexposure prophylaxis (PrEP) medications.

HIV testing guidelines recommend routine screening of all adolescents and adults aged 15 to 65 years, all pregnant women whose HIV status is unknown and at every pregnancy, and more frequent screening for persons at increased behavioral risk of vulnerability to HIV (eg, men who have sex with men [MSM], transgender individuals, youth, people who inject drugs [PWID], those seeking care for tuberculosis or sexually transmitted infections [STIs], and persons prescribed PrEP).\(^11\) With signifi-
cant progress and advancements made in antiretroviral therapy (ART), HIV disease rates have gradually declined in the past few years.10 People with HIV are living longer and achieving durable virologic suppression due to potent ART regimens, making HIV a manageable chronic disease. However, given the continued global and national burden of the HIV epidemic and its associated comorbid conditions, HIV response from individuals and development of a vaccine remain critical targets of HIV care. Other vital goals include increasing appropriate diagnosis, treatment, and transmission prevention efforts as well as improving public health response overall. A comprehensive understanding of the management strategies for HIV prevention and treatment is essential for health care providers to help reduce transmission rates of HIV, as well as offer appropriate ART to people living with HIV.

Pathophysiology

HIV primarily attacks the CD4+ T helper cells that express specific receptor proteins to which the virus binds. CD4 cells are white blood cells that are an essential part of the immune system.12 In the eclipse phase that occurs between weeks 1 and 2 after an individual acquires HIV, the virus replicates and spreads from the initial site of transmission to the host tissues and organs that will become potential sites for viral replication. HIV viremia (presence of virus in the blood) remains undetectable. Neither the host immune response nor manifestations of symptoms are visible yet. The acute phase occurs from 2 to 4 weeks after an individual acquires HIV disease and is characterized by relatively high levels of viremia (≥10^7 copies of viral RNA/mL blood).12 During the acute phase, symptoms can occur and may include flu-like illness such as fever, enlarged lymph nodes, malaise, and generalized body rash. At peak viremia, the host immune system responds by producing antibodies against the viral proteins. CD8+ T cells are also activated and target cells expressing HIV antigens.12 The level of viremia declines at the end of the acute phase due to partial control by the host immune system and exhaustion of activated target cells. During this phase, there is also a transient decline in CD4 cells in the blood (FIGURE 1).12

There is an inverse relationship between the CD4 T cell decline and viremia increase at the beginning of the HIV disease and over time. The patterns of disease may vary from one patient to another.

Often, people living with HIV recover from acute symptoms, enter the asymptomatic phase, and are unaware that they have acquired the disease. Individuals eventually enter chronic or the “clinical latency” phase, which is characterized by a constant or slowly increasing level of viremia ranging from 1 to 100,000 copies/mL with gradually falling levels of CD4 cells. This steady phase is also characterized as the person’s “set point.” Over time, untreated HIV disease will take a toll on the host immune system. As the number of CD4 cells decline to approximately 200 cells/mm^3, the person is at high risk for opportunistic infections and AIDS-associated complications, such as dementia or encephalopathy, and sequelae, such as wasting syndrome and chronic diarrhea.6,12,13

### Sidebar: Main Points to Include During a Comprehensive Patient Assessment and Medical Review6,14

#### HIV History
- Approximate date of initial HIV acquisition and date of diagnosis of HIV
- Risk factors related to HIV acquisition
- Prior HIV-associated complications and comorbidities (eg, opportunistic infections, malignancies)

#### Past Medical History
- Chronic medical conditions
- Past surgical history
- Psychiatric history (eg, history of depression, bipolar disorder, posttraumatic stress disorder)

#### Allergy and Medication History
- Allergies and intolerances to medications
- Past and current medications, over-the-counter medications, dietary and herbal supplements

#### Sexual History
- Sexual behavior and practices (eg, gender of partners, sexual positions, condom use, contraceptive use)
- HIV status of partners
- Disclosure of patient’s HIV status to sexual partner(s)
- History of STIs and past treatments

#### Substance Use History
- Past and current use of alcohol, tobacco, and other substance use
- Past and current treatment for any substance use disorders
- If substance use present, assess impact on daily activities

#### Social and Family History
- Social support, employment status and history, financial status, marital status, and housing situation
- Family health history
- Desires for family planning and reproduction

#### Travel History
- Past and current residence or travel to regions endemic for certain diseases (eg, histoplasmosis or coccidioidomycosis)
What is important to include in a comprehensive patient assessment and medical review encounter for an individual living with HIV? What baseline laboratory tests are important?

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

Initiating Treatment and Monitoring for Treatment-naïve Patients

**Patient Assessment**

At the initial clinic visit, an evaluation should be performed to determine whether the individual is newly diagnosed with HIV or has established HIV disease and is new to the clinic. The initial encounter should be patient centered and conducted in an open and nonjudgmental manner. The health care provider should assess the individual’s readiness to begin ART, re-establish HIV care, provide information about treatment options, and describe the benefits of being on ART as well as the importance of medication adherence to prevent HIV-related complications and reduce HIV transmission risk. Additionally, it is important to conduct a physical examination and determine the individual’s social and family support networks, medical history, sexual history, allergy and medication history, and substance use history. A summary of main points to include in a comprehensive patient assessment and medical review encounter can be found in the SIDEBAR.6,14

**Laboratory Evaluation**

In addition to the patient assessment as part of the initial evaluation, baseline laboratory analyses should be determined before treatment initiation. These baseline laboratory tests include:14,15:

- HIV-1/2 antigen-antibody immunoassay
- Plasma HIV RNA level (or viral load)
- CD4 cell count with percentage
- HIV drug-resistance genotype
- HLA-B*5701 allele (if considering abacavir-based regimens to rule out risk for hypersensitivity reaction)
- Basic comprehensive metabolic panel (eg, serum creatinine, electrolytes, glucose, liver function tests) and complete blood count
- Hepatitis panel (eg, hepatitis A immunoglobulin G, hepatitis B [surface antibody, core antibody, and antigen], and hepatitis C virus [HCV] antibody)
- STIs (eg, syphilis test [nontreponemal test and fluorescent treponemal antibody absorption test], chlamydia, and gonorrhea via nucleic acid amplification tests of 3 sites of sexual contact [oral, anal, and genital or urine])
- Tuberculosis screening (eg, QuantiFERON-TB Gold) and toxoplasma immunoglobulin G
- Pregnancy (if applicable)
- Other labs: fasting lipid panel, fasting plasma glucose or hemoglobin A1c (HbA1c), and glucose-6-phosphate dehydrogenase

It is important to note that immediate initiation of ART or “rapid start” of HIV treatment on the same day of HIV diagnosis is recommended for newly diagnosed individuals, even when the viral resistance test results are not available, to engage them in HIV care, hasten their time to achieve viral suppression, and reduce the risk for them to transmit HIV to others.6 After initiating patients on ART, it is vital to emphasize the importance of adherence to ART regimens and medical and laboratory visits, as well as monitoring for virologic and immunologic response to their regimens (FIGURE 2).6

Follow-up HIV RNA viral load monitoring should be obtained within 4 weeks and no later than 8 weeks after treatment initiation. Viral loads should be repeated every 4 to 8 weeks until the HIV RNA is suppressed. Once viral load suppression is achieved, HIV RNA monitoring could be performed every 3 to 4 months thereafter. For individuals who have consistently suppressed their HIV RNA levels for at least 2 years and have stable CD4 counts (>200 cells/mm³), follow-up RNA monitoring could be extended to every 6 months.6

The current recommended ART regimens are highly potent and effective, where the patients’ immunologic response (CD4
count) could increase to 50 to 150 cells/mm³ during the first year of treatment. An additional increase of 50 to 100 cells/mm³ could occur annually until steady state is reached.16,17 Similar to the frequency of HIV RNA level monitoring, follow-up CD4 count monitoring should be obtained 3 months after treatment initiation, and should be repeated every 3 to 6 months during the first 2 years of treatment. For individuals who have maintained long-term virologic suppression and whose CD4 counts are consistently between 300 and 500 cells/mm³ or greater, CD4 counts could be repeated once a year.6

Drug-resistance Testing (Genotype, Phenotype, Tropism Assay)

Testing for baseline HIV resistance to ARVs is an essential tool to select an effective, potent treatment regimen, as drug-resistant HIV can be transmitted from one individual to another. The 2 types of plasma drug resistance assays used in clinical practice to determine HIV resistance to ARV agents are genotypic and phenotypic assays. The HIV RNA genotype test uses population or Sanger sequencing and involves multiple steps to sequence the polymerase gene, which encodes HIV reverse transcriptase and the protease gene.18 The analysis of the HIV integrase gene is not part of the genotypic resistance testing and requires a separate laboratory request. The HIV drug resistance genotype can be performed reliably when the viral load is at least 500 to 1000 copies/mL.6,19,20 The HIV genotype report provides specific information regarding the amino acids in the patient’s HIV sample that differ from the wild-type HIV strains. Baseline testing for integrase resistance is not recommended because of a low frequency of transmitted resistance. In cases where there is evidence of individuals acquiring HIV from another person with a known integrase inhibitor-based regimen, then a baseline integrase genotype test should be considered.21 In short, an HIV genotype report lists the wild-type amino acid, followed by the position of that amino acid in the protein, followed by the substituted amino acid that confers resistance.18 The genotype report interprets ARV drug susceptibility as either no evidence of resistance, low-level resistance, or high-level resistance.18,22,23

Conversely, the phenotype assay is considered in those with extensive HIV drug resistance, particularly with the protease inhibitor (PI) class. The phenotype assay involves polymerase chain reaction amplification of reverse transcriptase, protease, and envelope genes.22 Furthermore, it evaluates the susceptibility of HIV to ARV agents by directly measuring the viability of the predominant HIV strain in the presence of ARV medications.18 The phenotype report provides an IC₅₀ or IC₉₀ value—the drug concentration required to inhibit the replication of HIV by 50% or 90%, respectively—of the patient’s blood sample. Subsequently, the IC₅₀ or IC₉₀ is divided by a reference IC₅₀ or IC₉₀ value from wild-type virus to generate a fold change value, which represents relative resistance of the patient’s HIV to the ARV medication. As a result, the observed fold change value of the individual’s HIV could be interpreted as susceptible, hypersusceptible, or resistant to the ARV tested.18,21,22

Unlike the genotype and phenotype assays, the HIV co-receptor tropism assay is used to determine the type of CD4 cell that the virus can target based on the type of co-receptor recognized by glycoprotein 120. Binding to a C-C motif chemokine coreceptor 5 (CCR5) is known as R5 tropism, while binding to CXCR4 is known as X4 tropism, and binding to both is known as dual/mixed tropism.24 The tropism or Trofile assay is a molecular blood test that identifies the tropism of the person’s HIV strain.25 In essence, the tropism test results will show whether the person’s HIV strain is using the R5, X4, or both types of coreceptors to enter the CD4 cell. The tropism test is not recommended as part of the initial HIV resistance genotype test for treatment-naïve individuals, but it should be used when maraviroc, a CCR5 antagonist, is considered part of the ART regimen for treatment-experienced individuals; maraviroc should only be used in persons with R5 tropic virus.6

Types of Drug-resistance Mutations

Among the thymidine analogue-associated mutations (TAMs) related to nucleoside reverse transcriptase inhibitor (NRTI) resistance, the development of M184I/V and K65R mutations are of particular interest. The M184V mutation causes high-level resistance to emtricitabine and lamivudine, rendering these ARVs inactive against the virus. In contrast, the M184V mutation alone causes low-level resistance to abacavir and enhanced susceptibility to tenofovir and zidovudine.6,26 Clinically, emtricitabine or lamivudine is kept as part of the ART regimen’s backbone in the presence of M184V, even if it lacks antiviral activity, to reduce the replication fitness of the HIV virions and to confer hypersusceptibility to other NRTIs, such as tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF).27,28 Similarly, the K65R mutation causes high-level resistance to tenofovir and intermediate-level resistance to abacavir, emtricitabine, and lamivudine.29 The presence of the combination of M184V and K65R mutations causes high-level resistance to abacavir, emtricitabine, and lamivudine
and intermediate-level resistance to tenofovir.\textsuperscript{30,31} When this combination mutation occurs along with other TAMs, it is prudent to select alternative drugs from other ARV classes.

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) have a lower barrier to drug resistance compared with the PI inhibitor and integrase strand transfer inhibitor (INSTI) classes; therefore, resistant mutations can develop quickly.\textsuperscript{32} The K103N mutation is the most common single mutation that can confer cross-resistance to the first-generation agents efavirenz and nevirapine. The second-generation NNRTIs, including etravirine, rilpivirine, and doravirine, have a higher barrier to resistance than the first-generation NNRTIs and retain antiviral activity against HIV strains that have the K103N mutation.\textsuperscript{33} The G190E mutation is a major mutation that causes high-level resistance to almost all the NNRTIs and an intermediate-level resistance to etravirine.\textsuperscript{34} Selection of ARVs from other drug classes will need to be determined to design an effective, potent ART regimen when several mutations that will reduce the susceptibility and virologic response to the second-generation NNRTIs are present.

The PI class has a high genetic barrier to viral resistance. It requires multiple protease mutations to significantly affect the virologic response to a PI boosted with ritonavir or cobicistat.\textsuperscript{22,29} Among the boosted PIs, darunavir has the highest barrier to resistance, followed by lopinavir and atazanavir.\textsuperscript{35,36} Similarly, the INSTI class also has a high genetic barrier to viral resistance, particularly the second-generation INSTIs bictegovir and dolutegravir. Several mutations are required in HIV integrase to confer high-level resistance to bictegovir and dolutegravir. There have been few reports of resistance mutations (eg, Q148H/K/R, N155H, and R263K) that confer broad cross-resistance to the entire INSTI class and have led to treatment failures.\textsuperscript{37,38} In the instance where INSTIs cannot be part of the anchoring drug of the ART regimen due to resistance mutations, HIV management needs to be individualized based on the person’s genotype and phenotype reports; entry inhibitors may need to be included, such as the attachment and post-attachment inhibitors.

**STAR**

Which ARV classes are recommended for people living with HIV who are treatment naïve?

Recommended ARV Classes for Treatment-naïve People Living With HIV

As previously discussed, treatment should be initiated immediately after the HIV diagnosis is made. The main goals of using ART are to reduce morbidity and mortality, restore and strengthen the host immune system, and prevent HIV transmission to others.\textsuperscript{5} The clinical management of HIV for treatment-naïve persons is largely dependent on multiple factors, including medical comorbid conditions, underlying viral resistance, potential drug-drug interactions, adverse effect (AE) profiles, patient preferences (eg, pill burden and food requirements), and pregnancy status. There are 5 main ARV drug classes approved to treat HIV including the NRTIs, NNRTIs, PIs, INSTIs, and entry and cell attachment inhibitors. These drug classes target the essential steps of the life cycle of the virus in the CD4 cell: fusion and attachment to the surface of the cell, viral replication, insertion of the viral genetic material into the human host DNA, viral assembly, and budding from the CD4 cell (FIGURE 3).

**Integrase Strand Transfer Inhibitors**

Recommended initial ART regimens are dosed once daily and should include 2 or 3 fully active ARVs. These regimens comprise an INSTI as the anchoring drug combined with at least 1 NRTI as the backbone.\textsuperscript{6} The second-generation INSTIs bictegovir and dolutegravir are preferred over PIs as the anchor ARV in combination with the NRTIs because of their high efficacy, high genetic barrier to viral resistance,
good tolerability profile, and minimal drug-drug interactions. Bictegravir- and dolutegravir-based regimens are equally potent and have similar virologic efficacy. 39,40 For most individuals, the recommended initial ART regimens include the combinations in TABLE 1. 6

### TABLE 1. RECOMMENDED INITIAL TREATMENT REGIMENS 6

<table>
<thead>
<tr>
<th>Integrase Strand Transfer Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors</th>
<th>Boosted Protease Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bictegravir/emtricitabine/TAF</td>
<td>• Darunavir/cobicistat/emtricitabine/TAF</td>
</tr>
<tr>
<td>• Dolutegravir/abacavir/lamivudine*</td>
<td>• Darunavir/cobicistat + emtricitabine/TDF</td>
</tr>
<tr>
<td>• Dolutegravir + emtricitabine/TAF or emtricitabine/TDF</td>
<td>• Darunavir + ritonavir + emtricitabine/TAF or emtricitabine/TDF</td>
</tr>
</tbody>
</table>

**Integrase Strand Transfer Inhibitor + 1 Nucleoside Reverse Transcriptase Inhibitor**

| • Dolutegravir/lamivudine\* |

**TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.**

\*Should not be initiated as a rapid start regimen and for individuals whose HIV viral load >500,000 copies/mL or who have hepatitis B virus infection.

**TABLE 2. PROTEASE INHIBITOR-BASED TREATMENT REGIMENS 6**

<table>
<thead>
<tr>
<th>Boosted Protease Inhibitor + 2 Nucleoside Reverse Transcriptase Inhibitors</th>
<th>• Darunavir/cobicistat/emtricitabine/TAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Darunavir/cobicistat + emtricitabine/TDF</td>
<td></td>
</tr>
<tr>
<td>• Darunavir + ritonavir + emtricitabine/TAF or emtricitabine/TDF</td>
<td></td>
</tr>
<tr>
<td>• Darunavir/cobicistat + abacavir/lamivudine*</td>
<td></td>
</tr>
<tr>
<td>• Atazanavir/cobicistat + emtricitabine/TAF or emtricitabine/TDF</td>
<td></td>
</tr>
<tr>
<td>• Atazanavir + ritonavir + emtricitabine/TAF or emtricitabine/TDF</td>
<td></td>
</tr>
</tbody>
</table>

**TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.**

\*If patient is HLA-B*5701 allele negative.

**Protease Inhibitors**

Boosted PI-based regimens could be considered as alternative treatment options when individuals cannot take INSTI-based regimens because of underlying HIV resistance, intolerance, or significant drug-drug interactions. Boosted darunavir- and atazanavir-based regimens are preferred over the older PIs because they are highly efficacious, better tolerated, and can be taken once daily with food. 41,42 Darunavir and atazanavir are also available co-formulated with cobicistat as single tablets. 6 Darunavir contains a sulfonamide group in its chemical structure and, therefore, may cause rash in patients with a sulfa allergy. 43 Atazanavir can cause hyperbilirubinemia, which is often mild but requires close monitoring for potential hepatic-related symptoms. 44 Preferred PI-based regimens include either boosted darunavir or boosted atazanavir combined with 2 NRTI agents (TABLE 2). 6

**Non-nucleoside Reverse Transcriptase Inhibitors**

The NNRTIs are noncompetitive inhibitors of the reverse transcriptase enzyme. They work in a similar manner as NRTIs by binding to a hydrophobic pocket close to the active site of the reverse transcriptase. 46 The NNRTIs are hepatologically metabolized, with minimal urinary excretion of the parent drugs. The first-generation NNRTIs include efavirenz and nevirapine. The second-generation NNRTI agents include etravirine, rilpivirine, and doravirine. Since the demonstration of viral potency of the INSTIs, the NNRTIs have been relegated to alternative treatment regimens because of their potential class AEs of rash and hepatotoxicity, as well as variable food requirements and potential for drug-drug interactions with other ARVs. 6

**Nucleoside Reverse Transcriptase Inhibitors**

Historically, the NRTIs are the first class of ARVs developed for the treatment of HIV. Known as “nucleoside analogues,” NRTIs competitively inhibit the reverse transcriptase enzyme by incorporating false nucleic acids into the newly forming viral DNA chain, resulting in chain termination. 45 Consequently, the HIV genetic material cannot be incorporated into the host genetic material of the CD4+ cell, and viral replication is prevented. Currently used NRTIs include zidovudine, lamivudine, abacavir, emtricitabine, TDF, and TAF. With the advancements of HIV treatment with the INSTIs, either 1 or 2 NRTI agents is used as an active backbone with an anchoring agent to make an effective first-line ART regimen. Furthermore, patients with HIV and hepatitis B virus (HBV) coinfections could benefit from an ART regimen that has an active ARV against HBV, such as TDF or TAF. The preferred NRTI agents comprise either abacavir plus lamivudine or TDF or TAF plus emtricitabine. 6

**Selection of Initial ART**

There are several factors to consider when selecting an appropriate initial ART regimen, including baseline or pretreatment HIV RNA viral load level, CD4 cell count, underlying HIV RNA resistance, food requirements, renal function, bone health, mental health, cholesterol level, weight gain, pregnancy status, and cardiac condition. Discussion of some considerations will follow, and a summary of the preferred first-line ART regimens to initiate for treatment-naïve people with HIV is shown in TABLE 3. 6
Baseline HIV RNA Level

Individuals with baseline viral load levels greater than 100,000 copies/mL should not be initiated on rilpivirine-based regimens, abacavir/lamivudine (in combination with efavirenz or ritonavir-boosted atazanavir), and raltegravir plus ritonavir-boosted darunavir because of higher rates of virologic failure. Dolutegravir/lamivudine should not be considered for those with viral loads greater than 500,000 copies/mL because the regimen was not studied in these individuals.6

Baseline CD4 Cell Count

CD4 count is a major indicator of immune function. It is the key factor in determining the need for opportunistic infection prophylaxis, which occurs when there are fewer than 200 cells/mm³. Raltegravir plus ritonavir-boosted darunavir and rilpivirine-based regimens should not be used in individuals who have baseline CD4 count fewer than 200 cells/mm³ because of higher rates of virologic failure.6

HIV Viral Resistance

In situations where the HIV genotypic drug resistance test results are not readily available at the time of treatment initiation, INSTI- or PI-based regimens are preferred because of their high genetic barrier to resistance. These regimens include bictegravir/emtricitabine/TAF, dolutegravir/abacavir/lamivudine (if HLA-B*5701 negative), dolutegravir plus emtricitabine/TAF or emtricitabine/TDF, or darunavir (boosted with cobicistat) plus emtricitabine/TAF or emtricitabine/TDF. The NNRTI-based regimens should be avoided for initial therapy. Viral resistance testing is recommended for all pregnant women, especially before initiation of ART.6

Proviral DNA resistance test can be considered in persons whose HIV viral load is undetectable but who have a history of multiple virologic failures and unknown previous genotype results. However, identification of some or all existing resistance mutations may be missed. The clinical utility of obtaining this type of test is not yet known.6

Food Requirements

Certain ARVs should be taken with food to improve their bioavailability or to minimize gastrointestinal AEs; these include rilpivirine, ritonavir- or cobicistat-boosted atazanavir, ritonavir- or cobicistat-boosted darunavir, elvitegravir/cobicistat/emtricitabine/TDF, and elvitegravir/cobicistat/emtricitabine/TAF. Efavirenz should be taken on an empty stomach to minimize central nervous system AEs.6

Renal Function

TDF and fixed-dose regimens containing TDF should be avoided in individuals who have a baseline estimated glomerular filtration rate (eGFR) less than 60 mL/min. Emtricitabine/TAF and fixed-dose regimens containing emtricitabine/TAF should be avoided in persons with eGFR less than 30 mL/min. Other NRTI agents could be considered with renal dose adjustments. Abacavir is the only NRTI agent that could be safely administered at its standard dose in persons with renal insufficiency or on hemodialysis.6,47

Bone Health

TDF and fixed-dose regimens containing TDF should be avoided in persons with known osteoporosis. Of note, the decrease in bone mineral density associated with TDF is reversible after discontinuation.38 Abacavir and TAF-based regimens are associated with smaller declines in bone mineral density.6

### TABLE 3. SUMMARY OF THE RECOMMENDED FIRST-LINE ART REGIMENS FOR TREATMENT INITIATION6

<table>
<thead>
<tr>
<th></th>
<th>BIC/FTC/TAF (Biktarvy)</th>
<th>DTG/ABC/3TC+ (Triumeq)</th>
<th>DTG/3TC (Dovato)</th>
<th>DRV/cobi/FTC/TAF (Symtuza)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-tablet formulation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>High resistance barrier</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Food requirement</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Drug-drug interactions</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Major</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HIV/HBV coinfection</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ABC, abacavir; ART, antiretroviral therapy; BIC, bictegravir; cobi, cobicistat; DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; HBV, hepatitis B virus; TAF, tenofovir alafenamide; 3TC, lamivudine.

*HLA-B*5701 must be negative before initiation of DTG/ABC/3TC regimen.
Mental Health
Efavirenz, and possibly rilpivirine and doravirine, have been associated with worsening psychiatric symptoms. Dolutegravir alone and in combination with rilpivirine has also been reported to cause neuropsychiatric AEs. Efavirenz should be avoided in persons with psychiatric illness and dementia, and close monitoring for worsening psychiatric symptoms is recommended for patients on rilpivirine, doravirine, or dolutegravir-based regimens.

Hyperlipidemia
The INSTI class, darunavir, and atazanavir are lipid neutral. TDF has a favorable impact on lipids; however, TAF is associated with increased lipids. Other ARVs that can cause dyslipidemia include ritonavir-boosted PIs, cobicistat-based regimens, and efavirenz.

Weight Gain
Second-generation INSTIs bictegravir and dolutegravir in combination with TAF are associated with significant weight gain, particularly in women and Black and Hispanic persons. Moreover, female sex was associated with ≥10% weight gain compared with male sex, with Black women experiencing more weight gain than non-Black women. Noticeable weight gain was also observed when patients were switched from TDF-based regimens to TAF-based regimens, excluding INSTIs.

Hepatitis B/C Coinfections
Four NRTIs that are active against HIV and HBV include emtricitabine, lamivudine, TAF, and TDF. TAF and TDF are active against HBV and have a higher genetic barrier to HBV drug resistance than emtricitabine and lamivudine. Clinically, TAF or TDF should be combined with emtricitabine as a fixed-dose combination as part of a fully suppressive ART regimen for individuals with HIV and HBV coinfections for dual antiviral coverage. It is important that individuals with HIV and HBV coinfections do not stop their ART regimens to prevent HBV reactivation and potentially serious hepatic inflammation or flares (defined as an alanine transaminase [ALT] increase at least 3 times greater than baseline ALT level).

Individuals with HIV and HCV coinfection should be initiated on ART regimens before HCV treatment until HIV virologic suppression is achieved. The main reason is to ensure medication adherence and the patient’s tolerability of the ART regimen. Pangenotypic direct-acting antiviral (DAA) regimens are generally considered for treatment because they are highly potent and active against all HCV genotypes 1-6. These include glecaprevir/pibrentasvir and sofosbuvir/velpatasvir. The recommended duration of DAA treatment ranges between 8 and 12 weeks for glecaprevir/pibrentasvir (without cirrhosis) and sofosbuvir/velpatasvir, respectively. Individuals with HIV/HCV coinfection with compensated cirrhosis could receive glecaprevir/pibrentasvir treatment for a longer duration of 12 weeks. Monitoring for potential drug-drug interactions between the ARVs and DAAs is strongly recommended.

Pregnancy
Combination ART regimens should be initiated immediately for all pregnant women living with HIV. Effective ART regimens should include at least 3 active ARVs to reduce the risk of perinatal HIV transmission and prevent maternal HIV-related complications. For pregnant women naïve to HIV treatment, an effective, fully suppressive regimen should include dolutegravir as the anchoring ARV because of its high genetic barrier to resistance plus 2 NRTIs. Moreover, dolutegravir-based regimens can be continued in persons already taking them and who become pregnant. Based on the final data analysis of the Tsepamo study in Botswana, the prevalence of neural tube defects associated with dolutegravir was not significantly higher than the prevalence of neural tube defects in infants born to women with HIV receiving non-dolutegravir regimens at conception. In circumstances where the person with HIV is already on an active suppressive ART regimen and becomes pregnant, the current regimen should be continued. Bictegravir and cobicistat have insufficient data for their use in pregnancy at this time. Raltegravir is the other INSTI that could be considered as part of a fully active, suppressive regimen. Raltegravir is not co-formulated in any fixed-dose combination, so pill burden will need to be considered for the individual. The high-dose formulation of raltegravir (1200 mg) has not been studied in pregnancy and should not be used for treatment. PI-based regimens that include boosted darunavir with cobicistat should be avoided in treatment-naïve pregnant women due to pharmacokinetic data showing lower levels of darunavir during pregnancy. Currently, there are insufficient data for the bictegravir-based and doravirine-based regimens to recommend their use in pregnancy. Similarly, individuals who become pregnant while taking cabotegravir/rilpivirine should be switched to a preferred 3-drug ART regimen because...
### TABLE 4. ROUTINE HEALTH CARE MAINTENANCE FOR PERSONS LIVING WITH HIV

<table>
<thead>
<tr>
<th>Monitoring parameter</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA level</td>
<td>At baseline and every 4-6 weeks after initiation of ART until viral load &lt;50 copies/mL, then approximately every 3 months. The viral load could be measured every 6 months for people with consistent viral suppression and stable CD4 count for more than 2 years.</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>At baseline, 1 month, and every 3-6 months for the first 2 years after initiating ART, or if viremia develops, or if CD4 count &lt;300 cells/mm³. CD4 count could be measured every 12 months if CD4 count is 200-500 cells/mm³ and HIV RNA suppressed for 2 years.</td>
</tr>
</tbody>
</table>

**Screening and monitoring for metabolic disorders**

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>At every clinic visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>At every clinic visit</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Every 1-3 months after initiating or changing ART; follow the ACC/AHA lipid guidelines and ASCVD risk calculator.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Test for diabetes 1-3 months after initiating or changing ART; HbA1c is not used to diagnose diabetes in persons on ART. It may also be used for screening and monitoring. Refer to the American Diabetes Association Practice Guidelines for Diabetes Care. Urine microalbumin or urine protein/creatinine ratio: in patients with diabetes, repeat at least every 6 months (more frequently if clinically indicated).</td>
</tr>
<tr>
<td>Bone density</td>
<td>Baseline bone densitometry by dual-energy x-ray absorptiometry should be performed in all postmenopausal women and men ≥50 years.</td>
</tr>
</tbody>
</table>

**Screening for infectious diseases and vaccinations**

<table>
<thead>
<tr>
<th>Syphilis</th>
<th>Perform annually in asymptomatic persons; repeat every 3-6 months in asymptomatic persons if risk of acquisition is high.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia and gonorrhea</td>
<td>Perform annually in asymptomatic persons; repeat every 3-6 months in asymptomatic persons if risk of acquisition is high. Use of NAAT at all sites of sexual contact (rectal, oropharyngeal, vaginal, urine/urethral) is recommended for all sexually active persons with HIV.</td>
</tr>
<tr>
<td>Hepatitis A, B, and C</td>
<td>Check for acute hepatitis A, B, and C virus in persons with new abnormal liver function tests. Check hepatitis B surface antibody 1-2 months or next scheduled visit after completion of series. Perform hepatitis C screening annually in sexually active, HCV-negative MSM, transgender women, and PWID. Administer hepatitis A and B vaccines or boosters if not immune.</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Perform the QuantiFERON-TB Gold test annually in patients at risk for tuberculosis.</td>
</tr>
<tr>
<td>Vaccinations</td>
<td><strong>Pneumococcal vaccines (PCV13 , PCV20, and PPV23):</strong> repeat PPV23 once 5 years after first vaccination. Administer the third and final doses of PPV23 after age 65 years. All patients with HIV should receive 1 dose of PCV13 or PCV20 (adults only). If previously not vaccinated, this should be the first dose. If previously vaccinated, 1 dose of PCV13 at least 1 year after PPV23. As of 2022: PCV20 is recommended for pneumococcal disease prevention in adults aged ≥19 years who have not previously received PCV. <strong>Annual live-attenuated influenza vaccine only</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Meningococcal vaccine</strong> (series of serogroup A, C, W, and Y meningococcal vaccine) x2 doses; booster every 5 years depending on risk.</td>
</tr>
<tr>
<td></td>
<td><strong>HPV vaccine:</strong> administer if aged ≥26 years; consider vaccinating persons aged 27-45 years if unvaccinated or inadequately vaccinated.</td>
</tr>
<tr>
<td></td>
<td><strong>SARS-CoV-2 vaccine and boosters</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Herpes zoster:</strong> RZV vaccine x2 doses if aged ≥50 years and CD4 count &gt;200 cells/mm³.</td>
</tr>
</tbody>
</table>

ACC/AHA, American College of Cardiology/American Heart Association; ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; HCV, hepatitis C virus; HPV, human papilloma virus; MSM, men who have sex with men; NAAT, nucleic acid amplification test; PWID, people who inject drugs; RZV, recombinant zoster vaccine; STI, sexually transmitted infection; Tdap, tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis. Republished from Thompson MA, et al. Primary care guidance for persons with HIV immunodeficiency virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America, *Clin Infect Dis*, 2021, Vol. 73, No. 11, pages e3572-e3605, by permission of Oxford University Press.
there are no data on the use of a long-acting injectable regimen in pregnancy. 57

Calcium and Iron Supplementation

Certain polyvalent cations such as calcium and iron can chelate to the INSTIs, thereby resulting in reduced absorption of the second-generation INSTIs. To prevent the potential interaction, bictegravir could be coadministered with either calcium or iron together with food. 59 Similarly, dolutegravir could be coadministered with either calcium or iron together with food, or administered 2 hours before or 6 hours after the supplements. 60

Prolongation of QTc Interval

Efavirenz, rilpivirine, and fostemsavir are associated with QTc interval prolongation. These ARVs should be avoided in persons taking other medications that can prolong the QTc. 6

Routine health care maintenance should be continued after initiating individuals on ART regimens. These include follow-up HIV RNA levels, CD4 count, screening for metabolic disorders (eg, weight measurement, cholesterol, glucose intolerance or diabetes, bone mineral density), and screening for infectious diseases (TABLE 4). 6,61-63

TABLE 4. ROUTINE HEALTH CARE MAINTENANCE FOR PERSONS LIVING WITH HIV}\(^{\text{a,b,c}}\) (continued)

<table>
<thead>
<tr>
<th>Other health care maintenance</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC and chemistry panel</td>
<td>Perform regularly and as needed based on underlying conditions and need for management of ART and other medications.</td>
</tr>
<tr>
<td>Patient education</td>
<td>Emphasize the importance of Undetectable = Untransmittable (U = U). Regularly educate patients about sexual risk reduction to prevent STIs and HIV transmission (if not virally suppressed).</td>
</tr>
</tbody>
</table>

Management of HIV of Treatment-Experienced Persons Living With HIV

Treatment-experienced people living with HIV who have consistently suppressed the RNA viral loads can potentially benefit from a change in their ART regimens, particularly for reasons of updating or simplifying their regimens to reduce pill burden, preventing long-term AEs, avoiding challenges with food requirements, or avoiding major drug interactions. The overarching goal of switching ART is to improve the person’s quality of life while maintaining virologic suppression. Furthermore, simplifying ART regimens can improve medication adherence as these individuals are living longer and may be taking more medications for other chronic health conditions. 64,65 Factors that need to be considered in the decision-making process when switching or simplifying an ART regimen may include the patient’s history of virologic failure and resistance mutations, even if they have suppressed viral loads at the time of consideration, the current medication list for potential drug-drug interactions, including over-the-counter and herbal medications, AEs, food requirements, and cost of the new regimen.

When switching regimens, it is essential to determine if the switch of ARVs is within the same class, between classes, and/or with different barriers to resistance. Because the INSTIs have become the preferred anchor ARVs, switching from older regimens that were either PI- or NNRTI-based to an INSTI-based regimen is clinically prudent. Complete INSTI-based regimens have been studied for ART switches, such as dolutegravir/ rilpivirine and cabotegravir/rilpivirine. 66-68 Patients are eligible to switch to the fixed-dose regimen of dolutegravir/rilpivirine when they have maintained virologic suppression (HIV RNA level <50 copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known resistance mutations to either dolutegravir or rilpivirine. 69 Similarly, patients can replace their current ART regimen with the first available injectable complete ART regimen cabotegravir/ rilpivirine if they are virologically suppressed on a stable ART regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. Cabotegravir/rilpivirine is FDA approved for adults and adolescents (≥12 years and weighing ≥35 kg) for intramuscular administration at the ventrogluteal site once a month or every 2
months. The medications need to be administered by a health care professional in a medical office or clinical setting.

Conversely, management of treatment-experienced people living with HIV could be complex if they experience treatment failure from their ART regimens, defined as having persistent detectable HIV RNA levels (viral loads >200 copies/mL) from at least 2 consecutive laboratory visits. In cases where highly treatment-experienced individuals may not achieve virologic suppression, HIV treatment should be continued to preserve the CD4 count and delay clinical progression. In addition to seeking expert advice to help assess and manage highly treatment-experienced individuals, an evaluation of the individual’s HIV RNA and CD4 count, history of ART regimens, medication adherence and tolerability, potential drug-drug and drug-food interactions, and prior and current drug-resistance (genotype and phenotype) results should be conducted. Virologic treatment failures can be attributed to a host of factors, such as suboptimal adherence to ART, acquisition of drug-resistant HIV, and drug-drug or drug-food interactions that may lead to low plasma ARV concentrations.

When individuals experience virologic failure, genotypic (including the integrase) and phenotypic drug resistance testing should be performed when the HIV RNA viral load is greater than 1000 copies/mL. HIV drug resistance testing is preferred when the patient is taking a failing regimen or within 4 weeks of treatment discontinuation to best detect previously selected resistance mutations. A coreceptor tropism test should be performed if a CCR5 inhibitor is considered as part of the salvage regimen. The ART regimen should be changed to an active regimen that has a high barrier to resistance if drug resistance mutations are identified. If there are no drug resistance mutations identified, then the detectable viral load is most likely a result of poor medication adherence or as a result of therapy self-discontinuation. The main goal is to determine an appropriate, effective regimen that will virologically suppress the individual’s HIV. An effective and fully suppressive regimen should comprise 2 or 3 active ARVs with at least 1 that has a high barrier to resistance, such as dolutegravir or boosted darunavir.

Based on the individual’s genotype and phenotype resistance reports, the ART regimen should be individualized to include a CCR5 antagonist (if the virus is R5 tropic), CD4 attachment, and/or post-attachment inhibitors. Postemavir, a CD4 cell attachment inhibitor, and/or ibalizumab, a monoclonal antibody and CD4 cell post-attachment inhibitor, are salvage therapy treatment options that could be combined with the person’s optimized background therapy to durably suppress the viral load.

The Role of the Pharmacist in HIV Management

Transgender and gender-diverse care for individuals living with HIV requires an empathic and interprofessional approach. Transgender people identify with a gender different from their assigned sex at birth. It is important to ask them for their preferred terminology, particularly for pronouns. Of note, transgender people continue to experience heightened stigma, discrimination, and psychosocial barriers that negatively impact their quality of life and care. In communities that provide health care services to transgender people, there should be a comprehensive approach to create an inclusive environment where staff and health care providers receive training on gender diversity and cultural sensitivity. The clinic and pharmacy settings should have educational and health promotional materials designed for transgender people to create a more welcoming and accepting atmosphere.

It is important to recognize that transgender people will be taking gender-affirming hormone treatments to achieve their desired gender characteristics. Transgender women may be taking feminizing hormone therapy (eg, estrogen and antiandrogen medications) that may increase their risk of thrombosis and cardiovascular disease. Clinical results, such as breast growth, decreased muscle mass, softer skin, decreased sexual desire, and fewer erections, will occur between 6 and 12 months. Clinical evaluations and laboratory monitoring of estradiol and testosterone should be performed every 3 months for the first year and once or twice yearly thereafter. Potassium monitoring should be included at the same laboratory intervals for those on spironolactone. Oral conjugated estrogen formulations (eg, ethinyl estradiol) are not recommended because of increased risk of thromboembolic events. Target goal level for testosterone is less than 50 ng/dL and between 100 and 200 pg/mL for estradiol.

Transgender men using testosterone as the main masculinizing hormone therapy should expect clinical results following 3 to 6 months after initiation; these may include cessation of menses, voice deepening, increased muscle mass, and increased acne and sexual desire. Testosterone, hemoglobin, and hematocrit should be obtained at baseline and measured every 3 months for the first year and 1 or 2 times every year thereafter. Goal testosterone level is the normal physiologic male range.

For transgender people living with HIV, ART regimens could potentially interact with hormone therapy. All boosted PIs may
decrease estradiol levels and increase testosterone levels. A few NNRTIs, specifically efavirenz, etravirine, and nevirapine, may reduce estradiol and testosterone levels.\textsuperscript{61} Cobicistat has a mixed effect on estradiol, but it may increase testosterone levels.\textsuperscript{6} Close monitoring and dose adjustments of the hormone medications may be necessary.

**STAR**

How can pharmacists assist with patient engagement and retention in care while providing inclusive care?

### Addressing Implicit Bias Affecting Patients Living With HIV

To meet the goals of the federal End the HIV Epidemic proposal, it is crucial to address the underlying social and structural issues of implicit bias that fuel stigma and discrimination among health care providers and within the health care system. Biases could negatively influence patient-provider relationships, treatment plans, adherence, quality of care, and patient outcomes, among other issues. One approach to address health care providers’ implicit biases and provide patient-centered HIV care is to require formal education about health equity in the pharmacy school curriculum or to receive workplace training to learn how implicit biases could influence one’s practice and behaviors.\textsuperscript{79,80} Promoting shared decision making via open communication about treatment options and potential benefits and risks of the different ART regimens also reinforces patient-centered care.\textsuperscript{81,82} Other approaches to address implicit racial bias is to practice cultural humility and avoid making assumptions about the patient’s life and preferences, hiring a racially and ethnically diverse health care workforce that reflects the communities served, and developing and following nondiscriminatory and access to care policies.\textsuperscript{80}

### Optimizing Care, Monitoring, and Adherence

In a collective effort to end the HIV epidemic in the United States, pharmacists should work with an interprofessional health care team to enhance patients’ adherence to their ART regimens and medical care. Pharmacists could maximize their patients’ engagement and retention in care by promoting a stigma-free, culturally appropriate, and patient-centered environment. Approaches include having staff of the same race, culture, or lifestyle as well as providing reading material in the pharmacy that reflects the culture of the local community.\textsuperscript{83,84} During the counseling session, pharmacists could also speak with patients about their medication allergies and intolerances. They should ask patients about all their current medications, including dietary and herbal supplements that may interact with ARVs.

Similarly, strategies to optimize patients’ medication adherence can include simplifying the ART regimens to a single-tablet regimen (if possible), discussing the long-acting injectable medications if patients are eligible, determining preferred ART regimens that are on insurance companies’ formularies (eg, Medicare, Medicaid), and working with manufacturers to access drug co-pay cards and patient assistance programs, which are available on companies’ websites.\textsuperscript{84} Furthermore, pharmacists can work with case managers to enroll patients in the AIDS Drug Assistance Plan (ADAP) and Ryan White programs so they could receive their ART regimens at little to no out-of-pocket cost. Other potential solutions to address poor treatment adherence include extending the pharmacy hours for patients to pick up their ART regimens after normal business hours, providing complimentary pillboxes, educating patients about how to leverage their mobile devices to increase adherence through mobile health platforms, scheduling monthly medication refill pickups, and offering complimentary pharmacy delivery service to their homes.

With respect to discussions about sexual health and gender identity topics, pharmacists should feel comfortable conversing with their patients about their sexual history, including types of activity, partners and practices, sexual exposure sites, past STIs, and prior PrEP use, in an open, nonjudgmental manner.\textsuperscript{85} It is essential to communicate with patients about their preferred pronouns and understand the potential drug-drug interactions between the ARVs and hormone medications for transgender care.\textsuperscript{77} More importantly, counseling and education should emphasize that long-term ART efficacy is dependent on suppression of viral replication. This is solely achieved by maintaining almost 100% adherence to their ART regimens. People living with HIV should understand that having an “undetectable” HIV RNA level equates to having an “untransmittable” disease to their sexual partners, which will both improve their health and prevent HIV transmission to others; this concept is commonly referred to as “U = U.”\textsuperscript{86-89} Additionally, pharmacists can explain that HIV treatment does not protect patients from acquiring other STIs such as chlamydia, gonorrhea, and syphilis; therefore, patients should be advised to use condoms and other forms of barrier contraception, if applicable.\textsuperscript{61}
Pharmacists will need to be aware of and educate people living with HIV about the potential long-term adverse drug toxicities associated with taking ART regimens. For older persons and those with renal insufficiency and osteoporosis, TDF should be used with caution or avoided, especially with pharmacokinetic enhancers (eg, cobicistat). As a potential alternative, fixed-dose combinations of abacavir or TAF could be considered as the NRTI backbone of the regimen for this population.

Cardiovascular and metabolic disorders, such as weight gain associated with ART regimens, remain concerns for people living with HIV. Pharmacists can determine whether or not the patient’s current ART regimen is contributing to weight gain. Recent evidence, such as the ADVANCE study, showed weight gain was noticeably associated with the second-generation INSTIs bictegravir and dolutegravir independent of the person’s sex and race (eg, female, Black, Hispanic). Among the NRTIs, greater weight gain is associated with TAF compared with TDF and abacavir. The magnitude of weight gain is greatest when patients are taking a combination of TAF with either bictegravir or dolutegravir; therefore, education about maintaining a healthy dietary lifestyle and consistent exercise regimen to stave off drug-induced weight gain is crucial. If the weight gain is intolerable for the individual or leads to cardiovascular complications, the TAF-based regimen should be switched to an alternative ART that could include TDF and an NNRTI, neither of which cause as much weight gain.

Conclusion
The era of HIV treatment and management is hopeful and exciting despite the current lack of an HIV cure. There are potent, simplified ART regimens available as either single-tablet or combination injectable regimens for people living with HIV. Newer ART regimens are being investigated to include at least 2 active agents from novel ARV drug classes. Furthermore, they are formulated to last longer in the body so that their administration schedules range between monthly and bimonthly. Additionally, longer-acting ART regimens dosed every 3 to 6 months are currently being studied. The main goal of these newer ARVs is to address the suboptimal medication adherence that continues to be a pervasive problem among those living with HIV. By adequately addressing these barriers and concerns as a critical component of HIV care, pharmacists can maximize adherence to ART regimens to achieve successful viral suppression, reduce the risk of transmission to others, and end the HIV epidemic in the United States and globally.

REFERENCES
7. Gottlieb GS, Nickle DC, Jensen MA, et al. HIV type 1 superinfection with a dual-tropic virus and
23. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treat...


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POSTTEST QUESTIONS

Please use the following case scenario describing a treatment-naïve individual who is newly diagnosed with HIV to answer questions 1 and 2.

SH is a 35-year-old man who has sex with men (pronouns: he, him, his) and was diagnosed with HIV during his hospital admission. He was admitted to the hospital when his friend found him unconscious. SH’s workup revealed the following:
• Cardiac enzymes negative; normal electrocardiogram
• Urine drug screen: positive for opiates and benzodiazepines

Physical exam: BP, 152/88 mm Hg; pulse, 70 bpm; BMI, 27 kg/m²
Allergy: No known drug allergies

Laboratory values (from hospital admission):

<table>
<thead>
<tr>
<th></th>
<th>HIV RNA VL</th>
<th>CD4+ count</th>
<th>CD4%</th>
<th>HIV genotype resistance assay</th>
<th>HLA-B*5701 allele</th>
<th>Scr</th>
<th>Urea nitrogen (BUN)</th>
<th>CrCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA VL</td>
<td>165,000 copies/mL (5.31 logs)</td>
<td>250 cells/mm³</td>
<td>16%</td>
<td>Pending</td>
<td>Negative</td>
<td>1.2 mg/dL</td>
<td>18 mg/dL</td>
<td>68 mL/min</td>
</tr>
<tr>
<td>CD4+ count</td>
<td></td>
<td></td>
<td></td>
<td>FPG 110 mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CD4%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>HIV genotype resistance assay</td>
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<tr>
<td>HLA-B*5701 allele</td>
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<td>Scr</td>
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<td>Urea nitrogen (BUN)</td>
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<tr>
<td>CrCl</td>
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</tbody>
</table>

1. Based on his underlying health conditions and recent laboratory results, which antiretroviral therapy (ART) regimen should SH be initiated on?
A. Bictegravir/emtricitabine/tenofovir alafenamide (TAF)
B. Dolutegravir/abacavir/lamivudine
C. Dolutegravir/lamivudine
D. Rilpivirine/emtricitabine/TAF

2. As part of routine HIV health care maintenance, which laboratory tests should SH receive at the 1-month follow-up visit with his primary care physician?
A. HIV RNA viral load and CD4
B. Complete blood count and chemistry panel
C. Hepatitis B virus DNA viral load
D. Nucleic acid amplification test screening for chlamydia and gonorrhea

Please use the following scenario of a treatment-experienced patient with viral resistance to answer questions 3 and 4.

BB, a 34-year-old transgender woman (pronouns: she, her, hers), is diagnosed with AIDS. She has developed multiple resistance mutations to previous ART regimens, and she continues to have persistent high HIV viral loads and low CD4+ counts. She was recently hospitalized for pneumocystis pneumonia. BB complains that she has no appetite and still experiences nausea whenever she eats.

Allergy: No known drug allergies

Laboratory values (from hospital admission):

<table>
<thead>
<tr>
<th></th>
<th>HIV RNA VL</th>
<th>Ca</th>
<th>CD4+ count</th>
<th>Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA VL</td>
<td>3,110,000 copies/mL (6.50 logs)</td>
<td>8.5 mg/dL</td>
<td>18 cells/mm³</td>
<td>78 mg/dL</td>
</tr>
<tr>
<td>CD4+ count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4%</td>
<td></td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV resistance assay</td>
<td>M184V, K65R, and K103N mutations (HIV virus is still sensitive to some NRTIs, NNRTIs, PIs, and INSTIs)</td>
<td>HAV Ab Reactive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-B*5701 allele</td>
<td>Negative</td>
<td>HBV surface Ab Reactive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scr</td>
<td>0.53 mg/dL</td>
<td>HBV Ag Nonreactive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea nitrogen (BUN)</td>
<td>6 mg/dL</td>
<td>HCV Ag/Ab Nonreactive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl</td>
<td>138 mL/min</td>
<td>ALT 23 U/L</td>
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</tr>
<tr>
<td>Na</td>
<td>136 mmol/L</td>
<td>AST 43 U/L</td>
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</tr>
<tr>
<td>K</td>
<td>4.7 mmol/L</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Medications
• Efavirenz/emtricitabine/tenofovir disoproxil fumarate (TDF) 1 tablet PO daily
• Bactrim DS 1 tablet PO daily
• Azithromycin 600 mg 2 tablets PO every week
• Estradiol 2 mg PO BID
• Spironolactone 100 mg PO QAM
• Ensure oral liquid PO BID-TID

Continued on next page
POSTTEST QUESTIONS (continued)

3. Based on BB’s HIV resistance and lab results, efavirenz/emtricitabine/TDF is no longer active against the virus because of the M184V and K103N mutations. Which ART regimen would be most appropriate and effective for BB to switch to?
   A. Dolutegravir/lamivudine
   B. Darunavir/cobicistat/emtricitabine/TAF
   C. Dolutegravir/rilpivirine
   D. Rilpivirine/emtricitabine/TAF

   BB returns to the clinic 1 year later for continued follow-up HIV care. She has been virologically suppressed (HIV RNA level <50 copies/mL) on the ART regimen selected for her 1 year ago. Her CD4 count has also improved to 359 cells/mm³.

4. BB has seen an advertisement for cabotegravir/rilpivirine on social media and expresses interest in the injectable medication because she does not want to take a daily pill. She wants to know if she can switch therapies. Which would be the most appropriate response for BB?
   A. She should remain on the tablet formulation because it has kept her virologically suppressed and improved her CD4 count.
   B. She cannot switch to the injectable formulation because of the potential significant drug-drug interaction between omeprazole and rilpivirine.
   C. She can switch to the injectable formulation since she has maintained virologic suppression and her CD4 count has improved.
   D. She can switch to the injectable formulation but will need a nucleoside reverse transcriptase inhibitor (NRTI) backbone to make the regimen complete and fully active.

   Please use the following scenario to answer question 5.

DT, a 56-year-old cisgender woman (pronouns: she, her, hers), has been virally suppressed on bictegravir/emtricitabine/TAF for 1 year. She is unhappy with her weight gain of approximately 20 pounds over the past year during the COVID-19 pandemic.

Physical exam: BP, 146/72 mm Hg; pulse, 82 bpm; weight, 190 lb (86.2 kg); BMI, 34 kg/m²

Allergy: No known drug allergies

Past medical history
- Hypertension
- Type 2 diabetes
- Recently diagnosed with hyperlipidemia

Laboratory values
- HIV RNA VL: <50 copies/mL
- CD4+ count: 530 cells/mm³
- CD4%: 35%
- FPG: 93 mg/dL
- HbA1c: 7.0%
- Scr: 1.0 mg/dL
- CrCl: 86 mL/min

Medications
- Bictegravir/emtricitabine/TAF 1 tablet PO daily
- Lisinopril 20 mg 1 tablet PO daily
- Metformin 1000 mg PO BID

5. DT wants to know if there is an alternative ART regimen that she can take without risk of weight gain. Which ART regimen can be recommended for DT that would have the least weight gain as an adverse effect?
   A. Dolutegravir/lamivudine
   B. Dolutegravir/abacavir/lamivudine
   C. Darunavir/cobicistat/emtricitabine/TAF
   D. Darunavir/cobicistat + emtricitabine/TDF

6. A 36-year-old woman is newly diagnosed with HIV with a CD4+ count of less than 200 cells/mm³ and viral load greater than 130,000 copies/mL. Her provider wants to initiate her on an ART regimen comprised of dolutegravir/abacavir/lamivudine. What test needs to be performed before starting the patient on this therapy?
   A. CCR5 tropism assay
   B. Glucose-6-phosphate dehydrogenase
   C. HLA-B*5701 allele
   D. No test is required.
POSTTEST QUESTIONS (continued)

7. Which antiretroviral class has been strongly linked to an increase in truncal fat and treatment-emergent obesity?
   A. Integrase strand transfer inhibitors
   B. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
   C. NRTIs
   D. Protease inhibitors

8. Which entry inhibitor requires a tropism assay test before treatment initiation?
   A. Enfuvirtide
   B. Fostemsavir
   C. Ibalizumab
   D. Maraviroc

9. Which antiretroviral class has the least impact or minimal drug-drug interaction with gender-affirming hormone therapy such as estradiol and testosterone?
   A. NRTIs
   B. Unboosted integrase strand transfer inhibitors
   C. NNRTIs
   D. Unboosted protease inhibitors

10. Which is part of promoting a comprehensive, inclusive care environment for transgender people living with HIV?
    A. Asking their preferred terminology, especially for pronouns
    B. Training staff and providers about gender diversity and cultural sensitivity only when issues arise
    C. Providing the same health promotional materials as other patients with HIV so they do not feel isolated
    D. Promoting divided counseling sections for transgender and cisgender people in the pharmacy
Targeting the Clinical Course of Hypertrophic Cardiomyopathy: Keeping a Beat on New and Emerging Therapies

Introduction

Since hypertrophic cardiomyopathy (HCM) was identified, intensive study has led to progressively greater understanding of its etiology and spectrum of disease. Until recently, goals of treatment have been limited to minimizing symptoms and complications, but over the past decade, significant advancements from translational research have led to exciting therapeutics that target the underlying disease pathophysiology. The underlying causes of HCM will be examined, current and emerging therapies will be highlighted, and key opportunities for pharmacist involvement in the management of patients with HCM will be discussed.

Hypertrophic Cardiomyopathy Overview

Definition and Etiology

HCM is a progressive cardiac condition most commonly resulting from 1 or more inherited genetic mutations related to the myosin sarcomere protein structure that causes hyperactive myosin actin cross-linking leading to enhanced myocardial contraction ultimately causing ventricular hypertrophy.1-3 By definition, it differs from other forms of left ventricular hypertrophy (LVH) that result from secondary causes such as hypertension or aortic stenosis, in that secondary causes are often absent.2 LVH from secondary causes generally results in concentric or symmetric hypertrophy and tends to have more limited wall thickness enhancement, whereas HCM often results in asymmetric hypertrophy and the affected wall thickness is often significantly larger than LVH resulting from a secondary cause.2,4 Although clin-
ical manifestations associated with HCM share similarities with other forms of cardiomyopathy, management can differ due to the underlying pathophysiology and hemodynamic effects.

**Genetic Mutations**

Over 14 genes and more than 1400 mutations that encode portions of the myosin sarcomere have been identified that can lead to HCM.\(^1\) The majority of patients with HCM inherit a single autosomal dominant gene mutation, although some patients will inherit more than 1 mutation that may be associated with more severe forms of HCM.\(^1\) While approximately 60% of patients with HCM will express a genetic variant of known significance, some patients may display the HCM phenotype without a clear genetic cause.\(^1\) Conversely, some patients may be genotype positive but have yet to develop the HCM phenotype or clinical manifestations of the disease. These patients are at an elevated risk of developing clinical HCM throughout their lifetime and should be regularly evaluated for manifestations of the disease.\(^2\) While specific mutations lead to varied functionality of different portions of the sarcomere, ultimately, they all lead to development of hypertrophied myocytes, disorganized cellular structure, and interstitial fibrosis that causes ventricular hypercontractility and diastolic dysfunction.\(^2\)

**Epidemiology**

HCM is generally first identified in either very young patients or those in the mid-decades of life.\(^6\) Prior to 2000, the average age of diagnosis was 40 ± 14 years; however, in the past 20 years, the average age has increased to 51 ± 16 years.\(^6\) Previously, HCM was likely underreported due to varying definitions of the disease, the availability of genetic testing, and differences in genotype versus phenotype positivity. Past evidence estimated a prevalence of approximately 1:500 (0.16%-0.23%), but more recent data suggest it may be more than double those figures, with a prevalence rate closer to 1:200 (0.5%).\(^3\) Based on claims data analyzed by Maron et al in 2016, approximately 100,000 patients in the United States carried a diagnosis of HCM.\(^9\) While the question of true prevalence continues to be answered, it is clear the number of patients with HCM has increased over the past several decades.

A stark increase of HCM diagnoses since 2000 has been
observed. Before 2000, there were 35 diagnoses of HCM each year compared with 272 annually from 2000 to 2010, and 357 per year after 2010. This trend likely stems from increased use of electrocardiography and echocardiography, and increased guideline concordant genetic testing of family members with known HCM over this time period.

While HCM epidemiology and the disease course has been poorly characterized in the general patient population, this is especially true in minority populations. Eberly and colleagues reported that of over 2400 patients with known HCM in the United States between 1989 and 2018, only 8.3% were Black compared with 91.7% who were White. Black patients tended to be younger, with a higher prevalence of advanced heart failure (HF) at presentation, lower rates of sarcomere mutations with known significance, and overall lower rates of genetic testing. Of Black patients who did have genetic testing, they had higher rates of genetic variants of unknown significance. Black patients also receive lower rates of invasive treatment options shown to improve the clinical status compared with White patients. These racial biases continue to be identified in the study of novel treatment options, and further study is sorely needed to address these health care disparities in patients with HCM.

Pathophysiology and Clinical Types of HCM
As previously discussed, HCM is characterized by asymmetric LVH and progressive fibrosis (FIGURE 12). The changes that occur as HCM advances ultimately lead to diastolic dysfunction causing initial hemodynamic changes such as an elevated LV end diastolic pressure from impaired relaxation, increased preload that can cause decreased coronary artery blood flow, and increased myocardial oxygen demand causing angina and dyspnea. Furthermore, as a result of asymmetric LVH, anatomical changes to the mitral valve, such as elongated valve leaflets, enlargement of valve leaflets, and papillary displacement, can begin to limit blood flow through the LV outflow tract (LVOT), which is the area directly preceding the aortic valve (FIGURE 12). These mitral valve changes combined with the hypertrophy itself allow the leaflets to come in closer proximity to or in contact with the septal wall during systole, leading to obstruction of blood flow from the LV through the LVOT. The severity of LVOT obstruction is evaluated noninvasively through echocardiography by measuring the blood flow velocity through the LVOT to calculate an LVOT gradient both at rest and during provocation with either exercise or pharmacologic intervention.

Approximately 25% to 30% of patients with HCM have nonobstructive disease, where the peak LVOT gradient is less than 30 mm Hg at baseline and during provocation. The majority of patients will develop obstructive HCM (oHCM). Two forms of oHCM exist and can be differentiated based on an elevated LVOT gradient at rest (basal obstructive: resting gradient >30 mm Hg) or only upon provocation (labile obstructive: resting gradient <30 mm Hg but increases to >30 mm Hg during provocation).

Stages of HCM can be described based on several anatomical and clinical features displayed by a patient (TABLE 1). Some patients, especially younger patients, may have a genetic variant of known significance, but have yet to develop any clinical manifestations or anatomical features of HCM. These patients should be followed regularly for routine clinical assessment and monitoring according to the guideline recommendations discussed below. In contrast, patients with advanced HCM can develop progressive adverse LV remodeling, causing significant reduction in LV ejection fraction (EF) leading to HF with reduced EF in the late stages of the disease. These patients with advanced disease tend to have an overall poor prognosis, with a reported mortality rate of 11% per year.

![FIGURE 12](https://example.com)

**TABLE 1. STAGING AND CLINICAL CHARACTERISTICS OF HYPERTROPHIC CARDIOMYOPATHY**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Genetic mutation</th>
<th>Symptoms</th>
<th>LGE</th>
<th>LVEF</th>
<th>LVOT obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (subclinical)</td>
<td>Present</td>
<td>Absent</td>
<td>N/A</td>
<td>Normal</td>
<td>N/A</td>
</tr>
<tr>
<td>2 (classic)</td>
<td>Present</td>
<td>Present</td>
<td>&lt;5% fibrosis</td>
<td>&gt;65%</td>
<td>70% of patients with obstruction at rest or on provocation*</td>
</tr>
<tr>
<td>3 (adverse remodeling)</td>
<td>Present</td>
<td>Present</td>
<td>10%-15% fibrosis</td>
<td>50%-65%</td>
<td>May be absent</td>
</tr>
<tr>
<td>4 (overt dysfunction)</td>
<td>Present</td>
<td>Severe</td>
<td>&gt;25% fibrosis</td>
<td>&lt;50%</td>
<td></td>
</tr>
</tbody>
</table>

LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract.

*Through Valsalva maneuver.
causes often display a concentric hypertrophy and the wall thickness is routinely less than 20 mm, whereas those with HCM will typically have asymmetrical LVH, most commonly along the interventricular septum, that is thicker than LVH seen from a secondary cause (FIGURE 12). When cardiac magnetic resonance imaging is used, gadolinium (a contrast agent), distributes into the tissue and improves the clarity and accuracy of images obtained. Due to the fibrotic changes that occur in the areas of hypertrophy associated with HCM, late gadolinium enhancement (LGE) of myocardial tissue, due to slower distribution of gadolinium, can assist with determining the overall quantity of fibrosis in comparison with the mass of the LV. The degree of LGE can provide prognostic information related to disease progression and development of complications over time (TABLE 1).

HCM carries a wide spectrum of symptoms and symptom severity, ranging from completely asymptomatic to severe limiting symptoms of HF requiring invasive management strategies. Classic manifestations of HCM resemble those of patients with HF such as dyspnea on exertion, fatigue, presyncope or syncope, angina, and/or palpitations. Nocturnal dyspnea and orthopnea are less likely to be observed in patients with HCM unless the disease has progressed to advanced stages and LVEF is lower than normal (TABLE 1). Similar to patients with HF, patients with HCM should have their symptoms objectively assessed based on the New York Heart Association (NYHA) classification system to determine their functional capacity.

Screening and Genetic Testing
In patients with a known pathogenic or those likely to have a pathogenic genetic variant but are otherwise phenotype negative, regular clinic assessment should be performed to identify the development of symptoms. Periodic electrocardiogram and echocardiography should be performed every 3 to 5 years in adults or every 1 to 3 years in children and adolescents.

In patients with suspected HCM or those with a family history of HCM, downstream genetic testing for known pathologic or likely pathogenic variants should be performed. If a known or likely pathogenetic variant is identified, first-degree relatives should be genetically screened for the presence of genetic variants associated with HCM. If a known pathogenic or likely pathogenetic variant is identified, those individuals should adhere to the screening recommendations as described above.

Prognosis
The prognosis for patients with HCM is highly variable and based on a range of factors. Overall, patients with HCM treated according to current recommendations can expect a mostly normal quality of life without a significant reduction in life expectancy. Investigation into variables associated with changes in prognosis continues; however, a subset of patients diagnosed with HCM have been identified to be at heightened risk of complications. Some research has suggested patients with more than 1 genetic variant may have more severe forms of HCM, lower survival, and higher rates of sudden cardiac death (SCD). Additionally, patients with pathogenic or likely pathogenic mutations may have double the risk of developing adverse cardiac events such as arrhythmias or overt symptoms of HF. Younger patients diagnosed with HCM may also be at an elevated risk of complications such as arrhythmia and sudden cardiac death compared with patients who are diagnosed later in life. Lastly, patients with severe coronary artery disease (CAD) and HCM have upwards of a 40% higher risk of cardiac death compared with those without CAD. Treatment of CAD should be managed according to current recommendations, although it is unknown whether this modifies the risk of death specifically in patients with HCM. All patients with HCM should adhere to a heart-healthy diet to maintain or achieve a healthy weight, as obesity can contribute to the development of HCM symptoms and LVOT obstruction. Most patients with HCM should participate in mild-moderate intensity exercise to improve functional status and overall well-being, although more intensive activity may be associated with adverse cardiac events and should only be undertaken after careful risk-benefit evaluation with their HCM provider.

STAR
Which pharmacologic treatments are FDA approved and which therapies are in the pipeline that address potential unmet needs for the treatment of HCM?

Treatment Strategies: Current Approaches and Emerging Agents

Nonpharmacologic Treatment of HCM
Implantable Cardioverter-Defibrillator for SCD Prevention
Screening patients for SCD risk factors at the time of HCM diagnosis and routinely every 1 to 2 years is a pivotal step in preventing morbidity and mortality. Major risk factors for SCD include a personal history of cardiac arrest or sustained ventricular arrhythmia, personal history of cardiac-related syncope, family history of HCM-related SCD, cardiac arrest or sustained ventricular arrhythmia, LV wall thickness of more than 30...
mm, an LVEF of less than 50%, or an LV apical aneurysm. In patients with at least 1 of these high-risk features, an implantable cardioverter-defibrillator (ICD) is recommended according to current guidelines. For patients who do not otherwise meet the above criteria but are still felt to be high risk according to shared decision making, LGE of greater than or equal to 15% may be used to further guide the risk-benefit determination for an ICD. While various ICD devices are available, the decision for each type is beyond the scope of this activity, but more detailed information can be found in section 7.3 of the current American Heart Association/American College of Cardiology Guideline for Hypertrophic Cardiomyopathy.

**Surgical Intervention**

Invasive septal reduction therapies (SRTs) are reserved for patients with oHCM who remain symptomatic despite the use of first-line pharmacologic treatment options and have either resting or provoked LVOT gradient greater than or equal to 50 mm Hg. Septal myectomy, where a portion of the obstructing myocardium is excised, has been shown to significantly reduce symptoms of oHCM. This form of SRT is the most invasive intervention and may be preferred in patients who have a concomitant indication for cardiac surgery such as aortic stenosis or multivessel CAD. Alternatively, alcohol septal ablation can be used for those patients with contraindications to surgery. Alcohol septal ablation requires the insertion of a catheter into the coronary artery supplying blood to the area of hypertrophy. Once the catheter is delivered to the appropriate artery, ethanol is injected, which results in a localized area of infarction. Although there is some acute improvement in LVOT gradient, complete cardiac remodeling can take several weeks before definitive LVOT gradient improvement is complete. While some limited literature suggests a possible mortality benefit from SRT interventions, they are not recommended for purely survival benefit and remain indicated only in those patients with treatment-refractory, symptomatic oHCM.

**Current Pharmacologic Options for Treatment of HCM**

**β-blockers**

β-blockers have historically been the first-line treatment option for patients with dyspnea or angina due to HCM. β-blockers exert their effects by reducing heart rate and increasing relaxation time during diastole, which reduces LV filling pressure and decreases myocardial oxygen requirements. They have also been shown to mildly reduce LVOT gradients in patients with oHCM. As excessive arterial dilation can effectively worsen LVOT obstruction, β-blockers that have higher selectivity for β-1 blockade and do not impart additional α-1 antagonism are preferred in most patients. In both nonobstructive and oHCM, β-blockers carry a class 1 recommendation, but most evidence comes from small observational studies. Similar to patients treated with β-blockers for other forms of cardiomyopathy, low doses should be used initially and slowly titrated over several weeks to prevent acute decompensation and hypotension, which can be a medical emergency in patients with oHCM.

**Calcium channel blockers**

Calcium channel blockers (CCBs) are a suitable alternative to β-blockers in patients with HCM. Similar caution should be implemented in the choice of CCB therapies to prevent excessive vasodilation; thus, non-dihydropyridine (DHP) CCBs, such as diltiazem and verapamil, are preferred over DHP CCBs. As non-DHP CCBs still carry negative inotropic effects and at higher doses can exert vasodilating properties, clinicians should carefully monitor patients for worsening obstructive symptoms as therapy is initiated and titrated, particularly in those with known oHCM. Again, similar to β-blocker therapy, low doses should be used for initiation and slowly titrated until patients achieve an improvement in their symptoms. The use of combined β-blocker and non-DHP CCB therapy may be necessary in some carefully selected patients but should generally be avoided as first-line treatment in patients with oHCM due to potential for synergistic vasodilation and the increased risk of clinically relevant bradycardia and atioventricular blockade. In patients with more severe LVOT gradients (ie, >80 mm Hg) or those with more severe symptoms related to oHCM, verapamil has resulted in serious adverse effects (AEs), including death; thus, alternative therapies are preferred.

**Additional Therapies**

Disopyramide can significantly improve symptoms related to oHCM by reducing contractility and myocardial oxygen demand. Current guidelines recommend its use in patients with oHCM who remain symptomatic despite maximal therapy with either β-blockers or non-DHP CCB therapy, although these patients are also likely to be candidates for invasive SRT approaches, which may lead to longer-term improvements. Disopyramide also remains a viable option for patients who elect not to proceed with or are not candidates for SRT. Although disopyramide decreases myocardial excitability and ventricular
conduction, it can enhance atrioventricular node conduction.\textsuperscript{4,27} This can pose a hazard in patients at risk of developing or with known atrial fibrillation who are unable to maintain treatment with a rate-controlling pharmacologic agent. Additionally, disopyramide is a major substrate of the CYP3A4 system and is renally cleared. Potential drug-drug interactions (DDIs) and renal dysfunction may require dose adjustment or discontinuation to prevent drug accumulation that can lead to the development of systolic dysfunction and acute decompensation. Disopyramide commonly causes anticholinergic AEs, occurring in 20\% to 67\%.

<table>
<thead>
<tr>
<th>TABLE 2. PHARMACOLOGIC TREATMENT OPTIONS FOR HCM\textsuperscript{4,27-30}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacologic class</td>
</tr>
<tr>
<td>Symptomatic nonobstructive HCM with preserved LVEF</td>
</tr>
</tbody>
</table>
| β-blockers | 1 | Reduces heart rate, improves diastolic dysfunction, reduction in LV filling pressure, reduction in myocardial oxygen consumption | • Titrate to dose providing effective symptom reduction  
• Monitor for AV block and bradycardia |
| Non-DHP CCB | 1 | • β-blockers are the preferred first-line therapy  
• Use non-vasodilating β-blockers (metoprolol, bisoprolol, nadolol, propranolol, atenolol) |
| Loop diuretics | 2a | Reduces preload and symptoms of dyspnea and edema | Use minimal effective dose to prevent volume depletion and hypotension, which may precipitate obstruction |
| Obstructive HCM with preserved LVEF |
| β-blockers | 1 | Reduces heart rate, improves diastolic function, reduction in LV filling pressure, reduction in myocardial oxygen consumption | • Combination use with β-blockers is not supported by evidence.  
• In cases of severe symptoms (dyspnea at rest, hypotension, or high resting gradients) verapamil may be harmful (class 3 recommendation: harm). |
| Non-DHP CCB | 1 | • In cases of severe symptoms (dyspnea at rest, hypotension, or high resting gradients) verapamil may be harmful (class 3 recommendation: harm). |
| Disopyramide | 1 | Reduces myocardial conduction and contractility, thereby improving diastolic dysfunction-related symptoms | • If anticholinergic symptoms limit use of disopyramide, pyridostigmine may reduce severity of adverse effects  
• Requires renal dose adjustment  
• Review for potentially serious DDIs |
| Loop diuretics | 2b | Only to be used in patients who remain refractory to first-line treatment options and have persistent symptoms of volume overload | Decreased preload from higher than required dosing may exacerbate LVOT obstruction, leading to critical hypotension |
| Recently approved and potential therapies for obstructive HCM |
| Mavacamten | FDA approved April 2022 | Cardiac myosin inhibitor that reduces contractility, improves diastolic function, and reduces myocardial oxygen demand | • Currently approved for oHCM only  
• Indicated in patients with class 2-3 symptoms  
• REMS requirements for prescribing and dispensing |
| Aficamten (CK-274) | Currently in a phase 2 and 3 study | Second-generation cardiac myosin inhibitor that reduces contractility, improves diastolic function, and reduces myocardial oxygen demand | • Shorter half-life  
• Potentially fewer DDIs from reduced CYP enzyme metabolism  
• Ongoing studies include:  
° SEQUOIA-HCM  
° REDWOOD-HCM |

AV, atrioventricular; CCB, calcium channel blocker; COR, class of recommendation; DDI, drug-drug interaction; DHP, dihydropyridine; HCM, hypertrophic cardiomyopathy; LV, left ventricle; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; oHCM, obstructive hypertrophic cardiomyopathy; REMS, Risk Evaluation and Mitigation Strategy.
of patients who receive it. The addition of pyridostigmine may reduce the occurrence and severity of these symptoms without affecting the cardiac effects of disopyramide.\(^{34}\)

Patients with HCM, particularly those with oHCM, are sensitive to changes in both intravascular volume and venous and arterial tone. The use of diuretics may be required in patients with HCM for the management of symptoms; however, judicious use should be employed to prevent the development of acute hypovolemia and hypotension, which may also lead to worsening LVOT obstruction.\(^{3,14,31}\)

While angiotensin-converting enzyme inhibitors and angiotensin 2 receptor blockers have established safety and efficacy in patients with HF with reduced EF, including those with stage 4 HCM, their effects have not been well studied in patients with earlier stages of HCM. These vasodilating therapies, as well as hydralazine and DHP-CCBs may be used cautiously in patients with nonobstructive HCM to manage concomitant hypertension or other indications, but these agents pose risks in patients who develop oHCM.\(^{3,14,31}\) Digoxin is another common cardiac medication used in patients with atrial fibrillation that warrants scrutiny in patients with HCM due to its positive inotropic effects, which can worsen symptoms of HCM.\(^{4}\) Clinicians, including pharmacists, should carefully review a patient’s baseline medication therapy at the time of HCM diagnosis and throughout their disease course for the possible withdrawal of these therapies to prevent acute decompensation and worsening of LVOT obstruction.\(^{3,14}\)

Recently Approved Therapy

Mavacamten (Camzyos)

Mavacamten was approved by the FDA in April 2022 to improve functional capacity and symptoms in adult patients with NYHA class II to III oHCM.\(^{35}\) Mavacamten is a first-generation, reversible, selective allosteric inhibitor of cardiac myosin ATPase, which reduces the myosin-actin cross-bridging during systole and diastole.\(^{3,14,31}\) Through this novel mechanism of action, mavacamten reduces myocardial contraction and oxygen demand and improves relaxation during diastole.\(^{3,14,31}\) Mavacamten is primarily metabolized through CYP2C19 and CYP3A4 and has an extensive half-life of 6 to 9 days in most patients, but can reach up to 23 days.\(^{28,35}\) Inhibitors and inducers of these CYP pathways can lead to significant alterations in mavacamten drug concentrations.\(^{35}\) Additionally, mavacamten induces CYP3A4, CYP2C9, and CYP2C19 enzymes, and, as a result, may reduce serum plasma concentrations of drugs metabolized by these pathways. Mavacamten has not been studied in patients with moderate to severe renal dysfunction (estimated glomerular filtration rate <30 mL/min/1.73m\(^2\)) or in those with hepatic dysfunction; thus, it should be used with extreme caution.\(^{35}\)

In one of its initial phase 2 clinical trials, PIONEER-HCM, mavacamten was studied in an open-label manner in 21 patients with symptomatic oHCM.\(^{37}\) Eleven patients received treatment with mavacamten to determine effects on LVOT gradient and evaluate pharmacokinetics at doses of 10 or 15 mg daily depending on weight (cohort A), while 10 patients received mavacamten at lower doses of 2 to 5 mg daily (cohort B) and were used to further analyze pharmacodynamic effects at lower doses. At baseline, patients in both treatment groups were required to discontinue CCB and disopyramide therapy 2 weeks before receiving mavacamten; patients in cohort A also had to discontinue β-blockers, whereas patients in cohort B were able to continue previously initiated β-blocker therapy. Over the 12-week study period, patients in both treatment groups displayed a significant reduction in the primary outcome of post-exercise LVOT gradient. The average change in LVOT gradient was -89.5 mm Hg (95% CI, -138.3 to -40.7) in cohort A, whereas the mean change in cohort B was -25.0 (95% CI, -47.1 to -3.0). Additional secondary end points such as resting LVOT gradient, NYHA classification, Kansas City Cardiomyopathy Questionnaire, and N-terminal pro b-type natriuretic peptide (NT-proBNP) levels were also shown to improve with treatment in both groups by week 12 of therapy.\(^{37}\)

After the promising results observed in the PIONEER-HCM trial, the phase 3, multicenter, double-blinded, placebo-controlled study of mavacamten (EXPLORER-HCM) was conducted.\(^{29,38}\) More than 250 symptomatic adult patients with oHCM were enrolled. Patients were required to have NYHA class II to III symptoms, an initial LVEF of greater than or equal to 55%, and an LVOT gradient of at least 50 mm Hg after provocation with Valsalva maneuver or exercise. Patients with a recent history of syncope or sustained ventricular tachycardia (within 6 months), a QTc greater than 500 msec (based on Fridericia formula), or atrial fibrillation not on anticoagulation or were not receiving sufficient rate control were excluded. Additionally, patients who received SRT within 6 months of screening were also excluded. All patients were allowed to continue baseline β-blocker and/or CCB therapy but patients were not allowed to receive disopyramide concomitantly due to the potential for additive negative inotropic effects. Dosing of mavacamten was strictly regulated to prevent AEs.\(^{29,38}\) All patients were initiated at a dose of 5 mg daily. An echocardiogram was required to ensure LVEF was maintained at or above 50% at weeks 4, 

6, 12, 18, 22, 26, and 30 at the end of treatment. If the LVEF was greater than or equal to 50%, the drug concentration was less than 350 ng/mL, and the LVOT gradient after provocation remained greater than or equal to 30 mm Hg at weeks 8 and 14, the dose could be titrated from either 5 to 10 mg daily (week 8) or 10 to 15 mg daily (week 14). Additional safety assessment and clinical criteria were reviewed at weeks 4, 6, 8, 10, and 14 for possible down-titration or temporary discontinuation. If drug concentrations were between 700 and 1000 ng/mL at these time points, the dose of mavaCamten was decreased to the next available dosing tier. If patients were receiving a dose of 2.5 mg daily and the drug concentration exceeded 700 ng/mL, they were switched to receive placebo. Temporary discontinuation of mavaCamten was required if mavaCamten concentration exceeded 1000 ng/mL, the LVEF decreased to less than 50%, or the QTc was noted to increase by greater than or equal to 15% or exceeded 520 msec (>550 if patients had a wide QRS complex of ≥120 msec). During temporary discontinuation, the study drug was stopped, and patients would return for assessment 2 to 4 weeks after discontinuation. If criteria for temporary discontinuation resolved, patients were reinitiated on the study drug at the next lowest dose 2 to 4 weeks after reassessment. Simulated alerts were also created for those receiving placebo to maintain blinding throughout the study. The primary study outcome was a composite of peak oxygen consumption (pVO₂) increase of greater than or equal to 1.5 mL/kg/min, which is used as an objective surrogate marker for exercise capacity, and at least 1 class reduction based on the NYHA scale. Alternatively, patients could display a pVO₂ improvement of greater than or equal to 3 mL/kg/min with no worsening in NYHA class to meet the primary end point. 29,38

After screening, 123 patients were randomized to mavaCamten and 128 patients to placebo. 29,38 At baseline, approximately 75% of patients in each group were treated with β-blocker therapy and 20% of patients in the mavaCamten group were treated with CCB compared with 13% in the placebo group. The majority of patients in each group had NYHA class 2 symptoms at enrollment (>70%). The mean LVOT gradient at rest was approximately 50 mm Hg and after Valsalva was approximately 73 mm Hg in each group. At the end of treatment completion, 37% of patients treated with mavaCamten achieved the primary outcome compared with 17% in the placebo-treated patients (mean difference, 19.4%; 95% CI, 8.7-30.1). Additionally, 20% of patients treated with mavaCamten achieved both an increase in pVO₂ of greater than or equal to 3.0 mL/kg/min and an improvement in NYHA of at least 1 class compared with 8% of patients treated with placebo (mean difference, 12.5%; 95% CI, 4.0-21.0). A complete response documented by reduction in LVOT gradient of less than 30 mm Hg and achieving NYHA class 1 symptoms was seen in 27% of mavaCamten-treated patients compared with just 0.79% of placebo-treated patients (mean difference, 26.6; 95% CI, 18.3-34.8). All secondary end points displayed statistically significant improvements in patients treated with mavaCamten compared with placebo. Overall, while treatment-emergent AEs were reported in a high proportion of patients in each group, the rates of serious AEs were similar between the mavaCamten and placebo groups (8% vs 9%, respectively). There were more mavaCamten-treated patients who developed an LVEF of less than 50% throughout the study period (5.7% vs 1.5%), although all patients were able to resume treatment with a lower dose before the end of the treatment phase. Lastly, during the entire study period, no patients exceeded a plasma concentration of more than 1000 ng/mL. 29,38

Based on the results seen in the EXPLORER-HCM trial, mavaCamten demonstrated impressive improvements in both objective measures of oHCM as well as symptoms and quality of life. 29,38 Even in the presence of first-line treatment options, mavaCamten provided additive benefit to those with oHCM. Although the overall duration of the EXPLORER-HCM trial may be considered relatively short for this chronic progressive disease and the overall safety analysis was underpowered due to the small incidence of serious cardiac AEs, the ongoing MAVA-LTE trial is providing a longer-term analysis of the effects of mavaCamten. 39,40 MAVA-LTE is an extension study of patients enrolled in the EXPLORER-HCM study. Initial results presented in April 2022 suggest a sustained reduction in LVOT gradients and improvements in both cardiac biomarkers as well as NYHA class, with a majority achieving class 1 symptoms. 39,40 The full results will provide a clearer picture regarding efficacy and safety of this novel therapy over several years. Whereas the EXPLORER-HCM trial only included patients with less severe symptoms of oHCM, the VALOR-HCM trial specifically assessed the efficacy of mavaCamten in a more advanced oHCM patient population. VALOR-HCM enrolled patients who, despite appropriate background therapy, continued to have severe symptoms. 41,42 These patients had progressive disease and were candidates for SRT intervention based on current guideline criteria. The primary outcome of VALOR-HCM measured the number of patients who decided to undergo SRT or remained guideline eligible for SRT after 16 weeks of treatment with mavaCamten or matching placebo.
Overall, 112 patients were randomized to either mavacamten (n = 56) or matching placebo (n = 56). In contrast to the EXPLORER-HCM trial, patients were allowed to continue therapy with disopyramide and patients with class IV symptoms could also be enrolled. Additionally, dose titrations occurred at weeks 8 and 12 compared with weeks 8 and 14 in EXPLORER-HCM. No pharmacokinetic drug levels were used to guide dose adjustments and were based purely on echocardiogram findings (LVEF and LVOT gradients). At week 16, 17.9% of mavacamten-treated patients were eligible for or decided to proceed with SRT compared with 76.8% of patients receiving placebo (P ≤0.001). This difference was primarily driven by a reduction in the number of patients who were guideline eligible, where just 14.3% of patients receiving mavacamten were eligible versus 69.6% of patients receiving placebo. Similar to EXPLORER-HCM, change in post-exercise LVOT gradient, NYHA and Kansas City Cardiomyopathy Questionnaire status, NT-proBNP, and cardiac troponin were significantly improved with mavacamten. There was a small but significant reduction in LVEF in patients who received mavacamten compared with placebo (-4.0%; 95% CI, -5.5% to -2.5%), and 2 patients treated with mavacamten developed an LVEF less than 50%, although they were able to resume treatment at a reduced dose after temporary discontinuation without further reductions in systolic function. The results from the VALOR-HCM trial highlight the favorable effects of mavacamten in this study of highly symptomatic patients with oHCM. Based on these results, mavacamten is able to reduce the need for more invasive nonpharmacologic therapies, which can be highly valuable for patients with oHCM. Currently, mavacamten is only approved for patients with oHCM. Initial phase 2 results from MAVERICK-HCM, which assessed mavacamten in patients with nonobstructive HCM, have revealed improvement in cardiac biomarkers with limited AEs. The MAVA-LTE trial is also including a cohort of patients previously enrolled in MAVERICK-HCM and will provide long-term safety and efficacy in patients with nonobstructive HCM.

Aficamten (CK-274)

While mavacamten has demonstrated initial improvement in symptoms and clinical findings of oHCM, additional therapies are on the horizon. Aficamten, a second-generation cardiac myosin inhibitor, has been granted breakthrough therapy designation by the FDA based on the promising results of initial phase 2 REDWOOD-HCM clinical trial results. This randomized, double-blind, placebo-controlled study included patients with persistent resting LVOT gradient (≥30 mm Hg) and provoked LVOT obstruction (≥50 mm Hg); efficacy end points included resting and provoked LVOT gradients, NYHA class, and NT-proBNP over the course of 10 weeks. The study evaluated dosing regimens and outcome measures focused on safety and incidence of adverse effects observed with aficamten. Initial results suggest aficamten reduces LVOT obstruction and improves symptoms in patients with oHCM, similar to the effects of mavacamten. Treatment was generally well tolerated with aficamten as adverse effects seen were similar between the 2 groups.

Whereas aficamten and mavacamten share a similar mechanism of action, they differ based on the specific myosin target inhibition as well as their pharmacokinetic profiles. The predicted half-life of aficamten is currently estimated to be around 3 days, in contrast to the longer half-life of mavacamten. Aficamten also appears to have limited inhibition and induction of various CYP enzyme pathways. These features may allow for clinicians to titrate therapy more rapidly to desired effects and minimize the risk for potential DDIs with aficamten.

Results from the phase 2 REDWOOD-HCM and phase 3 SEQUOIA-HCM studies are expected over the next 1 to 3 years and may lead to an additional pharmacologic therapy targeting the underlying cause of HCM. The currently ongoing SEQUOIA-HCM is a multicenter, randomized, double-blind, placebo-controlled study that analyzes the safety and efficacy of aficamten in adults with symptomatic HCM and LVOT obstruction. Primary end points include change in peak oxygen uptake measured by cardiopulmonary exercise testing (CPET) up to 24 weeks; secondary end points include change in the Kansas City Cardiomyopathy Questionnaire score, proportion of patients with ≥1 class improvement in NYHA functional class, post-Valsalva LVOT gradient, and proportion of patients with post-Valsalva LVOT gradient <30 mm Hg, as well as change in total workload during CPET. Aficamten has been investigated as once-daily oral dosing for patients. Results from these trials are not yet published, but there may be additional unmet needs filled that previous therapies for HCM have not addressed.
The Role of the Pharmacist in the Management of Hypertrophic Cardiomyopathy

Pharmacists may impact and improve the care of patients with HCM through symptom recognition, management of treatment expectations and adverse effects, and education on the importance of adherence to medications and management of comorbid conditions. Referral, greater access to counseling, and education regarding need for genetic testing for family members is also crucial. Shared decision making between health care professionals and patients when deciding on appropriate therapies based on individual preferences and associated comorbidities helps enhance engagement with patients. Since comorbid conditions, such as atherosclerotic cardiovascular disease, hypertension, obesity, and sleep-disordered breathing, may be prevalent in patients with HCM and contribute to heightened symptoms, proper counseling and management of these comorbidities can help improve the quality of life for these patients. For example, pharmacists are encouraged to provide comprehensive lifestyle interventions for maintaining weight loss and lowering risk of developing HF and atrial fibrillation for patients with HCM and obesity while lifestyle modifications and treatment with β-blockers and non-dihydropyridine CCBs are recommended to help control hypertension in patients with oHCM. Assessing symptoms of sleep-disordered breathing and referral to sleep medicine specialists for evaluation is another opportunity for education and involvement to reduce symptom burden for patients with HCM. Unfortunately, data suggest a large portion of patients with cardiomyopathy will experience nonadherence to their medications. The use of weekly pill boxes and/or mobile apps can significantly increase compliance to prescribed medication regimens. Medication adherence should be discussed regularly by all health care team members in an effort to identify barriers and develop solutions with the input from the patient. Developing strategies that work well for patients based on their schedules to optimize adherence to prescribed medications reduces heart failure exacerbations and hospitalizations, improves functional capacity, and lowers the risk of cardiac-related mortality.

This section will focus on the information currently available based on the approved agents, but it will be important for pharmacists to stay current with key educational points for HCM management as new therapies are approved as well. Due to the potential for development of HF from systolic dysfunction and the need for careful assessment of DDIs that may increase the risk of developing adverse cardiac events, the FDA approved mavacamten through a restricted Risk Evaluation and Mitigation Strategy (REMS) program. Prescribers must complete an initial knowledge assessment and enrollment before prescribing mavacamten. Once enrolled in the program, the certified health care provider must complete initial patient counseling regarding the potential for development of HF and review for DDIs before prescribing mavacamten. They must also adhere to strict requirements for regular echocardiogram monitoring and clinical assessments at weeks 4, 8, and 12, and then every 12 weeks thereafter if continuing on a stable dose (every 4 weeks after dose titration). Patients must also complete an initial enrollment form before they can begin therapy.

Pharmacists and specialty pharmacies play a crucial role in ensuring safe and effective use of this novel therapy. Pharmacists must certify with the Camzyos REMS program and train all staff according to the program before dispensing mavacamten. Specific monitoring of patients will be discussed below but before dispensing mavacamten, pharmacists must complete and submit a drug interaction and counseling checklist. After the checklist is submitted, authorization must be obtained through the online program or by calling the REMS call center, and no more than a 35-day supply can be provided to patients during each dispense. While specialty pharmacies and pharmacists are highly involved in ensuring access to this novel therapy, pharmacists may also be deployed in ambulatory care practices involved with the prescribing and monitoring of cardiac myosin inhibitors.

Dosing and Treatment Monitoring

Mavacamten dosing is dependent on several factors and pharmacists play a pivotal role in ensuring adherence to the dosing protocol set forth in the prescribing information. Mavacamten dosing should not be increased any earlier than 12 weeks after initiating therapy or after a dose modification. While dose decreases may be necessary as the result of new DDIs, additional findings such as low LVOT gradients (<20 mm Hg) at weeks 4 or 8 may require dose decreases during the initiation phase of mavacamten. If at any point a patient’s LVEF falls to less than 50%, therapy should imme-
Diately be interrupted. These clinical features will be submitted by the mavacamten-certified provider at the time of screening and the follow-up periods listed in Figure 2.\textsuperscript{35,49,50} Once patients have tolerated a stable dose of mavacamten for 12 weeks and meet the appropriate thresholds (Figure 2B),\textsuperscript{35,49,50} the dose can be increased to the next available dosage form (2.5-5 mg; 5-10 mg; 10-15 mg).\textsuperscript{35}

Mavacamten requires serial monitoring to assess for changes in LVEF and LVOT gradients.\textsuperscript{35,49} The current mavacamten REMS program requires echocardiography to be performed at baseline, then every 4 weeks for the first 12 weeks of therapy (Figure 2A).\textsuperscript{35,49,50} If the LVEF decreases to less than 50% at any time during this initial phase, mavacamten should temporarily be held and the echocardiogram should be repeated every 4 weeks to assess for improvement. Once the LVEF is observed to be greater than or equal to 50%, therapy can be reinitiated at 2.5 mg daily and a follow-up echocardiogram should be performed every 4 weeks after reinitiation.\textsuperscript{35,49} If a patient has an LVEF less than 50% twice while on the 2.5-mg treatment, despite appropriate temporary suspensions, therapy should be permanently discontinued. If the LVEF decreases to less than 50% while on higher maintenance doses, therapy should temporarily be held and should be restarted at the next lowest dose available once the LVEF is greater than or equal to 50%. Additionally, as doses of mavacamten are titrated, or patients are started on a weak CYP2C19 or moderate CYP3A4 inhibitor, reassessment with echocardiogram is required 4 and 12 weeks after either dose titration or initiation of the interacting medication.\textsuperscript{49}

---

**Figure 2. Dosing and Monitoring of Mavacamten**\textsuperscript{35,49,50}

**A. Initial Dosing and Monitoring**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 4*</th>
<th>Week 8*</th>
<th>Week 12+*</th>
</tr>
</thead>
</table>
| • Echo (LVEF ≥55%)  
• Initiate mavacamten 5 mg daily | • Echo  
• If LVOT gradient <20 mm Hg, decrease dose to 2.5 mg  
• If LVOT gradient ≥20 mm Hg, continue 5 mg | • Echo  
• If LVOT gradient <20 mm Hg, decrease dose by 2.5 mg (hold if previously reduced to 2.5 mg)  
• If LVOT gradient ≥20 mm Hg, continue current dose | • Echo  
• If LVEF ≥50% and previously held therapy, resume mavacamten 2.5 mg and continue dose for total of 12 weeks*  
• If previously on 2.5 mg or 5 mg, see Figure 2B |

**B. Dose Titration and Monitoring Week 12 and Further**

- **LVEF 50%-55% and any LVOT gradient**
  - Continue current dose and reassess echo in 12 weeks
- **LVEF >55% and LVOT gradient <30 mm Hg**
  - Continue current dose and reassess echo in 12 weeks
- **LVEF <55% and LVOT gradient ≥30 mm Hg**
  - Increase to next dose (2.5-5 mg; 5-10 mg; 10-15 mg)  
    - Reassess with echo in 4 weeks  
    - No further increase until completion of 12 weeks on current dose

---

Echo, echocardiogram; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract.

*If LVEF is less than 50% at any point, temporarily suspend mavacamten therapy; repeat echocardiogram every 4 weeks until LVEF is greater than 50%. Once LVEF is greater than 50%, resume therapy at next lowest possible dose.

*After resuming therapy after temporary suspension, repeat echocardiogram 4 weeks after restarting at the next lowest dose and continue dose for 8 weeks after echocardiogram if LVEF is greater than 50%.
While regular electrocardiograms are not a required monitoring parameter of the mavacamten REMS program, assessment may be required during concomitant use of mavacamten and therapies known to increase QTc duration to prevent arrhythmias.29,51

Patient Education and Counseling

The mavacamten REMS program requires pharmacists and pharmacies to submit appropriate clinical documentation before dispensing mavacamten.50 Before each dispense, pharmacists must assess for the presence of clinically relevant DDIs that may necessitate either a dose decrease or suspension of therapy. Patients who are prescribed moderate-strong CYP2C19 inhibitors or inducers, strong CYP3A4 inhibitors, or moderate-strong CYP3A4 inducers are contraindicated from receiving mavacamten and the mavacamten-certified health care provider should be notified. Examples of these agents can be found at the mavacamten REMS program website listed in the Additional Resources section at the end of this activity.50 Additionally, patients who are prescribed medications that are weak CY2C19 or moderate CYP3A4 inhibitors after initiation of mavacamten will require a dose decrease to the next available dose.35,50 For patients who are prescribed a weak CY2C19 or moderate CYP3A4 inhibitor before the initiation of mavacamten, the initial dose can be started at 5 mg daily without a decrease in the initial dose.35 Identification of these potential DDIs must be documented on the Drug Interaction and Counseling Checklist for Pharmacies document provided in the mavacamten REMS program. Patients must be counseled about the need to notify both the mavacamten-certified health care provider and pharmacy regarding any new medications prescribed in between dispensing of mavacamten therapy. Further requirements set forth in the REMS program included pharmacist attestation of patient counseling regarding cardinal signs or symptoms of worsening HF, including but not limited to shortness of breath, chest pain or discomfort, fatigue, palpitations, and/or swelling or rapid weight gain (>2 lb in 24 hours or 5 lb over the course of 1 week).50 Patients should also be alerted to commonly experienced AEs of therapy. Based on the current data, patients taking mavacamten reported a higher incidence of dizziness (27%) and syncope (6%).35 Patients should be instructed to rise slowly upon awakening or after prolonged periods of sitting down to minimize these events. Patients should also report the development and severity of these events to their mavacamten-certified health care provider, as these events may indicate the need for more urgent clinical evaluation. If patients report significant AEs, they should promptly be reported through both the FDA MedWatch program and the manufacturer.35

While pregnancy status is not included on the REMS pharmacy checklist, women should be educated on appropriate contraception during treatment due to potential fetal-embryo harm. Women should use effective contraceptive methods during treatment with mavacamten and for at least 4 months after the last dose due to the prolonged half-life of mavacamten.55 The package insert recommends patients avoid monotherapy with combined hormonal contraceptives, as mavacamten may reduce their efficacy due to CYP enzyme induction. Suitable alternatives or additional forms of contraception include intrauterine devices or condoms, respectively. If patients suspect pregnancy or become pregnant while taking mavacamten, they should immediately alert their mavacamten-certified provider and should also be encouraged to report pregnancy to the manufacturer, as there is an ongoing study to formally assess the safety of therapy during pregnancy. Pharmacists involved in the dispensing of mavacamten should also alert the patient’s mavacamten-certified provider and manufacturer if they discover a patient has become pregnant during therapy. Additional information will be needed to see if this is applicable for other agents in the class moving forward.

Conclusion

Over the past decade, significant research has led to development of novel pharmacologic treatments that target the underlying cause of HCM. Recent treatments that are first of its kind cardiac myosin inhibitors cannot only improve symptoms and functional status, but have the capability of reducing the need for more invasive surgical therapies that are not widely available to all patients with oHCM. While providers await longer-term data with both mavacamten and potentially with aficamten, pharmacists in various settings play a key role in ensuring safe and effective use of these agents. Whereas patients will require frequent monitoring by the health care provider, pharmacists should routinely be involved in screening for significant DDIs and be familiar with the appropriate dose titrations and need for temporary suspensions when appropriate. Additionally, pharmacists involved with the management of newer therapies for HCM should establish clear pathways for effective and timely
communication with providers to ensure patients can be treated safely and effectively.

**ADDITIONAL RESOURCES**

<table>
<thead>
<tr>
<th>Mavacamten</th>
<th><a href="http://www.camzyoshcp.com">www.camzyoshcp.com</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Camzyos REMS Program</td>
<td><a href="http://www.camzyosrem.com">www.camzyosrem.com</a></td>
</tr>
<tr>
<td>American College of Cardiology Hypertrophic Cardiomyopathy Resource Hub</td>
<td><a href="http://www.acc.org/guidelines/hubs/hypertrophic-cardiomyopathy">www.acc.org/guidelines/hubs/hypertrophic-cardiomyopathy</a></td>
</tr>
<tr>
<td>Hypertrophic Cardiomyopathy Association</td>
<td><a href="https://4hcm.org">https://4hcm.org</a></td>
</tr>
</tbody>
</table>

**REFERENCES**


INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.
Go to www.pharmacytimes.org/cardiomyopathy 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.
You may view your credit within 48 hours at www.mycpemonitor.net.

NOTE: Your CE credit will be automatically uploaded to CPE Monitor. Please ensure that your Pharmacy Times® account is updated with your 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.

FOR QUESTIONS ABOUT THIS INTERNET CPE ACTIVITY,
PLEASE CONTACT: ceinfo@pharmacytimes.com.
PRIVACY POLICY AND TERMS OF USE INFORMATION:
www.pharmacytimes.org/terms.

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POSTTEST QUESTIONS

1. Evidence of hypertrophic cardiomyopathy (HCM) includes which of the following criteria?
   A. Left ventricular ejection fraction (LVEF) less than 50%
   B. LV wall thickness greater than or equal to 15 mm
   C. LV outflow tract (LVOT) gradient less than 20 mm Hg
   D. Absence of late gadolinium enhancement

Case Vignette (for next 4 questions)

Patient AW is a 57-year-old man who has known HCM. He presents for his regular echocardiogram and routine clinical monitoring. He is maintained on metoprolol succinate 100 mg daily and disopyramide. His only other prescription medication is omeprazole 20 mg for gastroesophageal reflux disease. He takes no OTC medications. He describes symptoms such as dyspnea and fatigue when walking 2 or more flights of stairs or when walking more than 3 blocks. His resting left ventricular outflow tract (LVOT) gradient is measured as 25 mm Hg and after Valsalva maneuver the LVOT gradient is measured as 43 mm Hg. His LVEF is 75% on current echocardiogram.

2. Which would most appropriately describe the patient’s HCM type?
   A. Nonobstructive HCM
   B. Basal obstructive HCM
   C. Labile obstructive HCM
   D. Persistent obstructive HCM

3. After reviewing AW’s symptoms and gradients, his physician would like to initiate mavacamten. Which dose would be most appropriate to initiate for AW at this time?
   A. 2.5 mg daily
   B. 5 mg daily
   C. 10 mg daily
   D. 15 mg daily

4. After 8 weeks of therapy, AW presents for clinical follow-up after initiating his mavacamten therapy. He has had no medication changes since he started therapy. His physician asks the pharmacist to review his profile and determine whether his dose should be modified. Which statement would be most appropriate based on the current mavacamten Risk Evaluation and Mitigation Strategy requirements for dose titration?
   A. If LVEF is greater than or equal to 55%, LVOT gradient greater than or equal to 30 mm Hg, and QTc less than 520 msec, his dose should be increased to 10 mg daily.
   B. If LVEF is less than 50%, LVOT gradient greater than 30 mm Hg, and QTc less than 520 msec, his dose should be decreased to 2.5 mg daily.
   C. If LVEF is greater than or equal to 55%, LVOT gradient greater than or equal to 30 mm Hg, and QTc less than 520 msec, his dose should be maintained at 5 mg daily.
   D. If LVEF is greater than or equal to 55%, LVOT gradient greater than or equal to 30 mm Hg, and QTc more than 520 msec, his dose should be decreased to 2.5 mg daily.

5. Which medication is contraindicated in patients receiving mavacamten based on the mavacamten REMS program requirements due to a significant drug-drug interaction?
   A. Ritonavir
   B. Diltiazem
   C. Apixaban
   D. Furosemide

6. Which cardinal sign or symptom should patients immediately report during treatment with a cardiac myosin inhibitor?
   A. Diarrhea
   B. Bradycardia
   C. Dyspnea
   D. Headache

7. Which statement most appropriately highlights the potential mechanism for causing a reduction in the LVEF during the treatment with aficamten?
   A. Increased blood pressure
   B. Reduced actin myosin cross-linking and contractility
   C. Decreased diastolic filling time
   D. Increased oxygen demand

Case Vignette (Use for next 3 questions)
POSTTEST QUESTIONS (continued)

TL is a 68-year-old woman presenting to the specialty pharmacy for a refill of her mavacamten 10 mg daily. She has been taking mavacamten for 2 years and has been on her current dose for 18 weeks without any temporary discontinuations. She had her most recent assessment with the mavacamten-certified prescriber this week. Her echocardiogram reveals an LVEF of 60%, a peak LVOT gradient of 34 mm Hg, and a QTc of 504 msec (baseline 478 msec). She reports her previous symptoms of dyspnea and low exercise tolerance have improved dramatically. Her current medications include mavacamten 10 mg daily, metoprolol succinate 50 mg daily, atorvastatin 20 mg daily, aspirin 81 mg daily, and a multivitamin.

8. Which recommendation may improve the effectiveness and safety of her mavacamten therapy?
   A. Discontinue metoprolol succinate.
   B. Start low-dose verapamil.
   C. Increase mavacamten.
   D. Stop mavacamten.

9. Two weeks later, patient TL’s mavacamten prescriber calls the pharmacy to tell the pharmacist she was informed the patient would be initiated on indefinite ciprofloxacin therapy due to an infection. She asks if anything needs to be done for her mavacamten at the next fill. Which recommendation would be safest for the patient?
   A. Continue current dose of mavacamten.
   B. Decrease current dose of mavacamten.
   C. Stop mavacamten.
   D. Increase current dose of mavacamten.

10. Which of the following is the primary outcome examined in the SEQUOIA-HCM trial for aficamten?
    A. Proportion of patients with ≥2 class improvements in NYHA functional class
    B. Change in post-Valsalva LVOT gradient
    C. Number of patients that decide to undergo septal reduction therapies
    D. Change in peak oxygen uptake measured by cardiopulmonary exercise testing
Individualizing the Management of Primary Immunodeficiency Disorders: Considerations in the Selection of Intravenous Immunoglobulin or Subcutaneous Immunoglobulin

Etiology, Pathophysiology, and Incidence

Primary immunodeficiency disorders (PIDDs) are a large and diverse group of medical conditions that are caused by intrinsically defective or diminished immune function. Most PIDDs are rare and inherited genetic disorders, and, to date, over 450 unique single-gene inborn errors of immunity (IEI) have been characterized. It is believed that at least 1% of the population is affected by PIDDs. This estimation indicates the true prevalence is higher than has been historically appreciated. Even more monogenic errors of immunity are expected to be characterized as gene sequencing access and affordability expands. The National Institutes of Health estimates that approximately 500,000 Americans are living with undiagnosed PIDDs. Globally it is believed the vast majority of individuals with PIDDs (70%-90%) are undiagnosed.

Susceptibility to infection is considered the hallmark feature or clinical manifestation of PIDDs. The severity of this presentation is highly variable. Mounting evidence suggests that vulnerability to infectious disease may not be the only presenting feature, however. Malignancy, autoimmunity, and other dysregulatory features of immune function are often observed at greater incidence in those with PIDDs.

PIDD should not be confused with immunodeficiency disorders that arise from
<table>
<thead>
<tr>
<th>IUIS group</th>
<th>PIDD category</th>
<th>Characteristics</th>
<th>Examples</th>
<th>Physician-reported prevalence (United States)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Immunodeficiencies affecting cellular and humoral immunity (combined)</td>
<td>Recurrent viral, fungal, and bacterial infections</td>
<td>SCID, DOCK8 deficiency, CD40L deficiency, MHC I/II deficiency</td>
<td>4.5%</td>
</tr>
<tr>
<td>II</td>
<td>CID with associated or syndromic features</td>
<td>Recurrent viral, fungal, and bacterial infections</td>
<td>Hyper-IgE (STAT3), Wiskott-Aldrich syndrome, Cartilage-hair hypoplasia, 22q11.2 deletion syndrome, NEMO deficiency</td>
<td>16.5%</td>
</tr>
<tr>
<td>III</td>
<td>Predominantly antibody deficiencies</td>
<td>Recurrent bacterial sinopulmonary infections</td>
<td>X-linked (BTK) and autosomal recessive agammaglobulinemia, Autosomal recessive hyper-IgM, Selective IgA deficiency</td>
<td>56.4%</td>
</tr>
<tr>
<td>IV</td>
<td>Diseases of immune dysregulation</td>
<td>Lymphoproliferation, Autoimmunity</td>
<td>Chediak-Higashi syndrome, Perforin deficiency, ALPS, STAT3 gain of function, CTLA4 deficiency, LRBA deficiency, IL-10 deficiency</td>
<td>3.5%</td>
</tr>
<tr>
<td>V</td>
<td>Congenital defects of phagocyte number, function, or both</td>
<td>Severe bacterial infections of the skin, lungs, and lymph nodes</td>
<td>Chronic granulomatous disease, Leukocyte adhesion deficiency, GATA2 deficiency, Congenital neutropenias</td>
<td>4.9%</td>
</tr>
<tr>
<td>VI</td>
<td>Defects of intrinsic and innate immunity</td>
<td>Invasive bacterial infections (sepsis, meningitis) often in the absence of fever</td>
<td>IRAK4 and MyD88 deficiency, STAT1 gain of function, Interferon gamma receptor deficiency, IRF7 deficiency, TLR3 deficiency</td>
<td>0.9%</td>
</tr>
<tr>
<td>VII</td>
<td>Autoinflammatory disorders</td>
<td>Recurrent fever, rash, arthritis/arthralgia, Amyloidosis, Inflammatory bowel disease</td>
<td>Familial Mediterranean fever, Mevalonate kinase deficiency, Muckle-Wells syndrome, NLRP1 deficiency</td>
<td>2.0%</td>
</tr>
<tr>
<td>VIII</td>
<td>Complement deficiencies</td>
<td>Disseminated neisserial infections, Recurrent pyogenic infections, SLE, Atypical hemolytic uremic syndrome</td>
<td>Deficiency of complement components (C1 to C9), Properdin deficiency, Factor D deficiency, Factor H deficiency</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

ALPS, autoimmune lymphoproliferative syndrome; ALPS-SFAS, autoimmune lymphoproliferative syndrome due to somatic FAS mutation; BTK, Bruton tyrosine kinase; CD40L, CD40 ligand; CID, common immunodeficiency; CTLA4, cytotoxic T lymphocyte-associated antigen 4; DOCK8, dedicator of cytokinesis 8; GATA2, GATA-binding protein 2; IEI, inborn error of immunity; IgA, immunoglobulin A; IgE, immunoglobulin E; IgM, immunoglobulin M; IL, interleukin; IRAK4, IL-1 receptor-associated kinase 4; IUIS, International Union of Immunological Societies; LRBA, lipopolysaccharide-responsive beige-like anchor; MHC, major histocompatibility complex; MyD88, myeloid differentiation primary response protein 88; NEMO, nuclear factor-kappa-B essential modifier; NLRP1, NLR family pyrin domain-containing 1; PIDD, primary immunodeficiency disorder; SCID, severe combined immunodeficiency; SLE, systemic lupus erythematosus; STAT1, signal transducer and activator of transcription 1; STAT3, signal transducer and activator of transcription 3; TLR3, toll-like receptor 3; TNFRSF16: tumor necrosis factor receptor superfamily member 6.

*34,414 total patients; note: 3135 (9.1%) reported as “unspecified or other deficiencies” (not depicted in table).
### Table 1. International Union of Immunological Societies Phenotypic Classification of IEI (Continued)

<table>
<thead>
<tr>
<th>IUIS group</th>
<th>PIDD category</th>
<th>Characteristics</th>
<th>Examples</th>
<th>Physician-reported prevalence (United States)*</th>
</tr>
</thead>
</table>
| IX         | Bone marrow failure | • Macrocytic anemia and other cytopenias  
• Skeletal, nail, hair, and/or skin abnormalities | • Fanconi anemia  
• Dyskeratosis congenita | 0.17% |
| X          | Phenocopies of PIDD | • Various phenotypes | • ALPS-SFAS (somatic mutations in TNFRSF6)  
• Mucocutaneous candidiasis due to autoantibodies to IL-17 or IL-22  
• Mycobacterial infections due to autoantibodies to IL-6  
• Acquired angioedema due to autoantibodies to C1 inhibitor | 0.14% |

ALPS, autoimmune lymphoproliferative syndrome; ALPS-SFAS, autoimmune lymphoproliferative syndrome due to somatic FAS mutation; BTK, Bruton tyrosine kinase; CD40L, CD40 ligand; CID, common immunodeficiency; CTLA4, cytotoxic T lymphocyte-associated antigen 4; DOCK8, dedicator of cytokinesis 8; GATA2, GATA-binding protein 2; IEI, inborn error of immunity; IgA, immunoglobulin A; IgE, immunoglobulin E; IgM, immunoglobulin M; IL, interleukin; IRAK4, IL-1 receptor-associated kinase 4; IUIS, International Union of Immunological Societies; LRBA, lipopolysaccharide-responsive beige-like anchor; MHC, major histocompatibility complex; MyD88, myeloid differentiation primary response protein 88; NEMO, nuclear factor-kappa-B essential modifier; NLRP1, NLR family pyrin domain-containing 1; PIDD, primary immunodeficiency disorder; SCID, severe combined immunodeficiency; SLE, systemic lupus erythematosus; STAT1, signal transducer and activator of transcription 1; STAT3: signal transducer and activator of transcription 3; TLR3: toll-like receptor 3; TNFRSF6: tumor necrosis factor receptor superfamily member 6.

*34,414 total patients; note: 3135 (9.1%) reported as “unspecified or other deficiencies” (not depicted in table).

### Table 2. Most Commonly Diagnosed Primary Immunodeficiency Disorders

<table>
<thead>
<tr>
<th>Primary immunodeficiency defect</th>
<th>Global</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common variable immunodeficiency, unknown</td>
<td>15,969</td>
<td>23.4</td>
</tr>
<tr>
<td>Selective IgA deficiency</td>
<td>11,592</td>
<td>17.0</td>
</tr>
<tr>
<td>Isolated IgG subclass deficiency</td>
<td>6024</td>
<td>8.8</td>
</tr>
<tr>
<td>T8X1 (DiGeorge, Chromosome 22q11.2 deletion syndrome), AD</td>
<td>5373</td>
<td>7.9</td>
</tr>
<tr>
<td>Transient hypogammaglobulinemia of infancy</td>
<td>4799</td>
<td>7.0</td>
</tr>
<tr>
<td>Specific antibody deficiency (normal Ig and B cells)</td>
<td>4708</td>
<td>6.9</td>
</tr>
<tr>
<td>ATM (ataxia-telangiectasia), AR</td>
<td>3066</td>
<td>4.5</td>
</tr>
<tr>
<td>BTK (BTK deficiency, XLA) XL</td>
<td>2863</td>
<td>4.2</td>
</tr>
<tr>
<td>MEFV (Familial Mediterranean fever), AD</td>
<td>2502</td>
<td>3.7</td>
</tr>
<tr>
<td>TNFRSF13B (TACI deficiency), AR or AD</td>
<td>2417</td>
<td>3.5</td>
</tr>
<tr>
<td>DiGeorge Syndrome, unknown</td>
<td>2162</td>
<td>3.2</td>
</tr>
<tr>
<td>CIQA (Clq deficiency), AR</td>
<td>1818</td>
<td>2.7</td>
</tr>
<tr>
<td>CYBB (X-linked CGD (gp91 phox)), XL</td>
<td>1752</td>
<td>2.6</td>
</tr>
<tr>
<td>IgG subclass deficiency with IgA deficiency</td>
<td>1673</td>
<td>2.5</td>
</tr>
<tr>
<td>WAS [Wiskott-Aldrich syndrome (WAS LOF)], XL</td>
<td>1537</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>68,255</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; BTK, Bruton tyrosine kinase; CGD, chronic granulomatous disorder; Ig, immunoglobulin; XLA, X-linked agammaglobulinemia; XL, X-linked.

Secondary immunodeficiency is acquired and considered the result of factors extrinsic to the immune system. Secondary immunodeficiency can be the direct or indirect result of other diseases or environmental conditions such as infection, malnutrition, or malignancy. It is a well-known consequence of various immunosuppressive drugs (e.g., chemotherapy, disease-modifying antirheumatic drugs, biologic response modifiers, steroids).

While over 400 forms of PIDD exist, most are considered rare. Since 2013, the International Union of Immunological Societies Expert Committee on IEI has published an updated phenotypic classification of IEI that accompanies and complements their genotypic classification into 10 broad categories (see Table 1). As would be expected from any disease state that has substantial variability in etiology, the pathophysiology and mechanisms underpinning PIDD are complex.

TABLE 2 depicts the US and global prevalence of the 15 most commonly diagnosed PIDDs as reported by physicians.

Categorization of PIDD can also be simplified and divided into subtypes based on the deficient or defective cells or cell components. These subtypes include PIDDs that cause T-cell deficiency, B-cell deficiency, both T- and B-cell deficiency, complement deficiency, phagocyte deficiency, and immunoglobulin (Ig) A deficiency. The FIGURE lists the most common types of PIDDs (as well as some rare PIDDs) based on their cellular defect.

**Clinical Presentation and Diagnosis**

The clinical presentation of PIDDs is not always obvious, which can lead to delay in diagnosis. Variable and sometimes nonspecific symptoms may be conflated with other more commonly seen and diagnosed disease states. This variability can hinder a diagnosis of PIDD. Susceptibility to infection is the most common symptom of PIDDs but other less common symptoms may be harder to appreciate in a diagnostic evaluation, particularly given that presentation is highly variable between patients. In fact, noninfectious symptomology may present prior to recurrent infections and include swelling of the blood vessels, liver, spleen, or lymph nodes and autoimmune conditions such as inflammatory bowel disease or severe atopy. Cytopenias, pulmonary disease, autoimmune or autoinflammatory disorders, as well as malignancy may all be important manifestations of PIDD. Clinicians should consider potential secondary causes of immunodeficiency including Ig loss. Referral to a clinical immunologist should be considered for anyone experiencing recurrent infections.

Reasons for delays in obtaining a diagnosis of PIDD are multifactorial. Expertise within clinical immunology is rare for primary care physicians and a shortage of immunologists exacerbates this knowledge gap. According to the 2007 PIDDs in America Patient Survey Report, 51% of patients with PIDD did...
TABLE 3. 10 WARNING SIGNS OF PIDD FOR PEDIATRICS AND ADULTS

<table>
<thead>
<tr>
<th>Pediatrics</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ≥4 new ear infections within 1 year</td>
<td>1. ≥2 new ear infections within 1 year</td>
</tr>
<tr>
<td>2. ≥2 serious sinus infections within 1 year</td>
<td>2. ≥2 serious sinus infections within 1 year, in the absence of allergy</td>
</tr>
<tr>
<td>3. ≥2 months on antibiotics with little effect</td>
<td>3. 1 pneumonia per year for &gt;1 year</td>
</tr>
<tr>
<td>4. ≥2 pneumonias within 1 year</td>
<td>4. Chronic diarrhea with weight loss</td>
</tr>
<tr>
<td>5. Failure of an infant to gain weight or grow normally</td>
<td>5. Recurrent viral infections (colds, herpes, warts, condyloma)</td>
</tr>
<tr>
<td>6. Recurrent, deep skin, or organ abscesses</td>
<td>6. Recurrent need for IV antibiotics to clear infections</td>
</tr>
<tr>
<td>7. Persistent thrush in mouth or fungal infection on skin</td>
<td>7. Recurrent, deep abscesses of the skin or internal organs</td>
</tr>
<tr>
<td>8. Need for IV antibiotics to clear infections</td>
<td>8. Persistent thrush or fungal infection on skin or elsewhere</td>
</tr>
<tr>
<td>9. ≥2 deep-seated infections including septicemia</td>
<td>9. Infection with normally harmless tuberculosis-like bacteria</td>
</tr>
<tr>
<td>10. A family history of PIDD</td>
<td>10. A family history of PIDD</td>
</tr>
</tbody>
</table>

not receive a diagnosis until they had reached the age of 30 or older, with 26% not obtaining a diagnosis until age 45 or older.\(^{17}\)

The same survey showed that the average time to diagnosis after symptom onset appeared to be increasing, from 9.2 years in 2002 to 12.4 years in 2007.\(^{18}\) The patient survey from 2007 also indicated that they had experienced a permanent impairment prior to diagnosis. Survey data showed a shorter time from onset of symptoms to diagnosis, as immunodeficiency was associated with fewer permanent impairments due to loss of function in organs or organ systems.\(^{17}\)

In efforts to improve public awareness of the underdiagnosis of PIDD, the Jeffrey Modell Foundation has developed lists of warning signs of PIDD (see TABLE 3\(^1\)). The presence of 2 or more of these signs suggests the possible presence of PIDD and warrants further investigation.\(^1\)

Early diagnosis and effective treatment are critical to help reduce associated morbidity and mortality with PIDD. Without prompt treatment, patients with PIDD are liable to experience reduced quality of life (QOL) as well as serious, prolonged, and sometimes life-threatening infections or complications from autoimmunity.\(^1\) A multitude of comorbid conditions are found at higher rates within patients with PIDD compared with the general population. A retrospective cohort review using a large US insurance claims database showed various comorbidities were more prevalent in patients receiving intravenous (IV) or subcutaneous (SC) Ig compared with their age- and gender-controlled cohorts. The diagnoses observed at higher rates within the PIDD population included chronic obstructive pulmonary disease-asthma (51.5%), rheumatoid disease (14%), deficiency anemia (11.8%), hypothyroidism (21.2%), lymphoma (16.7%), neurologic disorders (9.7%), arrhythmias (19.9%), electrolyte disorders (23.6%), coagulopathies (16.9%), and weight loss (8.4%).\(^7\)

Compared with healthy adults and children, patients with PIDD have significantly lower general health with greater hospitalization rates and greater limitations to their physical, social, or school activities.\(^9\) Health-related QOL (HRQOL) outcomes are negatively impacted by delays in diagnosis and number of infectious episodes.

Management of PIDD With Immunoglobulin

Management of PIDDs is variable and is based chiefly on the specific immune defect. Underlying mechanisms of disease should be considered and, if feasible, the use of curative therapies such as bone marrow transplantation or gene therapy should be explored.\(^{20-21}\) Ig replacement therapy is considered the standard of care for an array of PIDDs. Goals of treatment for PIDD are centered on the prevention of infections and their associated complications. Similarly, improving HRQOL is a primary goal. Many studies have confirmed the efficacy and safety of Ig replacement therapy.\(^{22-25}\) It benefits pharmacists to have a complete understanding of available Ig products as well as their dosing, administration, and potential adverse effects (AEs). Pharmacists should also be capable of making dose recommendations when transitioning a patient from IV Ig to SC Ig therapy.

Ig replacement therapy is used in several PIDDs and helps prevent infectious disease episodes. Ig can be replaced either
IV or SC, and the route of replacement is frequently dependent upon patient preference. Both the patient/caregiver and the prescriber should decide on the route of administration that is best suited for the individual. All available options are clinically efficacious, and all therapies must be tailored to meet the individual’s needs. Pharmacists caring for patients with PIDD should understand the importance of shared decision making between the clinician and patient and be knowledgeable about management strategies for these clinical complications, including the dynamics of IVIg versus SCIg and the need to individualize therapy, which may improve patient adherence and clinical outcomes.

A patient-centered approach incorporates individual patient preferences when developing a care plan for treatment of PIDDs. This approach is important, as lifelong Ig replacement therapy imparts a substantial burden upon the patient. Research indicates that besides the well-recognized physical complications associated with PIDDs, many patients with PIDD also experience psychological distress. This can have a considerably negative impact on patient HRQOL. It is imperative that pharmacists understand that patients living with PIDDs face numerous challenges that may impact nearly every facet of their lives. HRQOL outcomes are improved when shared decision making is employed. Satisfaction with therapy helps aid in improving patient adherence. Some data suggest that even with treatment, patients with PIDD may experience worse HRQOL outcomes.

IVIg has historically been considered the standard route of administration. IVIg permits infusion of larger doses over a short time; however, it must be administered by a health care professional. SCIg was utilized as early as the 1970s, but its use did not gain FDA approval until 2006. Compared with IVIg, SCIg does not require venous access and instead relies upon the slow release of Ig from the SC tissues into the systemic circulation. This more gradual route of administration enables Ig levels to remain steadier between infusions. SCIg is given in relatively smaller doses at more frequent intervals when compared with IVIg. Smaller variations between peaks and troughs of Ig levels may reduce the likelihood of treatment-related fluctuations, including AEs, and improve the maintenance of functional ability.

**Immunoglobulin Therapy and Impact on Quality of Life**

According to the Immune Deficiency Foundation, among those receiving Ig replacement therapy in the United States, approximately 50% use IVIg and 50% use SCIg. However, the use of SCIg for PIDD is on the rise. Recent data demonstrated that SCIg is associated with improved patient QOL and decreased overall costs to the health care system when compared with IVIg.

Studies have also demonstrated that most patients prefer SCIg because it can be administered at home, is more convenient, allows them greater independence, and is considered better tolerated with fewer systemic reactions. Due to flexibility in dosing frequency and scheduling, patients can also achieve better steady-state Ig concentrations, resulting in fewer hospital days and fewer missed days of work. Self-infusion at home also decreases use of the health care system and, most importantly, empowers patients and promotes their responsibility. Still, some patients prefer IVIg and identify perceived inconvenience, concerns about adverse reactions at home, and apprehension over frequent needlesticks as their concerns. SCIg represents a popular alternative to IVIg for many patients with PIDDs. Studies have shown that for many patients, QOL and self-perception of health is improved following a conversion from IVIg to SCIg.

SCIg offers the convenience of self-administration, eliminates the need for venous access, enables shorter infusions with smaller volumes, and yields an improved safety profile due to the reduced treatment burden. Patients have identified Ig self-administration, home administration, shorter duration of administration, fewer needlesticks, and once per month administration as features that improve their HRQOL. In the pediatric population, a publication indicated that use of SCIg revealed numerous advantages over IVIg, including better health and improved school/social functioning. SCIg also reduced parental emotional distress and personal time limitations and exerted fewer limitations on family activities.

It is imperative that pharmacists understand that irrespective of method of administration, the initiation of Ig replacement therapy in patients with PIDD extends survival, diminishes morbidity, and overall improves HRQOL. Pharmacists caring for patients with PIDD should be aware of the various ways in which immune dysregulation may present. In addition to recurrent and severe bacterial infections, patients with PIDD also have an increased frequency of autoimmune disease, inflammatory disorders, and lymphoproliferative disorders, life expectancy is reduced, and recurrent infections cause significant morbidity and disability due to complications from chronic lung disease, inflammatory bowel disease, and autoimmune disorders.
Why are early diagnosis and treatment considered so important in patients with PIDD?

IV Versus SC Immunoglobulins and Individualizing Care for the Patient

Although both routes of Ig administration have been deemed safe and effective, the preferred route can be based on a multitude of factors (see TABLE 4 for pros and cons). These include factors such as the specific clinical circumstances, patient’s lifestyle, dose requirements, volume and infusion rates, target Ig level, the specific drug product used, site of care, AEs, adherence issues, support system, and the number of infusion sites, many of which can affect the cost of therapy.43

Regardless of the route of administration chosen, adherence to treatment is of paramount importance. Due to their drug expertise, pharmacists have a critical role in identifying patients exhibiting signs of or at risk for PIDDs. They can also be instrumental in educating patients about the initiation of Ig therapy, dosing, and proper administration. Treatment regimens should be individualized to improve adherence and clinical outcomes. Patient/caregiver education is integral to effective management, and when selecting an Ig therapy, health care professionals should consider the following29,42:

- Administration frequency
- Dosing
- Route of administration

The Role of the Pharmacist in Primary Immunodeficiency Disorder Management

Ig replacement therapy may be impacted by product-specific considerations or differences. These differences include variability between storage and stability requirements as well as whether reconstitution is necessary. Pharmacists can help play an important role in guiding the selection of therapy that best fits a patient’s specific needs. Product-specific differences in the sugar and sodium content, type of stabilizer used, relative IgA content, and other pharmaceutical differences may impact patient tolerability. Due in part to these differences, Ig products are not considered generic drugs and are not interchangeable.42

A typical PIDD dose for IVIg products is 400 to 600 mg/kg every 3 to 4 weeks (but individual products have dosing differences that range from 200-800 mg/kg). Converting a patient from IVIg to SCIg requires knowledge of the intended SCIg product to be administered. A product-specific conversion factor is multiplied by the patient’s IVIg dose and then divided by the number of weeks between IVIg doses. For most products, SCIg dosing begins 1 week after the last IVIg dose.26

Pharmacists can aid in identification of ideal candidates for SCIg. Various publications have demonstrated that SCIg may have benefits in patients experiencing AEs in QOL with IVIg

<table>
<thead>
<tr>
<th>TABLE 4. COMPARISON OF IVIg AND SCIg42</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros</strong></td>
</tr>
<tr>
<td>• Requires less frequent dosing (typical interval is 3-4 weeks)</td>
</tr>
<tr>
<td>• Historical efficacy and safety profile as well as risk mitigation strategies are well known</td>
</tr>
<tr>
<td>• Local site reactions unlikely</td>
</tr>
<tr>
<td>• Promotes more frequent contact between patient and health care professionals which may improve assessment of efficacy or treatment response and earlier identification of potential complications</td>
</tr>
<tr>
<td><strong>Cons</strong></td>
</tr>
<tr>
<td>• Venous access is required</td>
</tr>
<tr>
<td>• Requires greater health care system resource utilization (eg, an RN needed for administration)</td>
</tr>
<tr>
<td>• Greater variability in peak and trough IgG levels may impact efficacy and safety</td>
</tr>
<tr>
<td>• Systemic adverse drug reactions are more common</td>
</tr>
<tr>
<td><strong>IVIg</strong></td>
</tr>
<tr>
<td>• Flexibility of self-administration</td>
</tr>
<tr>
<td>• No venous access is required</td>
</tr>
<tr>
<td>• Improved steady state IgG levels</td>
</tr>
<tr>
<td>• Smaller infusion volume</td>
</tr>
<tr>
<td>• Most common adverse drug reactions are localized to site of administration</td>
</tr>
</tbody>
</table>

IVIg, intravenous immunoglobulin; RN, registered nurse; SCIg, subcutaneous immunoglobulin.

IVIg, intravenous immunoglobulin; RN, registered nurse; SCIg, subcutaneous immunoglobulin.
### TABLE 5. MANAGING ADVERSE DRUG REACTIONS WITH IVIg AND SCIg

<table>
<thead>
<tr>
<th>Adverse drug reaction to IVIg</th>
<th>Interventions/strategies for management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills/rigors</td>
<td>• Stop infusion</td>
</tr>
<tr>
<td></td>
<td>• Administer prescribed medications</td>
</tr>
<tr>
<td></td>
<td>• Restart infusion at a lower rate after symptoms subside (eg, the last tolerated rate)</td>
</tr>
<tr>
<td>Headache</td>
<td>• Give acetaminophen or NSAID</td>
</tr>
<tr>
<td></td>
<td>• Ensure adequate hydration on day of treatment</td>
</tr>
<tr>
<td></td>
<td>• Consider IV or oral hydration (500-1000 mL)</td>
</tr>
<tr>
<td>Migraine headache</td>
<td>• Administer anti-migraine medications at first sign of migraine. Consider premedication with anti-migraine medications (eg, triptans)</td>
</tr>
<tr>
<td></td>
<td>• Oral or IV steroids may help decrease headache intensity</td>
</tr>
<tr>
<td></td>
<td>• General nonpharmacologic interventions such as reducing noise and visual stimuli should be used</td>
</tr>
<tr>
<td>Malaise/flu-like symptoms</td>
<td>• Resting after an infusion may help minimize muscle aches or pain and may decrease excess fatigue</td>
</tr>
<tr>
<td></td>
<td>• Acetaminophen or NSAID use and adequate pre-hydration may help</td>
</tr>
<tr>
<td>Urticaria</td>
<td>• Stop the infusion. Administer prescribed antihistamines and/or steroids. Observe for true anaphylaxis</td>
</tr>
<tr>
<td>Vasomotor symptoms</td>
<td>• Stop infusion. Follow prescriber’s orders regarding use of IV fluid, diuretics or other interventions as indicated</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>• Stop the infusion. Administer antiemetic medications. Provide comfort measures</td>
</tr>
<tr>
<td>Back/hip pain, arthralgias, myalgias</td>
<td>• Stop or slow the infusion. Administer acetaminophen or NSAID for discomfort. Consider use of a heating pad</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse drug reaction to SCIg</th>
<th>Interventions/strategies for management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local itching</td>
<td>• Ensure that a dry needle insertion technique has been used</td>
</tr>
<tr>
<td></td>
<td>• Apply cold compress</td>
</tr>
<tr>
<td></td>
<td>• OTC topical steroid may be used (eg, hydrocortisone 0.5%)</td>
</tr>
<tr>
<td></td>
<td>• Consider a longer needle for future infusions.</td>
</tr>
<tr>
<td></td>
<td>• Decrease volume per site and work up to desired site volume gradually</td>
</tr>
<tr>
<td>Redness</td>
<td>• Cold compress</td>
</tr>
<tr>
<td></td>
<td>• Consider irritation from adhesives or tape and consider alternate product</td>
</tr>
<tr>
<td></td>
<td>• Assure patient that redness should improve over time with repeat administration</td>
</tr>
<tr>
<td>Burning</td>
<td>• Clamp off catheter for 5-10 minutes, if desired</td>
</tr>
<tr>
<td></td>
<td>• Slow the rate of infusion</td>
</tr>
<tr>
<td></td>
<td>• Cold compress</td>
</tr>
<tr>
<td></td>
<td>• Assess needle placement (ensure not intramuscular). Consider use of shorter needle for future infusions</td>
</tr>
<tr>
<td></td>
<td>• Assess antiseptic used for skin preparation</td>
</tr>
<tr>
<td>Swelling</td>
<td>• Warm compresses for 5-10 minutes</td>
</tr>
<tr>
<td>(Note some swelling will always occur with SC administration)</td>
<td>• If using a heating pad, lower the setting</td>
</tr>
<tr>
<td></td>
<td>• Gentle massage</td>
</tr>
<tr>
<td></td>
<td>• Adjust volume/consider alternate site of administration</td>
</tr>
<tr>
<td>Urticaria/hives</td>
<td>• Stop infusion</td>
</tr>
<tr>
<td></td>
<td>• Contact prescriber for instructions and to determine if infusion should continue</td>
</tr>
<tr>
<td></td>
<td>• Consider an antihistamine</td>
</tr>
</tbody>
</table>

IV, intravenous; IVIg, intravenous immunoglobulin; OTC, over the counter; NSAID, nonsteroidal anti-inflammatory drug; SCIg, subcutaneous immunoglobulin.


Continued on next page
Clinical data also indicate that patients with more motivation to self-administer (eg, those who travel frequently or are employed) are more likely to want to transition to SCIg, may be more engaged in learning self-administration, and obtain greater perceived benefit from efficient infusions. Pharmacists should have a thorough understanding of what factors drive efficiency in infusion and learning, and, in turn, treatment satisfaction and well-being can help guide best practices.

Pharmacists also play an important role in management of AEs with Ig therapy. Most IVIg reactions are related to the rapidity with which an infusion is given. Slower infusions are generally better tolerated. Each IVIg product carries a maximum final infusion rate, and this rate dictates the overall length of the infusion. All IVIg products carry a black box warning for risk of thrombosis, renal dysfunction, and acute renal failure. All Ig products may cause thrombosis. Risk factors for development of thrombosis include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, and cardiovascular risk factors. Ensuring patients are well hydrated prior to receiving IVIg may help reduce thrombotic complications. Hydration may also reduce the likelihood of renal dysfunction. Renal dysfunction secondary to Ig use has been characterized as osmotic in nature, similar to the mechanism underlying sucrose nephropathy. No currently marketed IVIg products use sucrose as a stabilizer. Other mechanisms are likely contributory to acute kidney injury caused by IVIg. In general, administering Ig products at the slowest practical rate is another valid strategy to reduce adverse reactions, including thrombosis. Live virus vaccines may not produce the intended immune response due to the passive transfer of antibodies following receipt of an Ig product.

Ig therapy may cause a variety of AEs that can be generally classified as immediate or delayed. Immediate AEs may be mild (eg, flu-like syndrome, flushing, headache, chills), moderate (eg, vomiting, chest pain, severe headache), or severe (eg, hypertension, anaphylaxis, bronchospasm). These systemic AEs are more commonplace with IVIg than with SCIg. While rare in occurrence, patients may also experience delayed adverse drug reactions (ADRs) due to Ig, but they can be severe. Examples may include thromboembolism, neurologic disorders (eg, aseptic meningitis, seizure), renal impairment, hematologic disorders (eg, hemolysis, neutropenia), and electrolyte disturbances. In general, the use of SCIg is associated with fewer ADRs, and premedication is typically not required. Severe reactions rarely occur, and patients who have had severe reactions to IVIg might be at a greater risk. Recommendations for managing ADRs based on route of administration can be found in TABLE 5.

**Conclusion**

PIDD represents an ever-expanding group of conditions that have historically been unappreciated. Standard therapies for treatment and management of PIDDs include antimicrobials for relevant infectious disease complications and replacement Ig therapy. Other curative treatments are less widely employed but include bone marrow transplant and gene therapy. Goals of therapy include reducing infectious disease...
episodes and improving QOL. Patient and clinician education represents a substantial area of need and pharmacists can help close that gap. A wide variety of factors should be considered in choosing a product for Ig replacement therapy, and treatment should be individualized to meet the patient’s goals.

REFERENCES


American College of Asthma, Allergy & Immunology Scientific Meeting; November 7-11, 2019.


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POSTTEST QUESTIONS

1. Globally, how many patients with primary immunodeficiency disorder (PIDD) remain undiagnosed?
   A. 0% to 30%
   B. 30% to 50%
   C. 50% to 70%
   D. 70% to 90%

2. Which is considered the hallmark feature of PIDDs?
   A. Susceptibility to infection
   B. Pulmonary edema
   C. Atopic dermatitis
   D. Anemia

3. Which PIDD is the most prevalently diagnosed both globally and in the United States?
   A. Wiskott-Aldrich syndrome
   B. DiGeorge syndrome
   C. Common variable immune deficiency
   D. Selective immunoglobulin (Ig) A deficiency

4. Which is true regarding PIDD?
   A. There are about 50 different established types of PIDD.
   B. Patient clinical presentation is more prevalent in children and leads to early diagnosis.
   C. Comorbid conditions are found at higher rates within patients with PIDD.
   D. PIDD is acquired and considered the result of factors extrinsic to the immune system.

5. Which is a potential benefit of subcutaneous (SC) versus intravenous (IV) Ig?
   A. SC Ig can be given in large volumes compared with IV Ig.
   B. Localized adverse effects (AEs) are less common compared with IV Ig.
   C. SC Ig only needs to be administered by a health care provider every month compared with every week with IV Ig.
   D. SC Ig improves patient quality of life compared with IV Ig.

6. Which is considered the mainstay of therapy for the treatment of a wide variety of PIDDs?
   A. Gene therapy
   B. Bone marrow transplant
   C. Anti-infective therapy
   D. Ig replacement therapy

7. Which is true regarding IV Ig therapy?
   A. More frequent treatment injections compared with SC Ig
   B. Minimal fluctuation in IgG levels compared with SC Ig
   C. Historically considered the standard route of administration
   D. Allows for patients to have greater independence

8. Which patient characteristic would influence a pharmacist to initiate SC Ig over IV Ig?
   A. Patient prefers a therapy with fewer treatments per unit time
   B. Extreme fear of needlesticks
   C. Patient expresses a desire to learn how to self-infuse
   D. History of chronic kidney disease

9. Which statement is most accurate regarding AEs from Ig replacement therapy?
   A. All AEs from Ig replacement therapy are mild in nature.
   B. Stop infusion or injection at first sign of AEs.
   C. Systemic AEs are more likely with IV Ig than with SC Ig.
   D. Local AEs are more likely with IV Ig than with SC Ig.

10. GS is a 37-year-old man with a past medical history relevant for common variable immune deficiency for which he receives Ig replacement therapy. He recently transitioned from IV Ig to self-administered SC Ig. Following the transition, he has reported greater satisfaction with treatment because it does not require him to drive 45 minutes each way to an outpatient infusion center. He has tolerated SC Ig fairly well but asks what he could do about burning and discomfort localized at his injection sites. Which would be an appropriate recommendation?
    A. Use of longer needles
    B. Ensure adequate pre-hydration
    C. Increasing the infusion rate
    D. Apply cold compress
**Tylenol 8 Hour Arthritis Pain**

Manufactured by Johnson & Johnson

Johnson & Johnson has introduced Tylenol caplets for arthritis and muscle aches and pain. The caplets provide fast-acting and temporary relief of minor arthritis, joint pain, and osteoarthritis. They contain 650 mg of acetaminophen and have a bi-layer design with 2 layers, 1 that dissolves fast for fast-acting relief, and a second that lasts up to 8 hours to help ease pain. The oral pain reliever is intended for adults and can also be used to reduce fever and relieve other minor body aches and pains.

**FOR MORE INFORMATION:**

tylenol.com

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**Mucinex Cough & Chest Congestion for Diabetes or High Blood Pressure**

Manufactured by Reckitt

Mucinex for cough and chest congestion have been released in liquid gel form. The gel capsules age formulated for individuals with diabetes or high blood pressure. Mucinex helps loosen phlegm and thin the bronchial passageways. By doing so, it helps relieve congestion and coughing, which can cause irritation in the throat. Each liquid gel is formulated with dextromethorphan HBr 10 mg, an expectorant.

**FOR MORE INFORMATION:**

coldeeze.com

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**Cold-EEZE Cold Remedy**

Manufactured by Mylan

Cold-EEZE is a cold remedy to help shorten the duration of a cold when it is taken at the first sign of symptoms and used as directed. Cold-EEZW zinc lozenges shortened the duration of the common cold by 42%, according to the website. It comes in either a natural cherry flavor or a sugar-free version of the same flavor. Active ingredient zinc gluconate starts releasing zinc ions in the mouth immediately. The release of zinc ions is thought to inhibit the cold virus’ ability to replicate, shortening the duration of the common cold.

**FOR MORE INFORMATION:**

mucinex.com

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United States Postal Service

STATEMENT OF OWNERSHIP, MANAGEMENT, and CIRCULATION

Required by 39 USC 3685

1. Publication Title: Pharmacy Times
2. Publication Number: 808740
3. Filing Date: 9-27-22
4. Issue of Frequency: Monthly
5. Number of Issues Published Annually: 12
6. Annual Subscription Price: $184.99
7. Complete Mailing Address of Known Office of Publication (Not Printer): Pharmacy & Healthcare Communications, LLC, 2 Clarke Dr, Suite 100, Cranbury, NJ 08512-3619
8. Full Names and Complete Addresses of Publisher, Editor, and Managing Editor - Publisher: Elizabeth A. Gunther, Pharmacy & Healthcare Communications, LLC, 2 Clarke Dr, Suite 100, Cranbury, NJ 08512-3619; Editor: Laura Jost, Pharmacy & Healthcare Communications, LLC, 2 Clarke Dr, Suite 100, Cranbury, NJ 08512-3619; Managing Editor: Caitlin Mollison, Pharmacy & Healthcare Communications, LLC, 2 Clarke Dr, Suite 100, Cranbury, NJ 08512-3619
9. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages or Other Securities: None
10. Owner - Full name: Pharmacy & Healthcare Communications, LLC, 2 Clarke Dr, Suite 100, Cranbury, NJ 08512-3619
11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages or Other Securities: None
12. Publication Title: Pharmacy Times
13. Issue Date for Circulation Data Below: September 2022
14. Extent and nature of circulation

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<th>Average No. Copies Each Issue During Preceding 12 Months</th>
<th>No. Copies of Single Issue Published Nearest to Filing Date</th>
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<td>(4) Requested Copies Distributed by Other Classes Mailed Through the USPS</td>
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<td>i. Percent Paid and/or Requested Circulation</td>
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2. Publication of Statement of Ownership – Will be printed in October 2021 issue of this publication.

3. I certify that all information on this form is true and complete. Signature and title of Editor, Publisher, Business Manager; or Owner – Jonathan Severn, Circulation Director; 9-28-21

October 2022 pharmacytimes.com 149