Opioid-Induced Adverse Drug Events
Podcasts Deliver Information and News to Pharmacists, Students, and Technicians

IN A CONTINUING QUEST TO be a one-stop shop to pharmacy professionals and students, Pharmacy Times® has upped its game on the podcast front in 2021 and will continue to introduce more podcasts in 2022.

Pharmacy Times® offers 7 podcasts: Pharmacy Focus, Women in Pharmacy, Move the Needle Monday, Pharmacy Tech Talk, Psychedelic Pharmacy, Independent Rx Forum, and for students, Study Break. In 2022, we plan to introduce Forensic Pharmacy, OTC Product Show, and Public Health Matters.

The rich array of podcasts is, of course, in addition to our many other offerings, including videos, webcasts, and conference coverage.

In this print issue of Pharmacy Times®, we look at pain management, including in our cover feature, “Monitor Patients for Opioid-Induced Adverse Drug Events,” in which Kathleen Kenny, PharmD, RPh, discusses using the lowest effective dosages to prevent constipation, sedation, and respiratory depression. Other related articles cover back pain, migraines, and OTC analgesics.

Elsewhere in the issue, we offer coverage of avoiding infusion pump errors, JAK inhibitors as treatment options for atopic dermatitis, and off-patent generic drugs.

Meanwhile, Editor in Chief Troy Trygstad, PharmD, PhD, MBA, discusses Walgreens doubling down on care-team integration in his Editor’s Note, noting that the role of the pharmacy chain in health systems, primary care, and specialty remains uncertain.

Looking ahead to the December issue, check out our cough and cold issue as winter approaches. Coverage of cough and cold as well as influenza can also be found on PharmacyTimes.com.

As we approach the end of the year, we wish pharmacy professionals and pharmacy students a happy and safe holiday season. We hope that pharmacists and other pharmacy staff members get a well-deserved break after working so hard in 2021.

And we once again salute pharmacists and pharmacy technicians for all they have done during the COVID-19 pandemic to keep communities and patients safe.

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At the completion of this activity, the participant will be able to:
• Explore the history and growing role of biosimilars as well as the clinical and economic impact of their role in the management of inflammatory bowel disease (IBD)
• Examine immunogenicity, extrapolation of indications, interchangeability, and switching of biosimilars in clinical practice for IBD management
• Analyze data regarding the safety and efficacy of biosimilars in the management of IBD and the mechanism of action of biologic anti-TNF agents
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104 The Role of the Pharmacist in Addressing the Challenges of Treating Pulmonary Arterial Hypertension Associated With Connective Tissue Diseases

At the completion of this activity, the participant will be able to:
• Examine the epidemiology, pathophysiology, risk factors, prognosis, and challenges associated with connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH)
• Explore the mechanisms of action and efficacy and safety data associated with therapies for CTD-PAH
• Use current guidelines to tailor therapy to meet individual patient goals
• Identify the role of the pharmacist in making clinical recommendations to improve management and clinical outcomes in patients with CTD-PAH
We recently asked what advice you would give pharmacy students today, and you answered.

**Shelby L said,** "Prioritize your mental health. Find good people to surround yourself with and do not tolerate toxicity. It’s an interesting and engaging profession, but it does require effort."

**Tiffany K said,** "That it’s worth it! Challenges are part of the process but if it was easy everyone would do it. You can make the profession greater by becoming the best practitioner you can be, and that foundation is laid in pharmacy school. Keep going—you are needed!"

**Ore S said,** "Don’t get stuck in a box. You have so many different career options available to you beyond the conventional retail, hospital, or industrial roles. There’s more out there."

**Jessica H said,** "Find a good preceptor who still loves the job. I still love mine after almost 20 years."

**Tommy L said,** "Remember what you love about the profession and make an effort to stay engaged."

**Karl F said,** "Pharmacy is a great profession [and] pharmacists are doing great things! Look at how we all helped with the pandemic."

**Linda K said,** "Plan to do a residency (or two) after you graduate. It’s good to have options."

**Holly J said,** "Go to pharmacy school for the right reasons. Go because you have a passion to care for patients, a desire to serve others, and the ability to work with your brain, your hands, and people."

Tell us why you’re proud to be a pharmacist and why the profession is so important. Use #APharmacistIs on social media or email submissions to Aislinn Antrim at aantrim@pharmacytimes.com.
Editor’s Note

Walgreens Doubles Down on Care Team Integration
But Role of the Pharmacy Chain in Health Systems, Primary Care, and Specialty Is Uncertain

By TROY TRYGSTAD, PHARM, PHD, MBA, EDITOR IN CHIEF

IN LATE SEPTEMBER 2021, WALGREENS announced a $970 million investment in Shields Health Solutions, increasing its stake in the company to 71%. The new investment allows Walgreens to integrate more fully into health systems’ medication and patient-provider flows and referrals.

Forbes has reported that “more than 1 million specialty patients across more than 30 disease states, with more than 70 health system partners nationwide” have migrated to Walgreens over the past few years owing, at least in part, to its stake in Shields. Only a week after the Shields deal was announced, word got out that Walgreens was evaluating a buyout of Evolent Health, a care management and population health company with a market capitalization of more than $2 billion that has an even higher volume of care team member and health system clients.

Just 2 weeks later, Walgreens announced a purchase of controlling ownership in VillageMD, with the goal of opening 600 primary care clinics adjacent to the pharmacy chain’s locations by 2025 and 1000 by 2027. The price for a 33% increase in ownership was $5.2 billion, making Walgreens’ total planned spending spree in September 2021 nearly $9 billion. Walgreens had a market capitalization of more than $40 billion as of October 2021, so these investments represent a significant move for the pharmacy chain.

Patient Capture Goes Well Beyond Foot Traffic

Although CVS was the first pharmacy chain to enter the basic primary care services business with MinuteClinic, it was soon followed by others, such as Kroger’s Little Clinic in the “convenience care” marketplace. The most recent trend has been to expand on-site services, or
in the case of VillageMD, sometimes near-site services, to potentially include primary care physicians and combine chronic care delivery and convenience. With Walgreen’s large investment into health system integration and stand-alone primary care clinics, the company is betting big on the theory that pharmacies will be the new front door to the health care system. Even CVS has changed its branding and service strategy toward so-called health hubs to align with this trend.

Continued Fallout From Lack of Movement on “Provider Status”
Let's be honest. “Provider status” is all about the ability of pharmacists to bill payers for cost-effective and patient-friendly service. Some consider collaborative practice agreements to be a variant of provider status or even a means of billing “incident to” to a credentialed provider under direct supervision.

Yet in nearly all the scalable services-based revenue generation circumstances that are most common across the United States, pharmacists must be tethered to credentialed providers who can bill for health care services delivery. At this point, corporate boardrooms have tired of the promise of pharmacist billing and are not looking at pharmacies as places where pharmacists can provide billable health services. Rather, they are viewing pharmacy locations as the best points of patient capture, driven by OTC needs and prescription dispensing, allowing for more streamlined non-pharmacist engagement and referral and leading to a visit with a billable provider or laboratory. If pharmacists cannot bill, they will surround themselves with providers who can. If pharmacies cannot own 340B inventory, they will surround themselves with providers who can.

Pandemic Changes Consumer Expectations About Community Pharmacies
Community pharmacies are providing a huge number of COVID-19 vaccinations. Many pharmacies are testing for COVID-19 and some are independently treating patients with monoclonal antibodies; interestingly, this most often occurs by referral from other care team members. The past 2 decades have brought about a slow rebranding of pharmacies as locations of health care services delivery. The pandemic has been an accelerant. We regularly see administrators and policymakers giving an encouraging message about “going to your local pharmacy for [fill in the service].”

The most recent trend has been to expand on-site services, or in the case of VillageMD, sometimes near-site services, to potentially include primary care physicians and combine chronic care delivery and convenience.

What Is the Role of the Pharmacist in a Modern Pharmacy?
It seems somewhat comical as well as scary to pose this question. But it is a measured and serious one when we consider that many Fortune 30 companies are in the pharmacy business in some way, though it is not necessarily their principal business. Rather, pharmacy has become a means to another end.

Walgreens Boots Alliance’s new CEO Roz Brewer mentioned pharmacist involvement in a recent interview with CNBC. According to the article, she said that clinics will simplify care for patients and that “Walgreens and VillageMD will have pharmacists and physicians who work together. They will have access to the same tech platform that pulls together medical records. And they’ll be at a convenient location, a short walk or ride away.”

Time will tell how well pharmacists and physicians work together in these new integrated settings of care.

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<th>Drug name</th>
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<td>Maralixibat (Livmarli)</td>
<td>Indicated as an oral solution for the treatment of cholestatic pruritus in patients with Alagille syndrome age 1 year and older</td>
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<td>9/29/21</td>
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<td>Brexucabtagene autoleucel (Tecartus)</td>
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<td>Dexamethasone ophthalmic insert (Dextenza)</td>
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<td>Abemaciclib (Verzenio)</td>
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<td>Pembrolizumab (Keytruda)</td>
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<td>Flucelvax quadrivalent</td>
<td>Indicated to prevent influenza in adults and children as young as 6 months</td>
<td>Seqirus</td>
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<td>Atezolizumab (Tecentriq)</td>
<td>Indicated as adjuvant treatment following surgery and platinum-based chemotherapy for adults with stage II-III A non–small cell lung cancer whose tumors express PD-L1 of 1% or greater</td>
<td>Genentech</td>
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<tr>
<td>Varenicline solution nasal spray (Tyrvaya)</td>
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<td>Oyster Point</td>
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<td>Naloxone hydrochloride Injection, USP (Zimbi)</td>
<td>Indicated as a high-dose naloxone injection product for use in the treatment of opioid overdose</td>
<td>Adamis</td>
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<td>Celecoxib and tramadol hydrochloride (Seglentis)</td>
<td>Indicated for acute pain management in individuals with pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate</td>
<td>Esteve Pharmaceuticals</td>
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<td>Bictegravir, emtricitabine, and tenofovir alafenamide (Biktarvy)</td>
<td>Indicated for pediatric patients with HIV weighing between 30.8 and 55.1 lbs who are virologically suppressed or new to antiretroviral therapy</td>
<td>Gilead Sciences, Inc</td>
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<td>Dupilumab (Dupixent)</td>
<td>Indicated as an additional maintenance treatment of patients between 6 and 11 years of age with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid-dependent asthma</td>
<td>Regeneron Pharmaceuticals, Inc and Sanofi</td>
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<td>VENTANA PD-L1 Assay</td>
<td>Indicated as a diagnostic test to evaluate patients with non–small cell lung cancer who are eligible to receive atezolizumab</td>
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<td>Ranibizumab (Suszimo)</td>
<td>Indicated as an injection for intravitreal use via ocular implant for the treatment of individuals with wet, or neovascular, age-related macular degeneration who have previously responded to at least 2 antivascular endothelial growth factor injections</td>
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<td>Asciminib (Scemblix)</td>
<td>Indicated for the treatment of patients with Philadelphia chromosome–positive chronic myeloid leukemia in chronic phase who were previously administered 2 or more tyrosine kinase inhibitors</td>
<td>Novartis</td>
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<tr>
<td>Pilocarpine HCI ophthalmic solution 1.25% (Vuity)</td>
<td>Indicated for the treatment of presbyopia in adults</td>
<td>AbbVie</td>
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**Study: mRNA Vaccines Have Stronger Initial Response**

**THE MODERNA COVID-19 VACCINE** elicited generally higher antibody responses that were also more durable compared with the Pfizer-BioNTech vaccine, according to the results of a study published in the *New England Journal of Medicine*.

The investigators compared the immune responses induced by 3 COVID-19 vaccines—Johnson & Johnson, Moderna, and Pfizer-BioNTech—and found that though the single-shot J&J vaccine resulted in lower initial antibody responses than the 2 mRNA vaccines, these responses were generally stable over time.

“Even though neutralizing antibody levels decline, stable T-cell responses and nonneutralizing antibody functions at 8 months may explain how the vaccines continue to provide robust protection against severe COVID-19,” Ai-ris Y. Collier, MD, a maternal-fetal medicine specialist at Beth Israel Deaconess Medical Center in Boston, said in a statement. “Getting vaccinated [even during pregnancy] is still the best tool we have to end the COVID-19 pandemic.”—*Skylar Kenney*

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**Patients With Cancer Have Unique Considerations When Receiving Vaccines**

**PATIENTS RECEIVING CANCER TREATMENT** may not achieve full immunity with the first 1 or 2 doses of COVID-19 vaccines. Additionally, the type of treatment could influence the response they have, according to findings from 2 recent studies.

Results from the first study, published in *Nature Medicine,* by investigators at the University of Arizona Health Sciences, show that patients undergoing active chemotherapy had a lower immune response to 2 doses of the COVID-19 vaccine. However, the investigators found that a third dose increased patients’ response.

“We wanted to make sure we understand the level of protection the COVID-19 vaccines are offering our [patients with cancer], especially as restrictions were being eased and more contagious variants were starting to spread,” Rachna Shroff, MD, MS, chief of gastrointestinal medical oncology at the University of Arizona Cancer Center, said in a statement.

A team of investigators analyzed 53 patients receiving immuno-suppressive active cancer therapies, such as chemotherapy, to compare immune responses following the first and second doses of the Pfizer-BioNTech COVID-19 vaccine with responses from 50 healthy adults.

After 2 vaccine doses, most of the patients with cancer showed some immune response to the vaccine, which meant that they had antibodies for SARS-CoV-2, according to the study results.

“We were pleasantly surprised,” investigator Deepta Bhattacharya, PhD, said in the statement. “We looked at antibodies, B cells, and T cells, which make up the body’s defense system, and found [that] the vaccine is likely to be at least partially protective for most people on chemotherapy.”

However, the investigators noted that the immune response among patients with cancer was much lower than responses in healthy adults and a few of the patients had no response at all. This results in less protection against SARS-CoV-2 and especially the Delta variant, which is now the dominant strain in the United States.

Twenty patients returned for a third dose of the vaccine and most of these recipients had an increased immune response, according to the study results. The overall group immune response after the third shot reached levels similar to those of healthy adults after 2 doses.

Notably, the investigators said that they focused on patients with solid tumors, such as breast or gastrointestinal cancer, and excluded patients receiving immunotherapy.

In the second study, published in *JAMA Oncology,* investigators found that the type of cancer treatment patients receive influences their vaccine response. Specifically, patients undergoing chemotherapy had lower antibody levels than patients undergoing targeted therapy, according to the study findings.

The investigators in Austria and Italy studied antibody production following COVID-19 vaccination in more than 600 participants. The patients were split into 2 groups: those with blood cancers and solid tumors and a control group of healthy hospital staff.—*Aislinn Antrim*
No Connection Seen Between Allergic Diseases and Mental Health Issues

DESPITE PRIOR RESEARCH SHOWING an observational relationship between common allergic diseases and mental health, there is no proof that allergic diseases directly cause anxiety, bipolar disorder, or depression, according to investigators from the University of Bristol Medical School’s Population Health Sciences and School of Psychological Science in England.

Evidence of a causal relationship between the onset of allergic disease and mental health issues was limited, suggesting that the observational associations were due to confounding or other forms of bias, according to the study authors.

They concluded that intervening on the presentation of allergic disease is unlikely to improve mental health outcomes.

Even with these new data, more research is required into whether intervening on the progression of allergic disease after onset has any causal impact on mental health, according to the authors.

“Common mental health disorders such as anxiety and depression are some of the largest contributors to the global burden of disease, and the prevalence of these and allergic disease has been increasing for some time,” study lead author Ashley Budu-Aggrey, PhD, MSc, BSc, PhD, said in a news release. “Disentangling the nature of the relationship between allergic disease and mental health helps answer an important health question and suggests that the onset of allergic disease does not cause the onset of mental health traits or vice versa.”—Jill Murphy

Study Results Link Insulin Resistance, Risk of Major Depressive Disorder

INSULIN RESISTANCE HAS BEEN linked to an increased risk of developing major depressive disorder, according to the results of a study published in the American Journal of Psychiatry.

“If you’re insulin-resistant, your risk of developing major depressive disorder is double that of someone who’s not insulin-resistant, even if you’ve never experienced depression before,” Natalie L. Rasgon, MD, PhD, a professor in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine in California, said in a news release.

Approximately 40% of individuals with mood disorders are insulin-resistant, according to Rasgon.

Investigators analyzed data from 601 individuals who had never received a diagnosis of depression or anxiety. The 3 proxies of insulin resistance measured were fasting blood glucose levels, waist circumference, and ratio of circulating triglyceride levels to circulating high-density lipoprotein.

The results showed that a moderate increase in insulin resistance, as measured by the triglyceride-to-HDL ratio, was linked to an 89% increase in the rate of new cases of major depressive disorder. Every 5-cm increase of abdominal fat was related to an 11% greater rate of depression, and an increase in fasting plasma glucose of 18 mg/dL of blood was associated with a 37% increase of depression incidence, the results showed.

In another phase, investigators analyzed approximately 400 individuals who had never had major depression or any signs of insulin resistance. Within 2 years of the study, nearly 100 of the participants became insulin-resistant. Investigators compared this group’s likelihood of developing major depressive disorder in the next 7 years with that of the participants who hadn’t become insulin-resistant at the 2-year point.

Although the number of participants was too small to establish statistical significance for waist circumference and the triglyceride-to-HDL ratio, it was concluded that those who developed prediabetes within the first 2 years of the study had 2.66 times the risk for major depression by the 9-year follow-up, compared with those who had normal fasting-glucose test results at the 2-year point.—Ashley Gallagher

Solriamfetol Demonstrates Efficacy in Promoting Wakefulness

TREATING EXCESSIVE SLEEPINESS (ES), which is a symptom of narcolepsy and obstructive sleep apnea (OSA), with solriamfetol (Sunosi) could be successful as an initial or replacement therapy in patients who are not successfully treated by or experience adverse effects from armodafinil, modafinil, pitolisant, or other stimulants, according to results of a study published in Nature and Science of Sleep.

Investigators reviewed the safety profile of solriamfetol in treating ES associated with narcolepsy or OSA. They also looked at the drug’s clinical efficacy, pharmacology, and tolerability.

Study results showed that narcolepsy treatment is symptom based and depends on the patient. For example, in patients with narcolepsy, stimulants or wake-promoting drugs are add-on medications because they do not have an effect on other symptoms such as cataplexy, rapid eye movement phenomena, or sleep fragmentation. Mazindol is a second-line treatment because it carries a black box warning about cardiac valve dysfunction and primary pulmonary hypertension.

Additionally, the long- and short-term efficacy of solriamfetol has been demonstrated in the Treatment of OSA and Narcolepsy Excessive Sleepiness trials, with a dose-dependent reduction in ES, prolongation in mean sleep latency in the maintenance of wakefulness test, and increased percentages reporting improvement on the Patient Global Impression of Change compared with placebo. Common adverse events include anorexia, anxiety, constipation, dry mouth, headache, insomnia, irritability, nausea, nervousness, and palpitations, according to the study authors.

They noted that solriamfetol remains an adjunctive therapy for OSA, but it can also be effective as an initial or replacement therapy for residual ES in patients with OSA. For patients who have cataplexy or narcolepsy, it may be used as add-on therapy when ES is not controlled with medications such as pitolisant or sodium oxybate.

It also may be a better choice for patients with comorbid liver disease or those who are taking medications metabolized through the cytochrome P450 enzymes, including hormonal contraceptives.—Jill Murphy

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PARTICIPANTS IN A RECENT PHARMACY TIMES® Peer Exchange provided an overview of atopic dermatitis, the unmet needs that remain regarding treatment, the potential use of Janus Kinase (JAK) inhibitors in managing the condition, and the critical role of pharmacists.

Peter Lio, MD, moderated the discussion. Participants included Kristen Demundo, PharmD, supervising pharmacist at Long Island Apothecary in Commack, New York; Jamie L. McConaha, PharmD, NCTTP, BCACP, CDE, an associate professor of pharmacy practice at Duquesne University School of Pharmacy in Pittsburgh, Pennsylvania; and Shannon M. Rotolo, PharmD, BCPS, a clinical pharmacy specialist at University of Chicago Medicine in Illinois.

Following the discussion in September, the FDA approved JAK inhibitor ruxolitinib (Opzelura, Incyte) to treat atopic dermatitis.

There are 2 models of atopic dermatitis, McConaha told the panel. The first suggests that atopic dermatitis is caused by genetic epidermal barrier defects that trigger abnormal keratinocyte hyperplasia. The second is immune based, suggesting that abnormal epidermal phenotype in lesional atopic dermatitis is initiated by increases in cytokines that cause these abnormalities, she said.

The JAK and signal transducer and activator transcription pathway binds the ligands to the receptors and activates JAK, McConaha said.

The highest incidence of atopic dermatitis is reported in patients aged 3 to 6 months, and most cases develop...
by the age of 5 years, she said.

In terms of treatment for atopic dermatitis, topical options include calcineurin, pimecrolimus, and tacrolimus, though adverse effects (AEs) include burning, erythema, and pruritus, Demundo said.

In addition, crisaborole (Eucrisa), a newer medication, helps patients achieve clear or almost clear skin, she said.

Three systemic agents used for individuals with more moderate or severe cases can also be used for those who have not responded to topical therapies, McConaha said.

One of the agents, azathioprine, has AEs that include bloating, cramping, and vomiting. The second agent, cyclosporine, has AEs such as headaches, hypertension, necrotoxicity, and tremors. Finally, methotrexate has AEs that include bone marrow suppression, nausea, and pulmonary fibrosis.

Rotolo discussed dupilumab (Dupixent), the first systemic therapy for atopic dermatitis approved by the FDA, which may cause an injection site reaction.

**THERAPY SCHEDULE**

“Every 2 weeks is certainly more convenient than some of the daily therapies but can be a lot more challenging in terms of adherence for patients,” Rotolo said.

The panelists discussed the different treatment options with JAK inhibitors. JAK inhibitors are a “promising new class of drug,” because they block the pathway of these enzymes, which leads to cytokine production, Demundo said.

There are oral and topical JAK inhibitors. Abrocitinib is an oral JAK inhibitor being studied in adolescents and adults that can be taken at 100-mg or 200-mg doses. Baricitinib is another oral drug with a 1-mg, 2-mg, and 4-mg dosage. Ruxolitinib (Opzelura) is a topical inhibitor that comes in 8.75% and 1.5% strengths and should be applied twice daily.

Upadacitinib, another oral JAK inhibitor, is available in 15-mg and 30-mg strengths. Other than Ruxolitinib (Opzelura), all these drugs are still in the drug trial phase and not approved by the FDA.

Rotolo discussed the features of JAK inhibitors and the unique management of atopic dermatitis, mentioning that there may be some limitations for individuals with cardiac diseases or gastrointestinal disorders.

**PHARMACISTS’ ROLE**

Pharmacists have an important role in treating atopic dermatitis in terms of OTC recommendations.

“We’ve got hydrocortisone in a couple of different strengths in a couple of different formulations, in creams and in ointments,” Rotolo said.

She also discussed the importance of specifying dosages of topicals, given that the term “pea-sized amount” can mean different quantities to different individuals.

In terms of specific product lines, CeraVe and Eucerin work well to hydrate the skin, McConaha said.

Finally, if there is no improvement in a case of atopic dermatitis after 6 weeks or if it creates psychosocial disruptions, such as missed days at school or work, the pharmacist should advise the patient to see a physician, she said.
Monitor Patients for Opioid-Induced Adverse Drug Events

Use Lowest Effective Dosages to Prevent Constipation, Sedation, Respiratory Depression, and More

By KATHLEEN KENNY, PHARMD, RPH

Because opioids have no analgesic ceiling, they are the most powerful tool for managing acute and chronic pain. Over the past few decades, the number of prescriptions for opioids has increased substantially worldwide. In 2017, more than 191 million opioid prescriptions were dispensed to Americans.1 That same year, more than 47,000 deaths occurred as a result of opioid overdose.2 More than 50% of hospitalized patients receive opioids at some point during their stay. In addition, more than 95% of surgical patients receive opioids.3
Opioids are known to have opioid-related adverse drug events (ORADEs), which affect most organ systems and range from mild constipation to circulatory arrest. The more common ORADEs include nausea, physical dependence, respiratory depression, sedation, tolerance, constipation, and vomiting.

Opioids attach to opioid receptors on nerve cells and act to decrease pain perception. Opioid receptors are found extensively in the brain and spinal cord, as well as the circulatory, gut, and lung systems. Most common ORADEs occur in these systems.

**NAUSEA AND VOMITING**

Opioid-induced nausea and vomiting (OINV) occurs in approximately one-third of patients who receive opioids. It is a significant factor in several complications, including dehydration, electrolyte imbalances, and pulmonary aspiration.

The exact mechanism of OINV is unclear. However, some studies have shown a correlation between nausea and vomiting with an intravestibular mismatch, similar to motion sickness. Therefore, prevention of OINV can be achieved if the patient stays still after opioid dosing. Moving the head less has been shown to decrease a patient’s OINV.

There are 4 options for treating OINV: dose reduction, opioid switch, route of administration change, and medications such as antiemetics, corticosteroids, and metoclopramide.

**CONSTIPATION**

Opioid drugs inhibit gastric emptying and peristalsis in the gastrointestinal tract. This results in delayed absorption of medications and increased absorption of fluids, leading to constipation and hard stools. Approximately 50% of patients taking opioids develop opioid-induced constipation (OIC), which may occur immediately following the start of therapy or develop over time. This is not an adverse event (AE) that decreases over time.

To prevent OIC, patients should increase their dietary fiber, exercise, and fluid intake and begin laxative therapy and/or a stool softener at the same time opioid therapy begins. All types of laxatives can be used, except for bulk-forming laxatives such as psyllium. Bulk-forming laxatives can increase the bulk of the stool and distend the colon, contributing to the obstruction and worsening abdominal pain.

Once OIC has developed, treatment relief is often incomplete and slow. Stimulant laxatives, such as senna or bisacodyl with or without a stool softener, commonly are used to treat OIC. Daily doses of an osmotic laxative, such as polyethylene glycol, also can be used. Saline laxatives, such as magnesium citrate, are another option.

For refractory OIC, subcutaneous methylnaltrexone is the most effective. Other therapies include alvimopan (Enterex), liposomes, naldeemedine, and naloxegol.

**SEDATION**

Sedation is a dose-dependent effect of opioids and occurs in approximately 40% of patients. Most patients will develop a tolerance to the sedative properties of opioids, but some may need a dose reduction.

The best way to prevent sedation and other dose-related AEs is to use the lowest effective opioid dose. If sedation persists, switching to another opioid may help. In addition, minimizing unnecessary medications or using antipsychotics and stimulants judiciously may help manage central nervous system AEs.

**PHYSICAL DEPENDENCE AND TOLERANCE**

Physical dependence on opioids develops after repeated use over a long period of time. When the drug is discontinued, the body goes through
withdrawal, which can be life-threatening. To prevent withdrawal, patients should taper doses of opioids gradually.\(^8\)

Tolerance to an opioid develops when a patient no longer responds to the drug dose that worked at the beginning of therapy. It takes a dose increase to achieve the same pain relief they originally achieved.\(^8\)

**RESPIRATORY DEPRESSION**

Respiratory depression is a major OADE that often leads to death. The drug development community is investigating opioids that do not affect the respiratory system, as well as respiratory stimulants such as ampakines, 5-HT agonists, and phosphodiesterase-4 inhibitors.\(^9\)

Naloxone is the mainstay for treatment of opioid-induced respiratory depression (OIRD). Naloxone displaces opioids from the μ-receptors and reverses opioid overdose within minutes. It rapidly reestablishes independent breathing and return of consciousness. Unfortunately, naloxone has a short half-life, especially compared with the duration of action of many opioids. Thus, the effects of naloxone may wane before the respiratory depression effects of the opioid end, which may lead to a recurrence of OIRD. Repeat doses may be necessary.\(^9\)

**CONCLUSION**

With the increase in opioid overdoses, prescriptions, and use, it is important to know the common AEs and how to prevent and treat them.

Over the past few decades, the number of prescriptions for opioids has increased substantially worldwide. Keeping patients comfortable and safe is an integral part of what pharmacists do. It is imperative to monitor patients taking opioids to reduce diversion and manage some of the adverse events these opioids can create.

**REFERENCES**


PATIENTS COMMONLY SELF-TREAT PAIN WITH nonprescription analgesics, and pharmacists can help them choose the correct OTC products. Acute pain typically initiates abruptly and can often be attributed to a known cause such as an injury or surgery. Chronic pain typically lasts for 3 or more months and can be caused by a condition, disease, inflammation, an injury, medical treatment, or an unknown reason. Pain is a complex symptom that affects individuals differently, and therapy should be tailored to the individual’s needs. Left untreated, pain may affect quality of life, including cognitive, emotional, and physical functions.

Because of the opioid crisis in the United States, many health care professionals are exploring alternative approaches to pain relief, such as cognitive therapy, cold and heat treatments, physical therapy, and OTC oral and topical analgesics.

Many individuals frequently use nonprescription oral and topical analgesics to self-treat mild to moderate pain because the products are accessible, easy to use, and reasonably priced. Consumers spent $4.5 billion on oral analgesics and $1.1 billion on topical analgesics in 2020, according to a Consumer Healthcare Products Association report.

Selecting an appropriate nonprescription product may be overwhelming for many patients, especially if they have other medical conditions and/or are taking other medications. Therefore, pharmacists are in a critical position to advise patients on oral and topical nonprescription analgesics, as well as direct them to seek counsel from their primary health care providers when warranted. That is especially important if further evaluation is needed, the pain is severe, or self-treatment is not appropriate.

RECOMMENDATIONS AND RECENT NEWS
The American Academy of Family Physicians and the American College of Physicians (ACP) in August 2020 recommended the use of topical nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line therapy for treating acute, non–low back pain from musculoskeletal injuries in outpatient settings. Evidence has shown that topical NSAIDs are among the most effective options for pain reduction, physical function, symptom relief, and treatment satisfaction, and they have not been linked with any considerable adverse effects. The ACP guidelines suggest other treatment options when appropriate, including oral NSAIDs to diminish or relieve symptoms and acupressure and transcutaneous electrical nerve stimulation to decrease pain.
“These types of injuries and associated pain are common, and [as physicians] we need to address them with the best treatments available for the patient,” Jacqueline W. Fincher, MD, MACP, president of the ACP, said. “The evidence shows that there are quality treatments available for pain caused by acute musculoskeletal injuries that do not include the use of opioids. There are a number of recommended interventions that are not opioids to choose from, and topical NSAIDs should be the first line of treatment.”

The results of a study published in European Journal of Pain indicated that pain has been frequently described as a clinical feature of COVID-19, and the main pain syndromes that have been linked with the acute phase of the virus are arthritis, headaches, myalgia, and neuropathic pain.

The results of a study published in Nature Reviews Endocrinology issued a consensus statement cautioning against the use of nonprescription acetaminophen during pregnancy. The authors warned of possible links to adverse fetal development outcomes, called for additional investigation, and encouraged additional precautions prior to use in pregnancy.

However, some experts have indicated that more research is warranted and that the findings from the study should not change clinical decision-making. In response to the publication, medical societies including the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine have made statements continuing to encourage the safe administration of acetaminophen to patients who need it during pregnancy.

National Health Interview Survey data published in Pain indicated that 50.2 million, or 20.5%, of adults in the United States in 2019 experienced chronic pain. The estimated total value of lost productivity due to chronic pain is nearly $300 billion annually.

CONCLUSION
Pharmacists should advise patients about the proper use of the selected product, including adherence to manufacturer directions, dosage, potential adverse effects, and recommended duration of use. Pharmacists also serve as excellent resources in identifying possible drug-drug contraindications and interactions. Patients taking other medications and those with chronic medical conditions should always consult their primary health care providers before taking any nonprescription drugs. Pharmacists can also make recommendations about using nonpharmaceutical measures to alleviate joint and muscle pain. For example, the RICE protocol (rest, ice, compression, elevation) helps diminish inflammation and swelling associated with acute joint and muscle injuries, and localized heat therapy may be beneficial for patients with noninflammatory pain.

Encourage patients with continual, severe, or recurring pain to seek additional care from their primary health care providers, especially if pain worsens or they see no signs of progress after using nonprescription analgesics. Advise patients to limit the use of systemic analgesics to 10 days unless otherwise directed by their primary health care providers.

REFERENCES
Good Hemp Wellness Softgels
Manufactured by Good Hemp Wellness

Good Hemp Wellness Softgels are oil-based, fat-soluble supplements designed to help maximize absorption in the bloodstream. Each softgel contains 25 mg of cannabidiol; each bottle contains 30 softgels for a total of 750 mg per bottle. The softgels contain beneficial cannabinoids with less than 0.3% THC, according to the company’s website.

FOR MORE INFORMATION: goodhempwellness.com

Florajen Eczema
Manufactured by Florajen

Florajen, which specializes in probiotics, has introduced Florajen Eczema. Each box contains 30 single-serve packets with ingredients that have been clinically shown to improve eczema symptoms such as inflammation, itchiness, and redness, according to the company’s website. The packet’s contents can be mixed into cold or room-temperature food (eg, yogurt or applesauce) or noncarbonated beverages (eg, juice or milk). Florajen Eczema should be taken daily for the best results. The packet’s contents are safe for individuals 6 months or older. If taking an antibiotic, patients should take Florajen Eczema at least 1 or 2 hours before or after the antibiotic prescription.

FOR MORE INFORMATION: florajen.com

Aspercreme Arthritis Pain Relief Gel
Manufactured by Aspercreme

Aspercreme’s new pain relief gel contains diclofenac, a nonsteroidal anti-inflammatory that helps reduce inflammation and relieve arthritis pain, according to its website. The gel is for use on hands, knees, wrists, and other joints. The product can be used 4 times a day for up to 21 days. It has not been shown to work for sports injuries, sprains, or strains.

FOR MORE INFORMATION: aspercreme.com

Zyrtec Non-Medicated Soothing Face Wipes
Manufactured by Zyrtec

Zyrtec face wipes refresh and soothe the face while removing dirt, dust, and pollen. The wipes also can be used to remove makeup and oil. They are infused with micellar water, which helps gently clean the skin. The wipes do not contain cetirizine, which is the main medication in Zyrtec for allergy relief, so they are gentle and safe to use on the face, according to the company website.

FOR MORE INFORMATION: zyrtec.com
Back Pain

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

CASE 1: Nonpharmacological Therapy

MP is a 54-year-old woman who has worked as an office manager at a desk all day for 25 years and who has a sedentary lifestyle. She also commutes 30 minutes each way to her office. MP does not engage in physical activity other than short evening walks after dinner when weather permits. MP helped her adult son move into a new home the day prior and lifted boxes and furniture. That caused lower back pain, and she thinks she may have strained her muscles. MP inquires about rest, ice, compression, and elevation (RICE) as a nonpharmacological approach to managing the back pain. What should the pharmacist advise?

Although acute back pain may be self-limiting, a nonpharmacological approach with RICE may help decrease the inflammation associated with muscle injury and promote recovery. The RICE method is best applied in the first 72 hours of injury and may be applied with or without pharmacological interventions.1,2

It is recommended that MP rest her back for 24 to 48 hours to promote healing. She should refrain from weight-bearing activities during this time. Encourage MP to apply ice to her back for 15 minutes 3 to 4 times daily for 24 to 72 hours. Compression can be applied to the back using an elastic bandage or wrap. To prevent future back pain due to bursts of activity, MP should aim for moderate physical activity and stretch to strengthen muscles.1,2

CASE 2: Osteoarthritis

JR is picking up acetaminophen for pain relief for his wife, MR, a 66-year-old woman with osteoarthritis. She has been experiencing lower back pain due to osteoarthritis of the hips. JR says that MR does not have a significant medical history apart from the osteoarthritis. She has been taking acetaminophen for many years, but it has not relieved her back pain. JR asks about other nonprescription relief for back pain resulting from osteoarthritis of the hip. What should the pharmacist recommend?

In previous years, acetaminophen was recommended as a first-line analgesic for arthritic pain relief instead of nonsteroidal anti-inflammatory drugs (NSAIDs) in relieving pain. In recent years, evidence-based guidelines have steered away from acetaminophen and changed the first-line recommendation for osteoarthritic pain. The 2019 American College of Rheumatology/Arthritis Foundation (ACR/AF) guidelines, for example, strongly recommend oral NSAIDs as first-line agents for this patient population. Similarly, the Osteoarthritis Research Society International (OARSI) 2019 guidelines removed oral acetaminophen for all forms of osteoarthritis. The caution taken in recommending NSAIDs as first-line pain relief is understandable, given the risk of serious adverse effects (AEs) such as cardiac events, gastrointestinal (GI) bleeding and ulcers, and nephropathy. Despite the risks, the ACR/AF and OARSI guidelines considered the benefits versus risks and recommended the use of NSAIDs first. Furthermore, the OARSI guidelines recommend the addition of a proton pump inhibitor to lessen the risk of GI ulcerations in cases where a patient is at high risk for AEs and if nonselective NSAIDs will be used continuously. Like the ACR/AF and OARSI guidelines, American College of Physicians guidelines on treatment of all chronic back pain recommend oral NSAIDs first rather than oral acetaminophen for pharmacological treatment.1,3-5

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Given the absence of significant risk of GI bleeding for MR and the data available, the pharmacist should recommend that she switch to NSAIDs for back pain relief.
CASE 3: Topical Anesthetics

Q
PM is a 27-year-old woman who calls the pharmacy for advice on treating lower back pain due to a recent sprain from a new workout class. She has tried acetaminophen, oral NSAIDs, and RICE therapy. PM does not want to continue taking systemic medications. She says she felt some relief when using 1 of her mother’s leftover prescription-strength Lidoderm patches. PM asks whether a similar OTC product is available. What information can the pharmacist provide?

A
PM has tried the first-line recommendations for acute back pain: oral NSAIDs and RICE. Like the prescription-strength transdermal patch, lidocaine is available over the counter, as is topical lidocaine, as a cream, gel, lotion, and ointment. The maximum OTC strength of lidocaine is 4%.6
Remind PM that topical lidocaine should not be applied more than 3 times daily for a maximum of a week. The absorption of lidocaine will increase with exercise, heat application, and skin moisture. PM should wash her hands after each application and avoid contact with mucous membranes. She should avoid applying lidocaine to areas with skin injury and discontinue if irritation occurs and clean the skin. If PM starts using the OTC patch, she can wear it on clean, dry skin for up to 8 hours.6

CASE 4: Heat

Q
EP is a 57-year-old woman with lower back pain and a history of osteoarthritis. She calls the pharmacy with questions regarding her back pain and stiffness. EP reports that she tried the RICE method last week after acute pain onset and has not yet felt relief. She has heard that heat may also be a potential intervention for this type of pain. What information can the pharmacist provide to EP regarding heat therapy for back pain?

A
For acute back pain and stiffness that is not inflammatory in nature, thermotherapy may deliver relief. Unlike ice therapy, heat should not be applied when inflammation is present, as the heat could perpetuate vascular leakage and vasodilation. The ACR/AF guidelines also recommend thermotherapy as a nonpharmacological treatment for osteoarthritic pain. Applying heat can decrease muscle spasms, increase blood flow to the affected area, and relieve stiffness. Different forms of heat applications studied include heating pads, hot-water bottles, and warm compresses. Newer products include heat-generating pads and wraps.3,4,7
Apply the heat for 15-minute periods 3 to 4 times daily. Overall, heat therapy should not be applied on areas of broken skin or recent injury, as this may increase the risk of skin burn. Ready-to-use heat wraps can be applied to the back for a maximum of 8 to 12 hours, depending on the product label. The adhesives should be applied to clean, dry skin. EP should avoid using lotions or topical analgesics underneath the heat application, as this may also increase the risk of skin burns. If she experiences burning, itching, or pain upon application of heat, she should remove the heat immediately.4,7
MIGRAINES ARE THE MOST COMMON type of headache, and approximately 14% of Americans have them, costing up to $13,000 per patient annually in lost work time and productivity.1-3

Women experience migraines roughly 3 times as much as men.1 Patients who have migraines typically self-treat until OTC medications no longer work. Then they visit a primary care provider (PCP) and eventually may need to see a specialist.4

DIAGNOSTIC CHALLENGE
Migraines are tricky. They can present with or without aura, occasionally are bilateral, and at other times may be felt at a different spot in the head.5 PCPs struggle to diagnose migraines because patients often report different clinical presentations over time. Additionally, many providers cannot isolate patients’ specific risk factors, such as fatigue, lack of sleep, mental tension, missed meals, and stress. Also difficult to isolate are triggers such as alcohol, changes in altitude or barometric pressure, light, menstruation, noise, odor, physical activity, smoking, and vasoactive substances in food.6

Pathophysiologic changes in the central nervous system (CNS), rather than the vascular system, seem to precipitate migraines.1 When the pain pathway is stimulated, the CNS releases messenger molecules, including calcitonin gene-related peptide (CGRP), nitric oxide, and serotonin.1 Thus, migraines are a neurological condition.

Because 70% of those who develop migraines have a first-degree relative who also has migraines, a genetic component is likely.1

Migraines can be chronic (occurring more than 15 days per month) or episodic (occurring fewer than 15 days per month). The index of suspicion for migraines rises when patients report at least 2 of the following criteria: light or sound sensitivity, moderate to severe head pain, nausea or vomiting, pulsating pain quality, and unilateral or 1-sided pain.

Table 1 describes a migraine's typical presentation.

Table 1. Migraine Symptoms1,7

- Moderate to severe pulsating, throbbing unilateral pain
- Sudden onset and pain that lasts 4 to 72 hours
- Possible nausea/vomiting* and/or aura and cutaneous allodynia, which is neuropathic pain and increased sensitivity to being touched
- Increased symptoms aggravated by light,* physical activity, and/or sound*
- Incapacitation for up to 3 days

* Either nausea/vomiting or light/sound sensitivity must accompany a migraine episode.1

Approximately one-third of individuals with migraines report aura, which is a language, motor, neurologic, sensory, speech, or visual disturbance lasting 5 to 60 minutes that signals a headache is starting.4 Some individuals experience depression, fatigue, food cravings, hyperactivity or hypoactivity, neck pain or stiffness, or yawning before a migraine (called a prodrome). These symptoms may also persist after the migraine resolves (called a postdrome).3

Some acute migraines respond to the patient resting in a dark room and applying cold packs with pressure to the forehead or temple areas.1 Table 2 lists medications for migraine management.
CLINICAL PEARLS

The American Headache Society’s Choosing Wisely recommendations indicate that butalbital-containing medications or opioids are not first-line interventions.\(^{17}\) Frequent, prolonged use of OTC pain medications is unwise because patients can become tolerant to specific drugs’ analgesic effects, magnifying migraine frequency and intensity. For these patients, detoxification may be necessary, and the migraine may worsen during the withdrawal period.\(^{17}\)

Preventive treatment helps patients who are unresponsive to or cannot tolerate abortive therapies or have recurring migraine attacks that interfere significantly with quality-of-life.\(^{3}\) Just one-third of patients who could benefit from preventive migraine treatment receive them. Discontinuation rates are also quite high once patients start prophylaxis.\(^{19}\) Preventive drugs with the strongest evidence supporting their use are anticonvulsants divalproex sodium and topiramate; \(\beta\)-blockers metoprolol, propranolol, and timolol; and frovatriptan for short-term prevention of migraines associated with menstruation.\(^{19}\) CGRPs and onabotulinumtoxinA also are approved for prevention.

Women who experience migraines with an aura should not take contraceptives containing estrogen.\(^{5}\) They have a 2-fold increase in the risk of ischemic stroke compared with women whose migraines are without an aura, and estrogen supplementation increases this risk.\(^{20}\)

CONCLUSION

Patients who have migraines may turn to pharmacists first. Pharmacists need to engage patients in conversation and encourage them to ask their prescribers about newly approved preventive therapies when appropriate.

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TABLE 2. Medications for Migraine Management\(^{8-16}\)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Class</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral: acetaminophen</td>
<td>Analgesics</td>
<td>• Not recommended as sole drug • Often combined with aspirin and caffeine</td>
</tr>
<tr>
<td>Injectable: onabotulinumtoxinA</td>
<td>Botulinum toxins</td>
<td>• Botulinum toxins are not interchangeable. • Must be administered by a trained professional</td>
</tr>
<tr>
<td>• Intravenous: eptinezumab (Vyepti) • Oral: rimegepant (Nurtec ODT) • Subcutaneous: erenumab (Aimovig), fremanezumab (Ajovy), and galcanezumab (Emgality)</td>
<td>Calcitonin gene–related peptide antagonists</td>
<td>• Good efficacy and safety/tolerability profile, especially in chronic, episodic, and frequent migraines; most common adverse effects include hypersensitivity with nasopharyngitis, constipation with injection site reactions, injection site reactions, and nausea • Monoclonal antibodies given monthly or quarterly intravenously or subcutaneously</td>
</tr>
<tr>
<td>Oral: dihydroergotamine and ergotamine • Nasal spray, suppository: dihydroergotamine</td>
<td>Ergots</td>
<td>• Common adverse effects include blood vessel contraction, cramps and tingling in the feet and hands, dysphoria, nausea, and vomiting.</td>
</tr>
<tr>
<td>Oral: lasmiditan (Reyvow)</td>
<td>Novel serotonin agonist (ditan)</td>
<td>• Common adverse effects are dizziness and sleepiness. • Good central nervous system penetration and a more favorable vascular adverse effect profile than the triptans • Women who are/may become pregnant should not take it.</td>
</tr>
<tr>
<td>Oral: aspirin, diclofenac, ibuprofen, and naproxen sodium</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>• Available in many dosage forms • Common adverse effects include dizziness, dyspepsia, gastrointestinal upset, headache, heartburn, and nausea. Serious adverse effects include changes in liver function, gastrointestinal bleeding, and ulcers.</td>
</tr>
<tr>
<td>• Nasal spray: sumatriptan and zolmitriptan • Oral: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, and zolmitriptan</td>
<td>Triptans</td>
<td>• Common adverse effects include a burning sensation over the skin; chest, jaw, or neck tightness; fatigue; nausea; numbness or tingling, especially involving the face; pressure or squeezing; and rapid heart rate. • More consistently effective when used to treat migraine earlier in the attack</td>
</tr>
</tbody>
</table>

FOR REFERENCES, GO TO PHARMACYTIMES.COM/PUBLICATIONS.
Paliperidone Palmitate Extended Release (Invega Hafyera)
Manufactured by Janssen

The FDA has approved paliperidone palmitate extended release (ER) injectable suspension, a twice-a-year treatment for adults with schizophrenia. It is a long-acting atypical antipsychotic injection that offers the fewest doses per year. The injection helps individuals with schizophrenia live without relapses. Before transitioning to the twice-yearly treatment, individuals must be treated with a once-a-month paliperidone palmitate ER injectable suspension (eg, Invega Sustenna) once a month for at least 4 months or a once-every-3-months paliperidone palmitate ER injectable suspension (eg, Invega Trinza) for at least a 3-month cycle.

FOR MORE INFORMATION:
janssen.com

Dihydroergotamine Mesylate Nasal Spray (Trudhesa)
Manufactured by Impel NeuroPharma

Dihydroergotamine mesylate is a nasal spray to treat migraines, with or without auras, in adults. The spray works by entering the vascular-rich upper nasal space and moving into the bloodstream. It provides consistent relief, even hours after the onset of the migraine.

FOR MORE INFORMATION:
impelnp.com

Rivaroxaban (Xarelto) With Aspirin Use
Manufactured by Janssen

The FDA has approved an expanded indication for rivaroxaban to be taken with aspirin for the treatment of lower-extremity revascularization resulting from symptomatic peripheral artery disease (PAD). It is the first treatment for both coronary artery disease and PAD. A regimen of 2.5 mg twice a day with aspirin 100 mg daily has been approved. The medication is used to reduce the risk of major adverse limb and cardiovascular events.

FOR MORE INFORMATION:
xarelto-us.com

Zanubrutinib (Brukinsa)
Manufactured by BeiGene

The FDA has approved zanubrutinib for the treatment of individuals with Waldenström macroglobulinemia. It is a monotherapy treatment used in combination with other therapies to treat various B-cell malignancies. The drug was designed to have sustained inhibition of Bruton tyrosine kinase protein. It is also approved to treat chronic lymphocytic leukemia, mantle cell lymphoma, and other diseases.

FOR MORE INFORMATION:
brukinska.com
Kerendia From Bayer

By MONICA HOLMBERG, PHARMD, BCPS

THE FDA HAS APPROVED KERENDIA (finerenone, Bayer) for reducing the risk of cardiovascular death, end-stage kidney disease, hospitalization for heart failure, nonfatal myocardial infarction, and sustained estimated glomerular filtration rate (eGFR) decline in adults with chronic kidney disease (CKD) associated with type 2 diabetes (T2D).1 T2D is the leading cause of end-stage kidney disease, with approximately 40% of patients with T2D developing CKD. Kerendia is the only nonsteroidal mineralocorticoid receptor antagonist to receive approval for this indication.2

PHARMACOLOGY AND PHARMACOKINETICS

Kerendia is a nonsteroidal, selective antagonist of the mineralocorticoid receptor. Mineralocorticoid receptor overactivation is thought to contribute to fibrosis and inflammation, which can lead to permanent structural damage of the kidney.1,2 Maximum plasma concentration is observed 0.5 to 1.25 hours after oral administration. Steady state plasma concentration is achieved after 2 days of treatment. The terminal half-life of Kerendia is approximately 2 to 3 hours. It is metabolized to inactive metabolites primarily by CYP3A4 and to a lesser extent by CYP2C8.3

DOSAGE AND ADMINISTRATION

Serum potassium and eGFR should be obtained before initiating treatment with Kerendia. Patients with a serum potassium concentration of greater than 5.0 mEq/L should not begin treatment with the medication. The recommended starting dose for patients with an eGFR greater than or equal to 60 mL/min/1.73 m² is 20 mg orally once daily. Patients with an eGFR of less than 60 mL/min/1.73 m² but greater than or equal to 25 mL/min/1.73 m² should begin treatment with 10 mg orally once daily. Kerendia should not be initiated in patients with an eGFR of less than 25 mL/min/1.73 m². The dosage may be increased to the target daily dose of 20 mg daily after 4 weeks of treatment and an assessment of eGFR and serum potassium levels. Kerendia may be taken with or without food.1

CLINICAL TRIALS

Kerendia was evaluated in a double-blind, multicenter, placebo-controlled, randomized study (NCT2540993) in adults with CKD associated with T2D. Patients who received a clinical diagnosis of chronic heart failure with reduced ejection fraction and persistent symptoms (New York Heart Association class II to IV) or who had significant nondiabetic kidney disease were excluded from the study. Participants were randomized to receive either Kerendia or a placebo and were followed for a median of 2.6 years. The study found that Kerendia reduced the incidence of the primary composite end point of a sustained decline in eGFR of greater than or equal to 40%, kidney failure, or renal death. Kerendia also reduced the incidence of the composite end point of cardiovascular death, hospitalization for heart failure, nonfatal myocardial infarction, and nonfatal stroke.1,2

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Treatment with Kerendia is contraindicated in patients with adrenal insufficiency or who are concomitantly using moderate or strong CYP3A4 inhibitors. Kerendia may cause hyperkalemia. Patients with decreased kidney function and higher baseline serum potassium levels are at a greater risk for developing hyperkalemia. More frequent serum potassium monitoring may be required for higher-risk patients, including those using medications that impair potassium excretion or increase serum potassium levels. Serum potassium levels should be monitored periodically during treatment with Kerendia, and the dosage should be adjusted when appropriate.

Patients using Kerendia should avoid consuming grapefruit and grapefruit juice. Because concomitant use with moderate or weak CYP3A4 inhibitors may increase the risk of adverse effects (AEs), serum potassium levels should be monitored during adjustment or initiation of either Kerendia or the moderate or weak CYP3A4 inhibitor, and the dose of Kerendia should be adjusted as needed. Kerendia should not be used concomitantly with moderate or strong CYP3A4 inducers. Patients should not breastfeed while using Kerendia and for 1 day after stopping treatment. Patients with severe hepatic impairment should not take Kerendia. Patients with moderate hepatic impairment may require additional serum potassium monitoring. The most common AEs are hyperkalemia, hyponatremia, and hypotension.1

REFERENCES


AUTHOR BIO

MONICA HOLMBERG, PHARMD, BCPS, is a pharmacist and Pharmacy Times® contributor.
A PATIENT, WHO HAD BEEN hospitalized after suffering a stroke, died following an inadvertent infusion of fentanyl.

Although the patient's condition at first had improved, he later developed difficulty swallowing. After aspirating food and suffering acute respiratory arrest, the patient was placed on a ventilator, during which he was sedated via an intravenous (IV) fentanyl infusion (10 g/mL) connected to 1 of multiple channels on a smart infusion pump. Over the next several days, the patient received fentanyl, ranging from 25 to 100 g per hour, with the dose titrated daily as needed for sedation. Several days later, the patient's physician discontinued the fentanyl infusion in the morning, hoping to extubate the patient that afternoon. The pump channel infusing the fentanyl was turned off, but the infusion container was left in place and remained connected to the patient's IV line.

Later that day, the smart infusion pump alarm went off, alerting practitioners that a bag of Lactated Ringer's, which was infusing via a different pump channel, was near completion. A nurse filling in for the patient's primary nurse responded to the pump alarm, turned off the corresponding pump channel, retrieved a new Lactated Ringer's infusion, attached it to the correct pump channel, and programmed the infusion correctly. However, she accidentally restarted the fentanyl infusion instead of the Lactated Ringer's solution. Although the pump alarm went off, the nurse silenced it, thinking that it had happened accidentally. An evening nurse caring for the patient also did not notice that fentanyl, not Lactated Ringer's, was infusing. The rate of the fentanyl infusion was not disclosed.

Several hours later, the patient's blood pressure had dropped significantly, and the error was recognized. Although the fentanyl infusion was then quickly discontinued, the prolonged hypotension caused by the fentanyl infusion caused serious brain and organ anoxia and ultimately resulted in the patient being removed from life support several days later.

SAFE PRACTICE RECOMMENDATIONS

Although the Institute for Safe Medication Practices (ISMP) has no additional details other than what could be gathered through the news media, there are several risk-reduction strategies that might have prevented this error.

Change-of-shift verification. Require oncoming nurses to verify all their assigned patients’ infusions, tracing the lines and inspecting the pump settings and infusion labels, and then matching each with orders. The oncoming nurse and the nurse finishing her shift should perform this verification process together.

Disconnect and discard all discontinued or held infusion bags/syringes. Discontinued or held infusions should be immediately removed from the pump, disconnected from the patient, and discarded. A discontinued infusion should not be left set up via a stopped
infusion pump that either remains connected to the patient and/or hanging on the patient’s IV pole at bedside. Also, the tubing should be changed to ensure no residual medication is left that could be inadvertently administered as a bolus when the tubing is used to administer other fluids and medications.

**Implement interoperability.** Implement bi-directional (ie, autodocumentation and autoprogramming) smart infusion pump interoperability with the electronic health record to reduce the risk of pump programming errors.

**Label the tubing and pump channel.** Labels with the name of the drug being infused and route of administration should be affixed to each access line (eg, epidural and IV) at the distal end of the tubing closest to the patient and on the tubing above the channel or pump. If available as a pump feature, ensure the name of the infusion is clearly visible on the pump screen.

**Manage operational alarms.** For a variety of reasons such as alert fatigue or poor warning design, operational alarms may be overlooked or quickly overridden. To maximize efficiency and response to operational alarms, establish thresholds for duration and frequency, identify the top alarms by type and care area/profile, and determine whether they are critical alerts. Remove non-critical alerts as needed to decrease alert fatigue.

**Trace the tubing.** When parenteral infusions are changed (new bag or syringe), reconnected, or started or the rate is adjusted, the tubing should be traced by hand from the solution container to the pump and then to the patient for verification of the proper channel/pump and route of administration.
Off-Patent Drugs That Lack Generic Competition Can Be Costly

Solutions Could Save Federal Government More Than $1 Billion Annually for These Single-Source Drugs

By SKYLAR KENNEY

THE FDA HAS BEEN WORKING since 2017 to encourage generic competition for off-patent, older drugs that do not have considerable existing competition.

Referred to as single-source drugs, they also have caught the attention of policy makers and politicians, who have offered many solutions including allowances for importation from manufacturers in other countries and instructing the federal government itself to manufacture these drugs.

These drugs account for more than $1 billion in federal spending. Reducing their cost could benefit the patients who depend on them, according to the results of a study published in the Journal of General Internal Medicine.  

PRICING AND AVAILABILITY

Using data from the FDA’s 2019 List of Off-Patent, Off-Exclusivity Drugs Without an Approved Generic and 2018 annual drug spending from the Medicaid and Medicare Parts B and D Spending Dashboards, investigators calculated median and total spending for all drugs on the FDA’s list except for duplicates, drugs not listed in the Medicare or Medicaid Drug Spending Dashboards, and drugs with direct generic competition or competition from near-identical products. The final study cohort consisted of 137 single-source drugs with available Medicaid or Medicare spending data in 2018, of which approximately 42% were administered orally, 26% were injected, and 33% had another route of administration.

On a per-drug basis, the median federal spending was $600,000 post rebate, with the total spending for all drugs in the study cohort reaching $1.6 billion. The top 20 drugs accounted for 89% of total spending, with varying estimates of rebate totals leading to a total spending range of $1 billion to $2.2 billion. Estimating that policies that increase competition or otherwise reduce the prices of these drugs would cut spending by 20% to 80%, the investigators concluded that the potential federal savings in 2018 ranged from $328 million to $1.3 billion. However, spending on these drugs represents just a fraction of the total annual drug spending by Medicaid and Medicare, which is more than $100 billion.

There are potential strong public health incentives for the reduction of cost for these medications, according to the investigators.

Many of the single-source drugs on the FDA list are essential medicines, meaning that price hikes result in significant financial burdens for patients who depend on them, according to the study. These include brinzolamide (Azopt), conjugated estrogens (Premarin), and octreotide acetate (Sandostatin LAR).

Although policies that lower the costs of these drugs are unlikely to make a substantial impact on the overall federal prescription drug spending, there is still a potential benefit cost benefit for patients.

POTENTIAL SOLUTIONS

A prior study established the potential for importing off-patent drugs from independent manufacturers outside the United States as a cost-saving solution. In a 2018 study evaluating whether off-patent prescription medications were available from independent manufacturers approved in other well-regulated settings across the globe, investigators reviewed novel tablet or capsule prescription drugs approved by the FDA since 1939 that were no longer protected by patents or other market exclusivity with 3 or fewer generic versions available. The study results showed that 64% of the 170 eligible study drugs had at least 1 manufacturer approved by a regulator outside the United States and 19% had 4 or more. There were 44 drugs without any FDA-approved generic version in the study cohort, 21 of which were available from at least 1 manufacturer approved by 1 of the 7 non-US regulators and 2 of which were available from 4 or more manufacturers.

Facilitating access to these manufacturers in the United States could help sustain access to off-patent drugs, especially those that are essential, according to the study authors.

However, although the drugs evaluated for the study were all capsule or tablet medications, some of the drugs on the FDA list may have little competition because of technical challenges in producing a generic, such as products delivered through inhalers and topical formulations. Generic drug manufacturers must ensure that the drugs they produce contain the same active pharmaceutical ingredients as the brand-name medications. For these medications, reducing prices may require enhanced government negotiating power.
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**Mycophenolate Mofetil for Oral Suspension**  
Marketed by Lannett

**Compare To:** CellCept  
Lannett’s mycophenolate mofetil for oral suspension 200 mg/mL has received first-cycle approval from the FDA. It is equivalent to CellCept oral suspension 200 mg/mL. The oral suspension helps prevent organ rejection in allogeneic heart, kidney, or liver transplant recipients, according to a company statement. It is to be used with other immune suppressants and is a new dosage for Lannett. It can be prescribed for individuals 3 months and older.

FOR MORE INFORMATION:  
lannett.com

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**Deferasirox Tablets**  
Marketed by Camber Pharmaceuticals

**Compare to:** Jadenu  
Camber Pharmaceuticals has added deferasirox tablets, the generic equivalent of Jadenu, to its lineup. Deferasirox is used to treat iron overload caused by blood transfusions and chronic iron overload syndrome caused by a genetic blood disorder. The tablets come in 90-mg, 180-mg, and 360-mg dosages in 30-count bottles. It has been approved for use in individuals 2 years or older who have iron overload caused by blood transfusion and for individuals 10 years or older with chronic iron overload syndrome.

FOR MORE INFORMATION:  
camberpharma.com
Carbamazepine Tablets
Marketed by VGYAAN

**Compare to:** Tegretol

The FDA has approved carbamazepine tablets 200 mg from VGYAAN Pharmaceuticals. The medication is for use in individuals with partial, generalized, tonic-clonic, and mixed seizures, and trigeminal and glossopharyngeal neuralgia nerve pain, according to a company statement. It is the generic equivalent of Tegretol 200 mg.

**FOR MORE INFORMATION:** vgyaan.com

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Reddy-Lenalidomide
Marketed by Dr. Reddy’s

**Compare to:** Revlimid

Reddy-Lenalidomide, a generic equivalent to Revlimid, has been approved by Health Canada, according to a statement from Dr. Reddy’s Laboratories. The medication is used to treat individuals with transfusion-dependent anemia because of low or intermediate 1-risk myelodysplastic syndromes from a deletion 5q cytogenetic abnormality with or without cytogenetic abnormalities. It is available in 2.5-mg, 5-mg, 10-mg, 15-mg, 20-mg, and 25-mg strength capsules in blister packs.

**FOR MORE INFORMATION:** drreddys.com

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FROM PIPELINE TO PATIENT

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ISSUE OF THE CASE
An employee of a construction company suffered serious injuries at work and subsequently received a recommendation from his physician that he use medical marijuana. Can the employer refuse reimbursement of the marijuana expense because the substance is illegal under federal law?

FACTS OF THE CASE
In 2001, a 28-year-old construction worker was at a job site in a Middle Atlantic state when a truck delivering concrete dumped its load on him.

The employer construction firm denied his workers’ compensation claim, saying that it was “investigating the matter.”

Fifteen years later when the employee’s claim was launched against the firm, the employer stipulated that the employee had experienced a “compensable accident” that led to a workers’ compensation claim.

By December 2001, the employee’s pain was preventing him from working, and he left the company. His firm-based health insurance coverage terminated the following month. That led to him being unable to afford the diagnostic testing and treatment recommended for him. In November 2003, he went to an emergency department with severe pain, leading to spinal surgery, the cost of which mistakenly thought would be covered by the firm’s workers’ compensation insurer.

For the next 12 years he sought relief by visiting a series of medical specialists, which led to him receiving a diagnosis of chronic debilitating pain in 2015.

On top of that, his chronic use of opioids for pain relief led to “dependency that is unlikely to respond to other treatments,” according to the claim.

He turned to a physician who was board certified in hospice and palliative care.

That physician was also certified pursuant to the relevant state statute to prescribe medical marijuana.

The practitioner considered the patient “a candidate for the medical marijuana program, due to his ‘intractable muscular skeletal spasticity and chronic pain.’”

He provided all the extensive documentation to get the man enrolled in the state’s medical marijuana program.

This new therapeutic approach led to the patient getting some relief
from his incessant pain; he had stopped taking oxycodone and was sleeping better. He used the prescribed amount of 2 oz of marijuana per month, paying $6.16 monthly out of pocket to purchase it.

The provider testified that the patient would need to use it for the rest of his life.

After several days of an administrative hearing before an administrative law judge, the employer reached an agreement with the former employee to cover medical bills, reimbursement for out-of-pocket medical expenses, and temporary disability benefits. Remaining to be decided by the administrative law judge were coverage for permanent disability and future medical treatment.

The administrative law judge decided that the former employee had 65% permanent partial or total disability, with 50% because of his orthopedic condition and 15% because of the effects of medical marijuana.

The judge reviewed, with the input of expert witnesses, the alternatives for the patient: using opioids or marijuana. The judge concluded that "a comparison of the risks leads inescapably to a conclusion that marijuana is the appropriate option."

By participating in the medical marijuana program, "the patient was able to improve his condition and had been opioid-free for several years."

The administrative law judge ordered compensation coverage for the patient's marijuana purchases.

The employer appealed to the state court, where the employer argued that it was "impossible to simultaneously comply with "the federal CSA and the state's Medical Marijuana Act [MMA]."

THE RULING
The court ruled that there was no conflict between the federal and state statutes.

THE COURT’S REASONING
It began its review by focusing on the wording of the federal CSA, which classified the substance as a Schedule I drug and declared it to be a criminal offense to engage in the “manufacture, distribution, or possession of marijuana.”

Turning to the wording of the state's MMA, the court pointed out that the statute “affords an affirmative defense to patients who are properly registered under the statute but are nevertheless arrested and charged with possession of marijuana.”

The court continued with a consideration of the law applicable to situations where federal and state laws are in conflict.

Its focus was on whether it is impossible to comply with both federal and state requirements or whether state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress."

The court concluded that "if an eligible patient can comply with both the CSA's prohibition of the manufacture, possession, or distribution of marijuana, and the MMA decriminalization of the possession of marijuana for medical use," then there is no triggering of preemption.

Legal research uncovered no prior case precedent in the state, and, despite 33 states having legalized medical marijuana, courts in just 2 states had considered whether their medical marijuana legislation is preempted by the CSA.

The legislation of this state did not require the employer to manufacture, possess, or distribute marijuana; it was merely being ordered by the administrative agency to provide reimbursement. Coverage for reimbursement was upheld by the court.
THE OVER-THE-COUNTER HEARING AID ACT of 2017 is legislation that amended the Federal Food, Drug, and Cosmetic Act to direct the FDA to classify hearing aids as nonprescription medical devices and propose regulations guiding the use of these products.1

The bipartisan bill, passed into law by Congress in August 2017, included a provision giving the FDA 3 years to propose regulations that would reasonably ensure the efficacy and safety of the OTC devices.

Congress specified that FDA regulations would override any state law restricting patient access to the OTC devices. The deadline given to the FDA to finalize these regulations was August 18, 2020. However, the FDA missed this deadline, citing other regulations that it deemed more consequential amid the COVID-19 pandemic. It is unclear whether the FDA will fulfill the regulation requirement contained in the legislation to increase the safety of devices that are already available for millions of patients with hearing impairment.2

The FDA does not require hearing aid manufacturers to provide evidence of efficacy and safety to receive clearance to market these products unless the hearing aid is classified as an implantable bone-anchored device. Because of the lack of safety evidence, the primary evaluation of devices comes from clinicians and patients. Under the Over-the-Counter Hearing Aid Act of 2017, Congress encouraged the FDA to pursue hearing aid review under the 510K pathway, which reviews hearing aids for efficacy and safety. The FDA previously cleared Bose Corporation’s self-fitting air-conduction hearing aids using this 510K pathway. Requiring the FDA to regulate these devices under this pathway will increase safety and decrease the risk of hearing loss due to overamplification by ensuring the maximum volume output of devices is safe.3

More than 30 million Americans have mild to moderate hearing loss. Hearing impairment is frequently associated with dementia, depression, injurious falls, and an overall negative quality of life. Although prescription hearing aids provide major improvements in a patient’s quality of life, they are frequently underutilized, with just 15% to 30% of individuals routinely wearing them. This disparity in hearing aid use is because of limited patient access to audiologists and the high cost of hearing aids. The average cost of hearing aids is $2,300, and they frequently are not covered by commercial insurance. Medicare does not cover hearing exams, hearing aids, or hearing aid fitting sessions. The COVID-19 pandemic negatively affected this population further with mask regulations and physical distance requirements,4 which means OTC hearing devices can improve even more patients’ quality of life.

AUDIOLOGISTS AND PHARMACISTS
Audiologists are health care professionals whose primary focus is to evaluate, diagnose, treat, and manage hearing loss in patients of all
Most audiologists have earned a doctor of audiology degree, a doctor of science degree, or a PhD in balance and hearing sciences. Audiologists help patients select hearing aids that are best for their lifestyles. With the emergence of OTC hearing devices, many audiologists are hopeful this will increase their role in patient care. Some audiologists are suggesting that this new accessible technology may even be beneficial for children with attention-deficit/hyperactivity disorder or autism.

These accessible devices also will open doors between pharmacists and audiologists to collaborate and ensure that the right device is selected for the patient.

There may be an opportunity for audiologists to guide pharmacists on the correct fitting and usage of OTC hearing aids and play a large role in setting counseling guidelines to protect patient safety.

Pharmacists as accessible patient care providers will be particularly affected by this bill, as they are frequently sought out for their counsel on a multitude of OTC products. The Over-the-Counter Hearing Act will place a large responsibility on pharmacists to assist patients selecting a device, help with accurate adjustment of the device, and counsel patients on signs and symptoms of damage because of overamplification. It is increasingly important for pharmacists to stay up-to-date on literature regarding the newest devices.

### REFERENCES

THE HOLIDAY SEASON IS OFTEN a stressful time for pharmacy professionals, but the COVID-19 pandemic has made life even more frenetic for pharmacist moms, who are working twice as hard at administering vaccines yet still need to take care of their families. Moms often try to get time off from work to spend more time at home, but they too frequently find themselves trying to “run an errand” to get away. In the best of times, stressors include maintaining a healthy diet and dealing with family members who are difficult or may not be around next year. With COVID-19, moms take on the additional stress of determining which guests are “safe” to invite over or visit.

I asked some pharmacist moms and colleagues for tips on how to make the holidays more of a celebration and less of a hassle. Here is some advice they shared.

Be flexible when traveling. Consider driving or renting a recreational vehicle to avoid overcrowded airports. Travel early or late so children can sleep in the car or on the plane. Keep in mind that airports will be much more crowded than in 2020. Consider buying travel insurance, in case fear takes over or someone gets sick.

Create a shared calendar. This helps families keep track of all arrangements, children’s and holiday events, and work commitments, including end-of-year deadlines or reviews.

Make a “safe” list. Decide in advance with whom to spend time and to pass up because of the pandemic. Many individuals still have a limited social circle and are not obligated to open it up during the holidays.

Purge and donate toys. This is the best time of year to get rid of clutter. Teach children about the spirit of giving and have them donate toys they no longer use.

Save the menu. If hosting, create a menu and save it. Pull it out each year and take notes so that nothing is forgotten in subsequent years.

Simplify shopping. Before moms built a family, and definitely before the pandemic, going to the mall to browse and maybe grab a latte was easy. Now shopping online is the way to go. Stalk family and friends’ Instagram or Pinterest accounts to get ideas. Or forget about gifts altogether and exchange recipes or donate to a charity instead.

Tap family and friends for childcare. Childcare can be a nightmare around the holidays. Day care centers do a better job of staying open than regular schools, but even day care centers close for breaks. Once children are in elementary school, they often have at least 1 to 2 weeks more time off than their parents do. The end of the year can be a busy time for deadlines, so enlist family members and friends to spend time with and watch the kids.

Finally, and most importantly during the holidays, be thankful. This can be a hard time of year for many, even during normal times, let alone during a pandemic. Those who are missing loved ones should think of ways to honor them during their festivities. Be grateful for family, friends, health, and a job, even while acknowledging that the past year and a half has been really difficult and that we have lost a sense of normalcy that many are only starting to regain.
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IT IS COMMON FOR A board of pharmacy to require a nonresident pharmacy to be licensed in its state before allowing that pharmacy to deliver, mail, or ship a prescription drug to any of its residents.

It also is becoming increasingly common for a board to require a pharmacist-in-charge to be designated and registered for a nonresident pharmacy to engage in such activity in that state. This process is understood by pharmacy practitioners engaged in cross-state dispensing and general pharmacy practice activity.

Recent actions by the Nevada Board of Pharmacy, however, are not common and are causing confusion and dismay.

After reviewing Nevada state law NRS 639.100(1)(a), the board has started issuing notices to nonresident pharmacies engaged in the pharmacy practice of compounding or dispensing prescription drugs for any controlled substance or “dangerous drug” for a Nevada patient.1

The supporting documents require any pharmacist engaged in such practice to pay a $250 annual registration fee to Nevada and to be subject to state oversight.2 This requirement goes beyond simply requiring a pharmacist-in-charge to register with the board. It applies to all pharmacists engaged in compounding or dispensing activities in Nevada.

It has long been understood that in Nevada only the nonresident pharmacy and a pharmacist-in-charge must be registered with the board. The turnabout by the board has been referenced in a recent opinion letter issued by the board’s general counsel. The July 22, 2021, letter makes clear that it is illegal for any pharmacist to dispense or compound a drug in Nevada unless that pharmacist is properly registered with the board. In addition to the financial burden for nonresident pharmacists paying the annual fee to Nevada, such pharmacists also will be subject to Nevada legal and regulatory oversight for any errors or omissions in their daily pharmacy practice. This appears to be the most extreme registration
requirement that any state has undertaken when it comes to the breadth of licensing requirements for nonresident pharmacy professionals in that they are directly legally binding for a pharmacist or pharmacy when engaging in compounding or dispensing.

The board’s general counsel says that NRS 639.100(1)(a) states that it is not lawful for any individual to compound or dispense, or permit to be compounded or dispensed, any drug into the state unless the individual “holds the appropriate certificate, license, or permit” required by applicable Nevada law.¹

If a pharmacist is dispensing into Nevada and is not licensed there, there is also the added complication that a third-party payer might not honor any claims submitted for reimbursement to the extent that it is alleged that the pharmacist was not engaged in the authorized practice of pharmacy because of not holding a valid license pursuant to Nevada law.

Many industry stakeholders have taken the position that the new interpretation by the board of its own statute is improper, and they are stunned that a longstanding statute is suddenly being interpreted in a materially different way. Further, stakeholders have voiced concern that this new requirement is onerous, unnecessary, and simply a way to generate revenue for Nevada. To obtain an independent opinion, the board recently asked the Nevada state attorney general (AG) to weigh in on whether the board and its counsel have properly interpreted the meaning of the statute. As of this writing, the board and industry are awaiting the issuance of an opinion letter from the AG’s office.

To ease the initial burden of licensure reciprocity, the board is offering applicants the option to obtain a temporary pharmacist registration request application, which can be found on the Nevada Board of Pharmacy website.² This new temporary registration is intended to be valid for 6 months after issuance or until pharmacists can reciprocity license with Nevada from their home state, whichever occurs first.

Pharmacies and pharmacists should determine their staffing needs accordingly when dispensing into Nevada under the new interpretation of the laws by its board. Business decisions and to what extent they intend to comply with the new requirements should not be taken lightly, and consultations with legal counsel are needed to understand the benefits and risks of pursuing this new form of licensure requirement. Because the landscape is evolving rapidly, stakeholders should take the time to analyze new developments frequently.

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MTM Consult

Consider a Career Move to Remote Medication Therapy Management

Growth of Telehealth Means Pharmacists Can Play an Important Role in Patient Care Even When Working From Home

By JENNIFER GERSHMAN, PHARMD, CPH

COVID-19 DRASTICALLY CHANGED THE PHARMACY work environment, including an expansion of telehealth services that has opened new opportunities for pharmacists to work remotely.

There was a 154% increase in telehealth visits during the last week of March 2020 during the COVID-19 pandemic compared with the same period a year earlier, according to a CDC report.¹

Telehealth is an effective way for pharmacists to provide services while enhancing patient care, evidence shows.² One study evaluated the effect of a pharmacist telephone intervention on nonadherent patients with diabetes and hypertension who were enrolled in a Medicare Advantage plan.³ The study results showed that the pharmacist telephone intervention resulted in significantly better medication refill adherence, which was measured by proportion of days covered during the 6 months following the phone consult.¹ Additionally, there were lower discontinuation rates among patients with diabetes and hypertension.³ Pharmacists’ expertise with drug information can help patients in rural areas, as well as individuals who are unable to travel, and address necessary medication therapy management (MTM) services through telehealth.

FINDING OPPORTUNITIES

There are a variety of flexible, remote opportunities for pharmacists to perform MTM services from their home offices. Molina Healthcare provides health plans for the Centers for Medicare & Medicaid Services (CMS), and it also offers insurance plans for patients through state health plan exchanges or marketplaces.⁴ The company offers remote MTM positions for pharmacists, and patients are eligible for services if they have 3 or more of the following conditions: chronic obstructive pulmonary disease, depression, diabetes, dyslipidemia, heart failure, and hypertension.⁵ Additionally, they must take at least 8 medications and meet the minimum annual Part D spending criteria to be automatically enrolled in the Molina Healthcare MTM program.⁶ Pharmacists perform yearly comprehensive medication reviews (CMRs) via phone and develop a medication-related action plan and a personal medication record for each patient.⁴ Additional MTM services include drug monitoring, formulary management, patient education, and regimen review.⁴ Completion of the American Pharmacists Association’s MTM certificate training program is a preferred qualification for this position.⁴

Cardinal Health is a health care products and services company that serves approximately 90% of hospitals in the United States.⁴ Cardinal Health offers both full-time and part-time remote MTM career opportunities.⁴ Job responsibilities include delivering CMRs, patient-centered adherence monitoring, and targeted medication reviews (TMRs).⁴ Pharmacists also play an important role in man-
aging medication costs through formulary and therapeutic interchanges and assessing for duplication of therapy. As part of an interdisciplinary team, pharmacists contact prescribers with interventions to ensure that medication therapy problems are resolved. Required qualifications for Cardinal Health MTM positions include the ability to become licensed in multiple states, if asked; the ability to work independently; a bachelor of science degree in pharmacy or a PharmD degree; the completion of an MTM course; a current license in the state(s) where the pharmacist is practicing; strong therapeutic skills; and technological competency. Pharmacists can join the Aspen RxHealth community through its website to start the process. There is a one-time $75 membership fee once opportunities are found in the pharmacist’s area. Pharmacists set their own flexible schedules for MTM services through this platform.

Humana is a health plan that serves more than 13 million members in the United States and offers MTM services as part of the annual and quarterly benefits. Patients qualify if they have 3 of the 5 following conditions: asthma, diabetes, dyslipidemia, heart failure, and rheumatoid arthritis. Additionally, patients must take at least 8 prescription medications and meet the required annual CMS spending criteria. Pharmacists perform yearly CMRs and quarterly TMRs for patients as part of the MTM services, with a focus on medication education. Other responsibilities include clinical outreach programs, cost-saving initiatives, and formulary management. Additionally, pharmacists provide drug information support for nurses, physicians, and other health care professionals in the Humana network. Humana offers a variety of MTM remote positions, and required qualifications include an active pharmacist license, computer proficiency, and strong communication and organizational skills.

Pharmacists interested in applying for remote positions should search the career section of company websites, because they are frequently updated. Pharmacists who do not see an opportunity listed on the company’s website should send an email to see whether there are part-time remote positions available.

Pharmacists also can set up a free LinkedIn profile and search for remote MTM positions in the jobs tab.

Networking is a great way to find a remote MTM position, because a colleague may provide information about an opportunity that is not yet posted.

REFERENCES
Pharmacists Play Critical Role in Pain Assessment
Their Unique Knowledge and Skills Assist the Care Team in Evaluating and Recommending Ways to Manage Pain

By ABIMBOLA FARINDE, PHD, PHARMD

FOR MOST PATIENTS, PAIN IS a very distressing symptom.

Pain should be considered the fifth vital sign, according to the American Pain Society, which is working to increase awareness of pain treatment. There have been many attempts within the health care industry to understand pain, but it remains a huge challenge. Pain is an indicator to the nervous system that there is a problem, and the unpleasant feeling is an alarm to the body that something must be done to alleviate it. Although pain can assist in diagnosing, it can also reach a point where it may no longer be curable, so it is imperative that immediate steps are taken to identify the underlying issue. Acute pain can transition to chronic pain and have a profound impact on an individual’s quality of life.

High predominance of pain and pain-related disease are leading causes of disability and disease throughout the world, according to results of the Global Burden of Disease Study 2016.

To fully combat pain, its contribution to disability must be understood within the context of biological, physical, psychological, and social factors.

It has been shown that patients are willing to accept pain, particularly postoperatively, given high pain intensity scores, so it is important for pain management to include a collaborative approach. A pain assessment is considered a significant first step toward achieving optimal pain management interventions. Pharmacists can play a key role in pain assessments, because they possess unique knowledge and skills to assist the care team with evaluating and recommending ways to manage pain. Pain management should focus on the description of the pain, duration, intensity, location, and identification of aggravating or alleviating factors. Additionally, it is important for pharmacists engaged in the interviewing process to have an awareness of the pathophysiology of the pain in combination with objective data, such as imaging or laboratory tests, that can help determine the gravity of a patient’s pain. For any health care professional, the performance of a comprehensive pain assessment screening to deliver adequate pain management is viewed as a universal requirement.

Pharmacists can begin an assessment by asking patients to rate their pain on a scale from 0 to 10, with 10 being the worst possible pain and 1 being no pain. Pharmacists should then ask how long the pain has been felt, whether the pain radiates to other locations, what the associated symptoms are, what events precipitate the pain, what type of pain it is, where the pain is located, and whether the pain is constant or intermittent. The more focused and thorough the assessment, the more likely that the pain’s characteristics can be identified and treated.

CONCLUSION
Pharmacists serve a critical role in pain management for patients, so it is vital that their expertise and training be used to the fullest when it comes to the thorough assessment of pain.
Medical Billing Is Now Part of Job Description

Technicians With Specialized Skills in Prescription Billing Can Help Pharmacists Focus on Clinical Services

By AMBER SUTHERS, MSAH, CPHT

A PHARMACY TECHNICIAN’S JOB DESCRIPTION is to “assist pharmacists in their daily tasks,” according to the Pharmacy Technician Education & Career Guide. “They are directly involved with the receiving and dispensing of prescriptions and client/patient contact. All work is done under the direct supervision of a licensed pharmacist.”

Technicians have traditionally served as patient advocates and support staff members for pharmacists. Retail duties have included coordination with physicians, filing, packaging, patient checkout, and prescription intake, as well as inventory and OTC management and ensuring cleanliness. Technicians in other settings have different duties, but they still fall under the umbrella of preparing medications, labeling them, and distributing them under the direct supervision of pharmacists.

But as pharmacists’ roles have evolved, technicians’ roles have followed suit. Some technicians now also handle clinical service implementation, data mining, patient engagement, practice management, and medical billing, and the expectations of and opportunities for many technicians within the practice will continue to expand. As new clinical opportunities and services arise for pharmacists as clinicians, technicians can absorb the administrative load of billing for services and reconciliation of insurance claims that includes coding services correctly, resubmitting denials, and troubleshooting software issues.

MEDICAL BILLING

Credentialing and Enrollment

To perform medical billing, pharmacists must be credentialed as providers in their respective states. That proves to insurance companies that they

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are legitimate providers. Pharmacist files are examined with each medical insurance enrollment and must be regularly updated. Although the entities and processes may differ, verification of location and provider, as well as enrollment with plans, is needed for both medical billing and prescriptions. Credentialing pharmacists may be the first step in managing medical billing for clinical services. After the enrollments with each specific payer are complete, pharmacists must practice within their scope of practice and bill for allowable services listed in the contract between the insurer and the provider. The technician is a great resource for completing this task, as there is a specific set of guidelines set forth for credentialing and enrollment. The pharmacist signs off on the final submission of documents and signs the medical contracts, comparable to the technician performing data entry and packaging and the pharmacist verifying the final product.

Billing and Reconciliation
After the enrollments are accepted and the pharmacist is in network, technicians cannot just bill for everything that is done and get paid. A service is performed, and from the documentation a code is calculated and submitted to the insurance company. These are called current procedural terminology codes, and insurance companies use them to determine payment. Adequate software platforms must be in place for submitting claims to each payer. Many issues may exist with the different computer programs properly deciphering each box, resulting in denials from the payer and the need to resubmit and reconcile claims. These tasks take a lot of troubleshooting, patience, and time with developers and payers to create a smooth billing workflow system. Pharmacists do not need to be unnecessarily burdened with these tasks. Technicians can use the same skill set for finding overrides, working through rejections, and obtaining prior authorizations for claims to troubleshoot billing issues for medical payers, implement new clinical services, and create a pharmacy billing profile for services rendered.

CONCLUSIONS
Technicians can apply the specialized skills needed to perform tasks directly related to production workflow and prescription billing to also support pharmacists in clinical practice and medical billing. Although technicians will continue to support pharmacists in traditional ways, their role will also continue to expand and evolve to meet the demands of new horizons of patient care.

REFERENCE

Some technicians now also handle clinical service implementation, data mining, patient engagement, practice management, and medical billing.
Flu Vaccine May Protect Against Severe Effects of COVID-19

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

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

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

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

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

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

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

Although more research is needed, the investigators said that they hope the flu shot can provide increased protection in countries where the COVID-19 vaccine is in short supply or help protect against new breakthrough cases in individuals who are already vaccinated against COVID-19.—Jill Murphy

Coadministration of Seasonal Flu Vaccine and Prevnar 20 Shows Promising Results

FINDINGS FROM THE PHASE 3 B7471004 study (NCT04526574) evaluating the immunogenicity and safety of pneumococcal 20-valent conjugate vaccine (Prevnar 20) coadministered with the seasonal influenza vaccine in adults 65 years and older showed positive top-line results, according to a statement from Pfizer.

A total of 1796 participants were enrolled and randomized in the study, with 1727 completing the study across 66 investigator sites in the United States. The responses provoked by Prevnar 20 for all 20 serotypes and by the seasonal influenza vaccine when given together were noninferior to those elicited by the vaccines when administered 1 month apart. Further, the safety profile of Prevnar 20 was similar when the vaccines were coadministered compared with when each was administered separately, 1 month apart, according to the study.

The investigators noted the importance of maintaining vaccination rates for conditions that can lead to respiratory issues, especially with COVID-19 cases still raising concern throughout the United States.

“Both Prevnar 20 and the influenza vaccine are important for helping protect adults against pneumococcal pneumonia and the flu, respectively. However, vaccination rates decline when someone needs to make multiple appointments to receive these vaccines,” Luis Jodar, PhD, senior vice president and chief medical officer at Pfizer Vaccines, said in a statement.

“The results of this trial support current CDC clinical guidance allowing coadministration during a single doctor or pharmacy appointment, so that more adults are able to help protect themselves against both of these respiratory diseases,” he said.—Jill Murphy

Ability to Produce Immunity to Influenza A (H3N2) Called Into Question

THE RESULTS OF A recent study published in Nature Communications shows that adults born in the 1960s and 1970s may be less able to produce neutralizing antibodies to modern influenza A (H3N2) virus strains, and thus middle-aged patients may be continuously susceptible to H3N2 viruses.

The study results show that children aged 3 to 10 years had the highest levels of neutralizing antibodies for the viruses. It also showed that most middle-aged adults did not have detectable neutralizing antibody titers against 3c2.A or 3c1.A2 H3N2 viruses. In fact, the lowest titers were measured in patients born in 1967, a year before H3N2’s introduction into human circulation. It should also be noted that there did not seem to be any significant hemagglutinin (HA) antigenic changes between the 2014–2015 3c2.A and 2017-2018 3c2.A2 strains, which usually results in at least some immunity after exposure.

The authors contend that childhood infections that current middle-aged adults experienced in the 1960s and 1970s primed antibody responses that are reactive but not neutralizing against modern 3c2.A H3N2 viruses. In short, individuals could produce nonneutralizing antibodies that could bind to the viruses’ HA but not prevent infection.

Although the exact reason for the decreased immune response in middle-aged adults remains unclear, these findings suggest that this patient population may be continuously susceptible to the 3c2A H3N2 infection, even with immunization. It also provides some insight into the high infection rates of adults during seasons when H3N2 is the dominant circulating strain and why 3c2A viruses continue to circulate despite minimal to no antigenic drift.

The study results also raise questions about the existence of other age-related immune responses. Further and larger studies are needed to fully evaluate immunity among different aged groups and birth years, investigators said.

Data from such studies could lead to a significant breakthrough in the understanding of immunity and subsequently change influenza prevention approach.—Marilyn Bulloch, PharmD, BCP
Pet Peeves

Wrong Place, Wrong Time
When patients ask you to transfer medications and give you the name of the wrong pharmacy.

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

Not-Helpful Nurse
When you call a doctor’s office and ask for clarification on a script, and the nurse just reads the directions.

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

What’s Bothering You?
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Case Studies
By STEFANIE C. NIGRO, PHARMD, BCACP, CDCES

CASE 1
RK is a 71-year-old woman who has questions about her prescription for doxycycline. She says her doctor told her that doxycycline can cause sun sensitivity and that she should avoid being outdoors while taking the medication. RK says that she completed her last dose of a 10-day course of therapy the night before. She wants to know whether she can enjoy outdoor time at the beach this weekend.

How should the pharmacist respond?

CASE 2
TM is a young man whose custodial grandmother wants him to get the COVID-19 vaccine. His grandmother says he is afraid of needles and has had a vasovagal reaction after other vaccinations.

Which COVID-19 vaccine should the pharmacist recommend and what counseling should be provided to ease their concerns?

Answers
**Fun Facts**

Denver, Colorado, is ranked as best city for mental health care in the US. According to CertaPet, a website for individuals seeking emotional support dogs, cities were ranked on a 50-point scale weighing indifferent factors that determine the best cities for mental health care. Denver was highest on the list, with a score of 40 out of 50 points, and Salt Lake City, Utah, was second, with a score of 37.4. There was a 3-way tie for third place among Hartford, Connecticut; Minneapolis, Minnesota; and Seattle, Washington, each with a score of 36.9.

The best-selling prescription drug is adalimumab. Adalimumab (Humira, AbbVie) was the best-selling drug of 2020, generating a massive $19.8 billion in total revenue, according to Drug Discovery & Trends. Sales of adalimumab accounted for close to 61% of AbbVie’s total net revenue in 2018 and were more than $5 billion higher than the net profits generated by runner-up pembrolizumab (Keytruda, Merck). Adalimumab is approved in Canada, Europe, Mexico, and the United States for the treatment of several autoimmune diseases, including ankylosing spondylitis, Crohn disease, plaque psoriasis, psoriatic arthritis, and rheumatoid arthritis.

The most expensive drug at a local pharmacy is lonafarnib. In terms of retail pharmaceuticals, lonafarnib (Zokinvy, Eiger Biopharmaceuticals) is the most expensive drug that can be obtained from a pharmacy, according to GoodRx. It is an orphan drug designed to reduce the risk of death for individuals with Hutchinson-Gilford progeria syndrome, which causes premature aging. Most individuals take 200 mg per day, which costs up to $86,040 a month, as each 50-mg capsule is priced at $717. However, the most expensive drug on the market is onasemnogene abeparvovec (Zolgensma, Novartis), which costs $2.1 million for a 1-time infusion. The medication is used to treat spinal muscular atrophy, a rare childhood disorder that results in muscular erosion.
PROPER USE AND THE ROLE OF BIOSIMILARS IN INFLAMMATORY BOWEL DISEASE TREATMENT TO IMPROVE OUTCOMES AND ACCESS TO CARE: KEY CONSIDERATIONS FOR PHARMACISTS

EDUCATIONAL OBJECTIVES

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

• Explore the history and growing role of biosimilars as well as the clinical and economic impact of their role in the management of inflammatory bowel disease (IBD).
• Examine immunogenicity, extrapolation of indications, interchangeability, and switching of biosimilars in clinical practice for IBD management.
• Analyze data regarding the safety and efficacy of biosimilars in the management of IBD and the mechanism of action of biologic anti-TNF agents.
• Determine the pharmacist’s role in the management of patients with IBD and strategies to incorporate the use of biosimilars into clinical practice.

TARGET AUDIENCE: Pharmacists

ACTIVITY TYPE: Application

RELEASE DATE: November 12, 2021

EXPIRATION DATE: November 12, 2022

ESTIMATED TIME TO COMPLETE ACTIVITY: 2.5 hours

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

Introduction

There has been a wide range of applicable uses for biologic agents since the first approval in 1982 for diabetes.1 Today, that treatment list has expanded to indications such as oncology, multiple sclerosis, and inflammatory disease states such as Crohn disease (CD) and ulcerative colitis (UC). When these agents entered the market, they revolutionized clinical practice due to their efficacy, expensive cost, and management. The research and manufacturing processes required for biologics are intensive, especially considering they are created from a biologic source such as plant or animal cells. This is where the term “biologic” gets the name, with a wide variety of products approved including therapeutic proteins, monoclonal antibodies, and vaccines.2 Despite the contributions these agents have had in practice, the benefits are accompanied with a significant burden to health care costs.3 As patents of brand products expire, the same is true for biologic agents, which presents an opportunity for biosimilars to emerge in the market to alleviate high cost and create clinical momentum.

Generic versus Biologics versus Biosimilars

The FDA defines a biologic product as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine applicable to the prevention, treatment, or cure of a disease or condition of human beings.”4 As most biologic products are proteins, the term “therapeutic protein products” has been used by the FDA for proposed products seeking biosimilarity approval.5 Essentially, biosimilars are products that must demonstrate structural, functional, and comparable pharmacokinetic (PK)
and pharmacodynamic (PD) properties to the reference product or original biologic. This differs from a generic product considering that generic products are chemically derived and can demonstrate bioequivalence very easily. Generic products have the same active ingredient as the brand, synthesized chemically to exhibit a similar clinical performance in patients. The only varying attributes are the inactive ingredients. Comparably, biosimilars also have the same “active ingredient,” or biological substance; however, the production methods for biosimilars vary, resulting in more scrutiny for approval.

The differences between chemical/generic and biologic/biosimilar products are summarized in Table 1. Considering the size of biologics, they are typically large and complex in nature when compared with a chemical agent that has a low molecular weight and simpler structure. The largeness in size of biologic agents makes it difficult to fully characterize the agent in terms of its structural properties. This challenge can ultimately have an impact on the product’s PK and PD parameters. Furthermore, the manufacturing process of chemical agents is chemically engineered with predictable results. However, biologics require a specialized process that is subject to greater variability, as the living systems from which they are derived can be different. Lastly, biologic agents are likely to have a higher rate of immunogenicity compared with chemical agents, meaning that patients may exhibit an immune response to the drug, resulting in therapy failure.

**Cost of Biosimilars**

Following the first biosimilar approval in 2015, many additional agents have since received approval, with several that are commercially available. As cost is a major barrier for both the patient and health plan, the utilization of biosimilars could result in substantial savings. In a large-employer case study of 392 patients using a biologic, it demonstrated that there could be a total employer savings between $838,000 and $2.8 million if the patient switched to a biosimilar. When considering that biologic agents accounted for nearly 40% of Medicare Part B spend in 2016, the cost savings from 100% biosimilar utilization is difficult to imagine with the current market landscape. Biosimilars will be covered under Medicare Part D like their original biologics, but it may take time for them to be accepted more in practice. In a study that evaluated close to 2600 Part D plans, coverage for biosimilar infliximab was just 10% compared with 96% of the reference product. When comparing the cost differences between biologics versus biosimilars, there is an average savings of 10% to 37%, which is not significant considering that generic medications are 80% to 85% less expensive than the brands.

**Table 1. Differences Between Biologic and Chemical Products**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Chemical/Generic</th>
<th>Biologic/Biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Low molecular weight</td>
<td>High molecular weight</td>
</tr>
<tr>
<td>Structure</td>
<td>Simple structure</td>
<td>Complex structure</td>
</tr>
<tr>
<td>Production process</td>
<td>Standard</td>
<td>Specialized</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>Chemically engineered</td>
<td>Produced through living cells</td>
</tr>
<tr>
<td>Purity and stability</td>
<td>Stable</td>
<td>Sensitive to storage and handling</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Characterization</td>
<td>Easily defined</td>
<td>Possible variability</td>
</tr>
</tbody>
</table>

**Requirements for Biosimilars**

In addition to the clinical requirements for biosimilars to enter the market, the process for approval is time consuming and costly. The Food and Drug Administration (FDA) defines a biosimilar to be “highly similar to the reference product” without any differences regarding “clinical meaningfulness” from the reference product with respect to “safety, purity, and potency.” In other words, they cannot be identical in the manufacturing process or components applied to the original biologic agent. The general requirements for biosimilar characterization include the following:

- The product must have the same mechanism of action to treat the same conditions as the reference product.
- The product must have the same route of administration, dosage form, and strength as the reference product.
- The product is manufactured, processed, or packaged in a facility that meets regulatory standards to establish that it is safe, pure, and potent.
- The product must demonstrate analytical studies to show it is “highly similar” to the reference product.
- The product must have animal studies that include assessment of toxicity.
- The product must have clinical studies to evaluate PK or PD parameters, including the assessment of immunogenicity in one or more of the conditions it is sought for licensure.

**Expanding Role of Biosimilars in Inflammatory Bowel Disease**

It is difficult to say that there will be a paradigm shift with increased application of biosimilars, but there is immense potential with respect to the benefits specifically in certain conditions. Inflammatory bowel disease (IBD) has been an area of focus for biosimilars simply due...
TABLE 2. SIMPLIFIED MANAGEMENT OF CROHN DISEASE AND ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Severity</th>
<th>Ulcerative colitis treatment</th>
<th>Crohn disease treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td>Aminosalicylate (5-ASA); corticosteroids induction (after 5-ASA failure); addition of budesonide to patients not responding to 5-ASA</td>
<td>Sulfasalazine; controlled ileal release budesonide</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>Budesonide to induce remission; systemic corticosteroids to induce remission</td>
<td>Oral corticosteroids; thiopurines; methotrexate</td>
</tr>
<tr>
<td>Biologic Consideration</td>
<td>Anti-TNF therapy using adalimumab, golimumab, or infliximab</td>
<td>Anti-TNF therapy using, adalimumab, certolizumab pegol, or infliximab, natalizumab, ustekinumab, vedolizumab</td>
</tr>
</tbody>
</table>

Based on treatment patterns in real-world use, there is a trend in the rising usage of biologics in IBD. The most common biologic agent used in UC was infliximab followed by adalimumab, while for CD it was adalimumab followed by infliximab. Both of these agents have biosimilars approved by the FDA, with infliximab biosimilars having commercial availability. Once they become more accepted in clinical practice, the indirect economic benefits could include significant medication savings, increased patient access, and reduction in the cost of illness.

FDA Regulatory Pathway

For a biologic to gain approval, a biologics license application (BLA), accompanied by significant clinical data, is required to be submitted. This process is expensive and lengthy to develop. To simplify these challenges, the Biologics Price Competition and Innovation Act of 2009 (BPCIA) was passed as part of the Affordable Care Act. The BPCIA allowed for an abbreviated licensure pathway for products that are shown to be biosimilar to their reference product. Ultimately, this allows existing data on the reference product to be used to prevent duplicative effort and time on clinical resources. Although manufacturers can use the abbreviated pathway to submit their clinical data for approval, they can submit a full BLA instead. However, this can create a new type of non-innovator product in addition to biosimilars and interchangeable biosimilars. For example, if a biosimilar is approved based on clinical and efficacy studies separate from the innovator product, the FDA considers this product to be neither a biosimilar nor interchangeable with the reference product. Accordingly, biologic products can be approved as an innovator product (BLA pathway), a biosimilar product (BPCIA pathway), or a non-innovator product.

Maintaining regulatory compliance is an important aspect to ensure biologic agents are safe and effective, and the same is valid for biosimilars. The requirements that the FDA has established for biosimilar approval are similar across other guidelines from the European Medicines Agency (EMA) and World Health Organization (WHO). The process incorporates a stepwise approach with the goals of "standalone" development and demonstration of biosimilarity. More specifically, the standalone goal requires verification that a product is safe and effective for the intended use through the clinical trial process. At the same time, the goal of biosimilarity is to prove that there is similarity between the reference product and the proposed product without independently establishing safety and effectiveness. Essentially, a head-to-head comparison evaluating the PK and PD parameters between the reference product and the proposed biosimilar is performed.

Biosimilar Approval Process

The regulatory pathway for biosimilar approval is more rigorous than the approval process for generic drugs. When a generic drug application is submitted to the FDA, the clinical considerations for approval are based on pharmaceutical equivalency, active ingredient being the same and effective, inactive ingredients being safe, the product not breaking down over time, and the right amount of the active ingredient getting to the place in the body where it has effect. Approval of generic products can be accomplished through analytical testing rather than comparative clinical studies. As biosimilars are different from their innovator (reference) product, the FDA requires a "totality of the evidence" approach for data generation and evaluation of residual uncertainty. Totality of
priorities is shown in development.\textsuperscript{13,24} For example, the analytic study results would provide impacts are evaluated before proceeding to the next phase of development.\textsuperscript{13,25} A review of the pivotal step is analytical studies to characterize the structure and function of the product, followed by animal testing, and then clinical studies. If any differences are observed at a particular step, their potential insights into the animal study step, and then the results of both analytic and animal studies would provide information to design the PK and PD requirements in the next clinical step.\textsuperscript{10,25} A review of the pivotal priorities is shown in \textit{TABLE 3}\textsuperscript{13} comparing the process for a reference product versus a biosimilar. Many tests for the reference product are based on the clinical studies to demonstrate safety, purity, and potency. On the other hand, biosimilars require more tests to establish quality to ensure that there is biosimilarity to the reference product.\textsuperscript{13}

As biologic agents may have multiple indications, the process of extrapolation streamlines biosimilar approval, avoiding unnecessary studies while reducing developmental costs.\textsuperscript{27} Extrapolation allows the efficacy and safety data from one indication to be used for another if biosimilarity to the reference product has demonstrated adequate safety, efficacy, and immunogenicity. The clinical trial for adalimumab-atto (Amjevita) was originally submitted as a BLA with efficacy and safety studies in moderate to severe plaque psoriasis and moderate to severe rheumatoid arthritis.\textsuperscript{28} Upon approval, based on the evidence presented, extrapolation allowed adalimumab-atto to be expanded for the other indications including moderate to severe CD and UC.

When a manufacturer submits their application for a biosimilar product, the data demonstrating biosimilarity must include analytical studies, animal studies, and clinical studies that are sufficient to establish the product’s safety, purity, and potency.\textsuperscript{29} Further data are also required showing that the biosimilar product produces the same clinical response as the reference product. Lastly, the data must demonstrate that interacting between the reference product and the biosimilar does not impact clinical safety and effectiveness. Although these requirements outline what is necessary to be included in the application, the FDA reviews each biosimilar product individually to determine which components can be waived if appropriate.\textsuperscript{30,31}

### Naming Biosimilars

Once a biosimilar is out on the market, it is important to distinguish it from the reference product. This has been a complex challenge since the first biosimilar came to market. The WHO has traditionally maintained the responsibility for providing nonproprietary names for the unique active ingredients of drugs. Biologic agents are named based on schemes that include cell therapies, gene therapies, or monoclonal antibodies.\textsuperscript{32} The arrival of biosimilars required a change in the nonproprietary naming process as they are not interchangeable with the reference product despite being highly similar. The most recent guidance published by the FDA states that all biologics and their biosimilars will share the core name of the reference product. This is the nonproprietary name in which the reference product was first approved (eg, adalimumab, infliximab). To distinguish each new biologic and biosimilar, a 4-letter suffix that is devoid of meaning will be attached to the nonproprietary name.\textsuperscript{33} \textit{TABLE 4}\textsuperscript{34} lists the biosimilars of tumor necrosis factor-alpha (TNF-\(\alpha\)) biologics with their proprietary names and approval dates.

When the United States adopted the WHO recommendation for biosimilar nomenclature in 2017, additional requirements were incorporated to ensure the safety of future products. Besides suffixes having

### TABLE 3. FOCUS AREAS OF PRODUCT DEVELOPMENT BETWEEN BIOSIMILAR AND REFERENCE PRODUCT\textsuperscript{13}

<table>
<thead>
<tr>
<th>Priority and focus</th>
<th>Biosimilar product</th>
<th>Reference product</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Analytical studies</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>Medium to high</td>
<td>Nonclinical studies</td>
<td>Clinical pharmacology</td>
</tr>
<tr>
<td>Medium to low</td>
<td>Clinical pharmacology</td>
<td>Nonclinical studies</td>
</tr>
<tr>
<td>Low</td>
<td>Clinical studies</td>
<td>Analytical studies</td>
</tr>
</tbody>
</table>

### TABLE 4. FDA-APPROVED BIOSIMILAR TNF-\(\alpha\) AGENTS\textsuperscript{34}

<table>
<thead>
<tr>
<th>Reference product</th>
<th>Biosimilar (brand name)</th>
<th>Approval by FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Adalimumab-atto (Amjevita)</td>
<td>September 2016</td>
</tr>
<tr>
<td></td>
<td>Adalimumab-adbm (Cylteza)</td>
<td>August 2017</td>
</tr>
<tr>
<td></td>
<td>Adalimumab-adaz (Hyrimox)</td>
<td>October 2018</td>
</tr>
<tr>
<td></td>
<td>Adalimumab-bwwd (Hadlima)</td>
<td>July 2019</td>
</tr>
<tr>
<td></td>
<td>Adalimumab-afzb (Abriliada)</td>
<td>November 2019</td>
</tr>
<tr>
<td></td>
<td>Adalimumab-fkjp (Hulio)</td>
<td>July 2020</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Infliximab-dyyb (Inflectra)</td>
<td>April 2016</td>
</tr>
<tr>
<td></td>
<td>Infliximab-abda (Renflexis)</td>
<td>April 2017</td>
</tr>
<tr>
<td></td>
<td>Infliximab-qbtx (Ixifi)</td>
<td>December 2017</td>
</tr>
<tr>
<td></td>
<td>Infliximab-axxq (Avsola)</td>
<td>December 2019</td>
</tr>
</tbody>
</table>

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4 distinct lowercase letters, they should also prevent confusion from currently marketed products that could lead to a potential medication error. These new characteristics posed a challenge to previously marketed products as they would not satisfy the new conditions for nomenclature. As a result, the FDA updated their guidance to reflect that suffix constraints would only be applied to new originator biologics.

**Interchangeability**

Once biosimilar agents are made commercially available, there is a question of interchangeability status. In 2019, the FDA published their guidance required for biosimilar interchangeability, expanding their need for additional analytical data for substitution consideration. Like generic products, an interchangeable biosimilar product qualifies as pharmacy level substitution, meaning that health care provider intervention would not be necessary. A pharmacist would be allowed to interchange from the reference product to an interchangeable biosimilar as appropriate under state pharmacy laws. The main reason the new interchangeability clause was introduced is due to the variable structure of biologic products. Generic products can qualify to be substituted because the composition of the product is not expected to change. The same is not true for biosimilar and biologic products due to the variability that is involved when living cells are used to manufacture it. However, the additional data for interchangeability status help ameliorate the safety concerns when switching agents. This is not to say that biosimilars that do not have interchangeability status are inferior. It means that the reference product and the biosimilar can be switched without any additional risk based on FDA’s determination. The Purple Book, a searchable online database, gives insight on biological products, biosimilar products, and biologic products with interchangeability status.

One of the biggest wins in the biosimilar landscape was the recent approval of the first interchangeable biosimilar insulin product, insulin glargine-yfgn (Semglee), the equivalent of insulin glargine (Lantus). As a long-acting human insulin analog, the product helps with glycemic control in adults and pediatric patients with type 1 and type 2 diabetes. Insulin glargine-yfgn also enters the market with a reduced price tag that is 65% less expensive than insulin glargine, allowing patients to have more affordable access. Also, a unique attribute to achieving interchangeability status is that the FDA provides 12-month product exclusivity before another interchangeable biosimilar is approved for that reference product. Hopefully, insulin glargine-yfgn can pave the way for future biosimilars to attain interchangeability status.

**Considerations When Switching From Biologics to Biosimilars**

To demonstrate interchangeability for a therapy switch, the FDA requires data from a switching study with multiple switches between the reference and biosimilar product. This is to ascertain the potential negative outcomes such as reduced efficacy and worsening of adverse effects. If a biosimilar product is interchangeable and there are opportunities for multiple switching, pharmacovigilance parameters present an exceptional challenge. With varying devices that are unique to their manufacturer’s standards, the differences in formulation, dosage, and patient support programs should be considered. Clinical experts tend to err on the side of caution when switching and would recommend consent from both the provider and patient before a change. Further clinical concerns include treatment failure and immunogenicity warranting closer review.

**Immunogenicity**

Immunogenicity can result in the lack of efficacy of a product and even cause adverse effects to manifest. As this was a concern when biologic products were first introduced, it is a larger problem with biosimilars, especially considering switches. If a patient is clinically stable on a reference product and then introduced to a biosimilar, there is a concern that their tolerance to the therapy may waiver. From an overall patient perspective, it is an important aspect to consider. If that product is the sole treatment for a chronic or life-threatening condition and a biosimilar switch resulted in immunogenicity, the long-term risk for that patient just increased. If there are multiple biosimilar switches, the immune system may start seeing contrasting products as a virus, resulting in an immune response. It is important that clinical trials are designed to evaluate immunogenicity thoroughly. NOR-SWITCH was one of the more well-known biosimilar trials to study this.

**NOR-SWITCH Study**

The biggest challenge with respect to switching therapies is the lack of data. Recently, the NOR-SWITCH study gained a lot of attention when it evaluated patients on infliximab (reference product) and randomized switches between the infliximab biosimilar and the reference product. As the study was a one-way switch, there were problems with addressing concerns of immunogenicity and antibody formation as reswitching did not occur (reference product to biosimilar then back to reference product). Another added concern was that the study evaluated various conditions (rheumatoid arthritis, psoriasis, IBD, etc). The resulting mixed patient population made it challenging to interpret the outcomes readily as it was not adequately powered. A large subset of patients with IBD (155 patients with CD and 93 patients with UC) were evaluated using the Harvey-Bradshaw Index (CD) and Mayo score (UC). Initially, there was a concern when patients with CD appeared to have better outcomes with the reference product with early data. However, at the end of the study, the biosimilar was proven to be
noninferior to the reference product despite the concern of the study not being large enough.

**STAR**
Which biologics used for IBD have FDA-approved biosimilars?

**Clinical Use of Biologics and Biosimilars in IBD**
Since the approval of infliximab, the first biologic used for IBD, there has been a significant increase in the number of new biologics entering the market with varying mechanisms of action. Although most biologic therapies used in IBD are TNF-α inhibitors, there are also cell adhesion molecules, interleukin inhibitors, and integrin inhibitors. **Table 5** lists each biologic with and without biosimilars that are FDA approved for UC and/or CD with their corresponding dosing. Usage of these agents has also expanded to pediatric indications for both adalimumab and infliximab, which presents a unique case for treating patients with biosimilars in that population. Additionally, the efficacy results from the original biologic trials are shown in **Table 6** with respect to efficacy and safety.

Focusing only on the biosimilars approved for IBD (adalimumab and infliximab), clinical studies have established their safe and effective use. However there has not been enough data exploring multiple biosimilar switches (eg, switching from biosimilar to reference product or switching from one biosimilar to an interchangeable biosimilar). Traditional one-way switch trials have been conducted to establish noninferiority between the reference product and the biosimilar in review. However, further clinical studies are necessary to evaluate the degree of biosimilar switching that is clinically appropriate regarding immunogenicity.

**FDA-Approved IBD Biosimilars**
Both infliximab and adalimumab biosimilars have had sufficient clinical trials in IBD to demonstrate their usage. Compiled data from clinical studies have demonstrated a pooled estimate of overall efficacy of infliximab’s biosimilar to be 83.5% at 24 weeks. However, analytical concerns with respect to sample size and randomization in the studies put a limitation on their overall relevance in practice. Immunogenicity is another worry considering that antibodies from the reference product could cross-react with the biosimilar, resulting in reduced efficacy and

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Mechanism of action</th>
<th>Adult indication</th>
<th>Pediatric indication</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>TNF-α inhibitor</td>
<td>UC + CD</td>
<td>CD</td>
<td>CD + UC: 160 mg SC on day 1, followed by 80 mg 2 weeks later (day 15). Two weeks later (day 29), 40 mg every other week</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pediatric CD: 6 years or older are dosed based on body weight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patients weighing 17-40 kg → day 1: 80 mg SC, day 15: 40 mg, day 29: 20 mg every other week</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patients weighing greater than 40 kg→ day 1: 160 mg SC, day 15: 80 mg, day 29: 40 mg every other week</td>
<td></td>
</tr>
<tr>
<td>Certolizumab</td>
<td>TNF-α inhibitor</td>
<td>CD</td>
<td>Not approved</td>
<td>CD: 400 mg SC initially, and at weeks 2 and 4. Maintenance: 400 mg every 4 weeks</td>
</tr>
<tr>
<td>Infliximab</td>
<td>TNF-α inhibitor</td>
<td>UC + CD</td>
<td>UC + CD</td>
<td>CD + UC: 5 mg/kg IV induction at 0, 2, and 6 weeks followed by maintenance of 5 mg/kg every 8 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pediatric CD + UC: 6 years of age or older: 5 mg/kg IV induction at 0, 2, and 6 weeks maintenance of 5 mg/kg every 8 weeks followed by maintenance of 5 mg/kg every 8 weeks</td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td>TNF-α inhibitor</td>
<td>UC</td>
<td>None</td>
<td>UC: 200 mg SC at week 0, 100 mg at week 2, and maintenance of 5 mg/kg every 8 weeks: 100 mg every 4 weeks</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>CAM-α integrin inhibitor</td>
<td>CD</td>
<td>None</td>
<td>CD: 300 mg IV infusion every 4 weeks</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>IL-12 and IL-23 inhibitor</td>
<td>CD</td>
<td>None</td>
<td>UC + CD: Initial dose varies based on weight (260-520 mg) IV infusion; maintenance dose: SC 90 mg every 8 weeks after initial IV dose, then every 8 weeks afterward</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>α4β7 integrin inhibitor</td>
<td>UC + CD</td>
<td>None</td>
<td>UC + CD: 300 mg IV infusion at week 0, 2, and 6 weeks, then every 8 weeks afterward</td>
</tr>
</tbody>
</table>

CAM, cell adhesion molecule; CD, Crohn disease; IBD, inflammatory bowel disease; IL, interleukin; UC, ulcerative colitis.

**Table 5. Biologic and Biosimilar Agents Indicated for the Management of IBD**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Mechanism of action</th>
<th>Adult indication</th>
<th>Pediatric indication</th>
<th>Dosing</th>
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<tr>
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<td>Certolizumab</td>
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<td>Infliximab</td>
<td>TNF-α inhibitor</td>
<td>UC + CD</td>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td>TNF-α inhibitor</td>
<td>UC</td>
<td>None</td>
<td>UC: 200 mg SC at week 0, 100 mg at week 2, and maintenance of 5 mg/kg every 8 weeks: 100 mg every 4 weeks</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>CAM-α integrin inhibitor</td>
<td>CD</td>
<td>None</td>
<td>CD: 300 mg IV infusion every 4 weeks</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>IL-12 and IL-23 inhibitor</td>
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<td>Vedolizumab</td>
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</tbody>
</table>
adverse effects. Finally, the risk of relapse has yet to be proven with infliximab or adalimumab biosimilars as these agents have similar safety and efficacy profiles to their reference product.

Use of Biosimilars in Pediatric Patients With IBD

There are currently 3 biosimilars approved for the pediatric population for CD and UC: infliximab-axq4, infliximab-dyyb, and infliximab-abda. Infliximab-qbtz is just approved for pediatric CD and not pediatric UC. Current studies are evaluating the use of the infliximab biosimilar only, and to date, there are no clinical studies examining adalimumab biosimilar as an option in pediatric IBD. A reason why limited studies are being conducted could be attributed to interchangeability and nonmedical switching. Nonmedical switching is defined as switching of patients in remission from a prescribed drug to another drug of equal equivalence. For example, if the prescriber writes for biosimilar infliximab, the patient’s insurance may decide which biosimilar is covered to dispense. This also brings up concerns of immunogenicity and there has been incredible pushback

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Indication</th>
<th>Trial name (n = population)</th>
<th>Efficacy (significance)</th>
<th>Common ADEs</th>
<th>Boxed warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>CD</td>
<td>CHARM (n = 854)</td>
<td>Patients in remission at 56 weeks: 36% adalimumab 40-mg group vs 12% placebo (P &lt; 0.001)</td>
<td>Upper respiratory infection, sinusitis, headache, rash</td>
<td>• Discontinue if patient develops serious infection (TB, bacterial, fungal, etc) or sepsis</td>
</tr>
<tr>
<td></td>
<td>UC</td>
<td>ULTRA 2 (n = 248)</td>
<td>Patients in remission at 52 weeks: 17% adalimumab 40-mg group vs 9% placebo (P &lt; 0.004)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certolizumab</td>
<td>CD</td>
<td>PRECISE 2 (n = 428)</td>
<td>Patients in remission at 26 weeks: 48% in infliximab 5-mg group vs 29% placebo (P &lt; 0.001)</td>
<td>Upper respiratory infection, urinary tract infections, arthralgia</td>
<td>• Discontinue if patient develops serious infection (TB, bacterial, fungal, etc) or sepsis</td>
</tr>
<tr>
<td>Infliximab</td>
<td>CD</td>
<td>ACCENT 1 (n = 573)</td>
<td>Patients in remission at 30 weeks: 21% of patients in group 1, 39% of patients in group 2 (P = 0.03), 45% of patients in group 3 (P = 0.0002)</td>
<td>Infusion-related reaction, upper respiratory infection, headache, sinusitis, diarrhea, abdominal pain, pharyngitis, cough</td>
<td>• Discontinue if patient develops serious infection (TB, bacterial, fungal, etc) or sepsis</td>
</tr>
<tr>
<td></td>
<td>UC</td>
<td>ACT 1 (n = 306)</td>
<td>Patients in remission at 54 weeks: 34.7% in infliximab 5-mg group vs 20% placebo (P &lt; 0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td>UC</td>
<td>PURSUIT (n = 464)</td>
<td>Patients in remission at 30-54 weeks: 23.2% in 50-mg group, 27.8% in 100-mg group vs 15.6% placebo (P = 0.004)</td>
<td>Upper respiratory infection, injection site reactions</td>
<td>• Discontinue if patient develops serious infection (TB, bacterial, fungal, etc) or sepsis</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>CD</td>
<td>ENCORE (n = 509)</td>
<td>Patients in remission at 12 weeks: 38% natalizumab 300-mg group vs 25% in placebo (P = 0.001)</td>
<td>Headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, depression, pain in extremities, abdominal discomfort, rash</td>
<td>• Risk of progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>CD</td>
<td>IM-UNITI (n = 509)</td>
<td>Patients in remission at 44 weeks: 53.1% in q8wk group (P = 0.005), 48.8% in q12wk group, vs 35.9% placebo (P = 0.04)</td>
<td>Nasopharyngitis, upper respiratory tract infection, headache, fatigue, diarrhea</td>
<td>No boxed warnings</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>UC</td>
<td>GEMINI 1 (n = 373)</td>
<td>Patients in remission at 52 weeks: 41.2% in q8wk group, 44.8% in q4wk group, vs 35.9% placebo (P &lt; 0.001)</td>
<td>Nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection</td>
<td>No boxed warnings</td>
</tr>
</tbody>
</table>

AED, adverse drug effect; CD, Crohn disease; TB, tuberculosis; UC, ulcerative colitis.

*Biologic has FDA-approved biosimilars.
from medical societies over the lack of long-term data in this patient population.

Utilizing Biosimilars for IBD Treatment

The biggest factor that determines how to use biosimilars effectively in practice relies on when utilization should be considered. Two clinical scenarios for switching biosimilar agents include nonmedical switching (changing the product when a patient is in remission) and switching when a patient is in the active phase of the disease.\(^3\)\(^4\)\(^6\) Despite this, there was still data from a German trial revealed patients on infliximab biosimilar switched back to the reference product, there were no significant initiated biosimilar. In that trial, of the 174 patients with IBD who patients switched back to the reference product from an originally study took it a step further to understand what could happen if unable as it only reviewed patient-reported adverse effects. Another unlike the German trial, there was not detailed safety data available as it only reviewed patient-reported adverse effects. Another study took it a step further to understand what could happen if patients switched back to the reference product from an originally initiated biosimilar. In that trial, of the 174 patients with IBD who switched back to the reference product, there were no significant changes in their remission status.\(^1\)\(^4\)\(^6\)\(^6\) Furthermore, a systematic review suggests that switching from infliximab (reference product) to infliximab biosimilar is safe and effective without concern of immunogenicity. Limitations in data and sample size still put a caution for definitive clinical applicability in practice.\(^1\)\(^4\)\(^6\)\(^5\)

The second scenario explores the use of a biosimilar given that a patient is naïve to biologic therapy, and the patient has active disease. That scenario was tested in the clinical trial that evaluated the efficacy between infliximab-dyyb and the reference product.\(^1\)\(^4\)\(^6\)\(^6\) The results demonstrated noninferiority, suggesting a biosimilar could be prescribed over the reference product. However, the trial was not adequately powered to demonstrate statistical difference among the investigated treatment groups. Infliximab-dyyb was further reviewed in a French multicenter cohort study to understand the impact of surgery, death, hospitalization, and therapy change.\(^1\)\(^4\)\(^6\)\(^7\) Even though there were not any differences observed, treatment duration being longer in the reference product group may have favored the results for the biosimilar.

Biosimilar Combination Therapy

Biologics have been used with other agents in combination and not just monotherapy, which begs the question, is the same true for newly approved biosimilars? Clinical studies for adalimumab biosimilars with methotrexate combination therapy have demonstrated comparable safety and efficacy profiles in the rheumatoid arthritis population.\(^6\)\(^8\) On the other hand, there have not been adequate clinical studies performed to evaluate the clinical appropriateness of combination therapy with biosimilars for patients with IBD.\(^1\)\(^4\) This could be due to safety concerns considering the history of biologic and immunosuppressive agent combination. During the clinical trials of the original biologic agents, there was a reluctance to using thiopurines with the biologic due to the risk of lymphoma. That view has since changed when the SONIC trial demonstrated superior clinical outcomes for combination therapy. Not only do thiopurines improve the clinical outcomes for the patient (fewer anti-infliximab antibodies), but they also improve PK values of infliximab (higher biologic drug levels).\(^6\)\(^9\) Just one clinical study has evaluated the usage of biosimilars with thiopurines for IBD. The results of this study favor combination therapy with respect to efficacy, but all-related clinical activity, endoscopic data, and anti-drug antibodies were not evaluated.\(^1\)\(^4\)

The Role of the Pharmacist

The clinical impact of biosimilars in current practice has yet to be seen in the United States, at least on a large scale. However, in Europe, where biosimilars have been in practice for 15 years, the long experience and surplus clinical evidence have substantiated biosimilar acceptance.\(^7\)\(^0\) Although it is difficult to estimate the potential implications of biosimilars in the United States, European practices with biosimilars can give some insight on how the US should move forward. To ensure that patients and physicians have awareness of biosimilars, educational initiatives about biosimilars can help close any gap of uncertainty through effective communication. Although the FDA has been at the forefront of the educational campaign, it is also imperative that the flow of information crosses between one provider to the next and one patient to another. The acceptance of biosimilars in the market will then help garner confidence in therapeutic switches from reference biologic to a biosimilar.\(^4\)

Outside of spreading education, larger regulatory changes could also bring more awareness and use of biosimilars. For example, some European countries such as France and the United Kingdom have established 80% biosimilar utilization targets, with provider incentives and patient programs to share biosimilar benefits.\(^7\)\(^0\) Although the FDA started efforts to support the use of more biosimilars, there are still barriers, especially when it comes to formulario access. Removing regulatory hurdles with regard to therapy competition is one step to help patients obtain access to biosimilars.
Additionally, rebate and brand gamesmanship should not prevent patients to access lower-priced biosimilars when compared with the original biologic. Pharmacists can help in this process by aligning payer and provider education with respect to safety and efficacy of biosimilar use.

Outside of encouraging education and achieving public acceptance of biosimilars, there will still be challenges in clinical practice when a biosimilar is discussed for a patient. Therefore, it is important to evaluate the clinical parameters and ensure any major concerns are resolved. With respect to biosimilar use in IBD, here are some key issues for pharmacists to keep in mind:

**Interchangeability**
Use the Purple Book to verify that the product has interchangeable status. If not, contact the provider and the patient to ensure alignment before dispensing. Also keep accordance with state laws for interchangeable use as it varies from state to state.

**Pediatric Population**
Only 3 biosimilar products (infliximab-axxq, infliximab-dyyb, and infliximab-abda) are approved for the pediatric population for both CD and UC. Infliximab-qntx is just approved for pediatric CD, and not pediatric UC. Biosimilar adalimumab is not currently approved for pediatric use, and there are no ongoing clinical trials being studied. Carefully review which products are approved for the prescribed indication and if necessary, verify with the provider and patient if the indication is not made clear.

**Nonmedical Switching**
Review the patient’s clinical status with the provider to confirm that the patient is in remission. Clinical studies for nonmedical biosimilar switching have demonstrated positive results with respect to safety and efficacy. Regarding concerns with immunogenicity, ensure patients are examining their clinical response to therapy.

**Combination Therapy**
Clinical studies are lacking to support their use. However, combination therapy has been studied in other disease states (ie, rheumatoid arthritis). Additional clinical data are necessary to evaluate all related clinical activity, endoscopic data, and anti-drug antibodies. If the biosimilar is written for combination therapy, discuss clinical concerns with the provider.

**Pharmacovigilance**
Due to the variability of biosimilar products, review the parameters for reporting as each biosimilar is unique with differing manufacturer requirements.

**Patient Education**
Ensure patients are properly educated about the biosimilar product that they are receiving. Patients must be told that they are receiving a biosimilar and not the reference product. It is important to educate the patient on the biosimilar product even if they have received the reference product in the past. Educating and counseling patients on biologics and their biosimilars is important to ensure they have a good understanding of their therapy, administration, clinical adverse effects, and patient monitoring. In addition to reviewing the standard monitoring requirements of the product with the patient, make sure they are also examining their clinical response to therapy.

Administration and adverse effects are going to be the main concerns for patients when starting any new therapy. Adalimumab and its biosimilars are administered as a subcutaneous injection every 2 weeks. When going over administration of subcutaneous injections, it is important patients are following the instructions of the device or syringe that contains the product. Additionally, patients should be counseled to keep their adalimumab stored in refrigerator when the device is not being used and can be left at room temperature for a maximum of 14 days. Patients should also be trained on the basics of administering their subcutaneous injection. This includes cleaning the injection site, allowing the medication to warm to room temperature or be removed from the refrigerator 15 to 30 minutes prior to injecting, and rotating the injection sites between the abdomen and thigh to prevent scarring. Infliximab and its biosimilars are administered via an infusion provided by a professional at the patient’s home, doctor’s office, or a medical clinic. These infusions last at least 2 hours and are given every 8 weeks. Regardless of how the biologic is administered, adverse effects may occur, and it is important patients be informed on how to manage them.

The most common adverse effects of biologic therapies are risk of infections, injection site reactions (bruising, rash, redness, and swelling), and in the case of biologic infusions, infusion-related reactions. Since biologics target the immune pathway, there is a risk that patients might be at risk of infections. Therefore, before any biologic or biosimilar is administered, it is important patients have a negative tuberculosis test and complete any live vaccines prior to therapy to avoid any further risk of infection. Most of the infections seen with adalimumab and infliximab are upper respiratory tract infections and on occasion, urinary tract infections. Patients should be referred to their provider if they are experiencing any signs and symptoms of infections including fever, chills, sweats, and cough.

In order to prevent or reduce injection site reactions, icing the area of the injection site before and after the injection can help.
rash, or infection. Cold packs can help with swelling and itching, and over-the-counter pain medications can help reduce pain and inflammation. Usually, injection site reactions are mild and resolve on their own. However, if the symptoms persist or there is presence of severe itching, skin rash, or hives, it is important patients seek medical help immediately.71

Lastly, with respect to infusion-related reactions (adverse effects in response to the infusion of the biologic), patients can present with varying symptoms. These include headache, nausea, fever or chills, pruritus, or chest or back pain. They are typically present in proximity with the timing of the infusion and not related to anaphylaxis and hypersensitivity. Usually therapy interruption is not required, but antihistamines, nonsteroidal anti-inflammatory drugs, and IV fluids may be initiated to help mitigate the reaction.71

**Patient Concerns**

Patients may be hesitant when switching from their biologic therapy to a biosimilar. It is crucial as a pharmacist to counsel patients on the similarities that the two share. The biologic and biosimilar product share similar safety, efficacy, mechanism of action, and much more. A full description of these similarities can be seen in TABLE 7.72 Appropriate education on biologics and biosimilars can ensure the patient feels more confident and comfortable with their therapy switch.

**Conclusion**

The journey of attaining biosimilar approval in the United States has been muddied with regulatory challenges but pivotal changes have been made to expedite the process. Although the BPCIA streamlined the requirements needed for biosimilar approval, additional studies are still required for these agents to be considered interchangeable. One-way switches (reference product to biosimilar) dominate what is in clinical trials, but multiple switch studies are necessary to establish stronger evidence for switching between biosimilars. Current support for biosimilar use in IBD is still limited to adalimumab and infliximab as the other biologic products have not been thoroughly evaluated in biosimilar trials. The clinical application of both agents needs to be reviewed carefully based on individual patient considerations such as remission status and clinical response. It is also important to use tools such as the Purple Book and abide by state laws with respect to interchangeability. Finally, educate patients about biosimilars and communicate with the provider if there are any clinical concerns. As more patients start biologic treatment and more biosimilars become commercially available, there will be a push to increase their utilization in practice. Once the biosimilar regulatory pathway evolves for awareness, education, and incentivization to take root, it could only be a matter of time before these agents bloom to reach the same standing as generics.

<table>
<thead>
<tr>
<th>TABLE 7. SUMMARY OF THE BIOLOGIC AND BIOSIMILAR SIMILARITY72</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biosimilar topic</strong></td>
</tr>
<tr>
<td>Biosimilars and generics</td>
</tr>
<tr>
<td>Safety and efficacy</td>
</tr>
<tr>
<td>Mechanism of action</td>
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<tr>
<td>Interactions and adverse effects</td>
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<td>Administration</td>
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<td>Cost of therapy</td>
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<tr>
<td>Naming</td>
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<tr>
<td>Interchangeability</td>
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</table>

**Interactive Patient Case Simulation**

This portion of the activity is unique and interactive, as it simulates real-life patient cases that highlight how to appropriately answer questions that patients may have regarding biosimilars and biologics. Access the simulation at www.pharmacytimes.org/IBD.

**ADDITIONAL RESOURCES**

- Crohn’s and Colitis Foundation: Crohnscolitisfoundation.org
- IBD Support Foundation: Ibdbsf.org
REFERENCES

interchangeable-biologics-more-treatment-choices
68. Bae SC, Lee YH. Comparative efficacy and safety of biosimilar adalimumab and originator
INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.

Go to www.pharmacytimes.org/IBD to access the online version of this activity.

Click "Proceed," then complete the online pretest.

Once completed, click "Next" until reaching the activity posttest.

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

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

NOTE: Your CE credit will be automatically uploaded to CPE Monitor. 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. The estimated cost savings from using biosimilars instead of the original biologic can range as high as ____% in the United States.
   A. 10%
   B. 20%
   C. 30%
   D. 40%

2. Which of the following is true regarding switching from one biosimilar to another biosimilar for the same reference product?
   A. Because biosimilars have interchangeable status, switching should not warrant any clinical concern.
   B. Clinical studies have demonstrated that switching decreases the risk of immunogenicity.
   C. The risk of immunogenicity has the potential to increase with biosimilar switching.
   D. The NOR-SWITCH study has proven that switching from one biosimilar to another biosimilar is safe and effective.

3. Which of the following biosimilars has demonstrated similar safety and efficacy to infliximab (Remicade)?
   A. Infliximab-axxq (Avsola)
   B. Infliximab-dtyr (Inflectriq)
   C. Infliximab-atti (Relanpso)
   D. Infliximab-torrh (Ixanda)

4. What is the difference between a biologic and a biosimilar?
   A. Biosimilars are small, simple, generic products that are the same as the original biologic with respect to safety.
   B. Biosimilars are large, complex, similar products that are efficaciously better than the original biologic.
   C. Biosimilars are small, simple, generic products that are the same as the original biologic with respect to safety.
   D. Biosimilars are large, complex, similar products that are efficaciously similar to the original biologic.

5. A patient wants to know if there are differences regarding administration, adverse effects, and interactions between their biosimilar and the original biologic. As a pharmacist, how would you respond?
   A. Clinical trials have demonstrated some biosimilars to have more adverse effects than the original biologic.
   B. Further clinical studies need to be conducted to demonstrate differences in FDA-approved biosimilars with respect to administration, adverse effects, and interactions.
   C. All clinical evidence that has been reviewed by the FDA has demonstrated that biosimilars have the same administration, adverse effects, and interactions to their original biologic.
   D. Biosimilars have shown to have fewer adverse effects than their original biologic in clinical trials; however, postmarketing data have demonstrated them to be similar.
The Role of the Pharmacist in Addressing the Challenges of Treating Pulmonary Arterial Hypertension Associated With Connective Tissue Diseases

EDUCATIONAL OBJECTIVES

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

• Examine the epidemiology, pathophysiology, risk factors, prognosis, and challenges associated with connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH)
• Explore the mechanisms of action and efficacy and safety data associated with therapies for CTD-PAH
• Use current guidelines to tailor therapy to meet individual patient goals
• Identify the role of the pharmacist in making clinical recommendations to improve management and clinical outcomes in patients with CTD-PAH

TARGET AUDIENCE: Health-system and specialty pharmacists

ACTIVITY TYPE: Application

RELEASE DATE: November 15, 2021

EXPIRATION DATE: November 15, 2022

ESTIMATED TIME TO COMPLETE ACTIVITY: 2.0 hours

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

Introduction

Pulmonary hypertension (PH) is a broad term used to describe an array of clinical conditions that result in elevations in the pressures within the pulmonary vasculature and contains a heterogeneous group of etiologies that are driving these increases in pressure. Treatment is based on the World Health Organization (WHO) 5-group clinical classification scheme. Pulmonary arterial hypertension (PAH) is classified as WHO group I PH, which itself includes a host of underlying conditions leading to the development of PAH, including PAH associated with connective tissue disease (CTD-PAH). PAH is a rare disease with an estimated incidence of 2 to 7.6 cases per million adults per year and a prevalence of 11 to 26 cases per million adults and remains underrecognized with a median of 1.1 years from time of symptom onset to diagnostic right heart catheterization. Patients tend to present in the 5th decade of life with women impacted at a higher rate than men. Prognosis has improved over time with current median survival of 6 years and 1-year survival of 90%. PAH is characterized by progressive narrowing of the pulmonary vasculature due to hyperproliferation, vasoconstriction, and vascular remodeling which, left untreated, results in elevated pulmonary vascular resistance, progressive right ventricular (RV) failure, and death.

Symptoms are nonspecific and related to progressive RV dysfunction, the most common of which is shortness of breath. Additional symptoms include fatigue, weakness, angina, and syncope. These tend to be exertional early in the disease process but occur at rest as RV failure worsens. Symptom severity is graded using the WHO functional class (WHO-FC), with increasing severity represented by a higher number. Class I patients have no symptoms, with class II patients beginning to experience symptoms with strenuous ordinary activity.
ties that begin to slightly limit functional status. Progression to class III is marked by symptoms with less than ordinary activity and severe limitation of functional status, and finally class IV patients exhibit symptoms at rest with inability to perform any activity without symptoms.

CTD-PAH is the second most common cause of PAH. The CTD-PAH population has a higher proportion of older (6th decade) female (nearly 2-fold) patients and an increased comorbid burden of interstitial lung disease (ILD) and left heart disease (LHD). Nearly three-quarters of CTD-PAH cases occur in patients with systemic sclerosis (SSc) with PAH affecting about 10% of the SSc population. The prevalence of PAH appears to be much lower in other CTDs (<5% in systemic lupus erythematosus [SLE] and mixed connective tissue disease [MCTD]); however, these estimates may not accurately reflect the true burden due to lack of routine screening recommendations outside of SSc.

The underlying pathophysiologic mechanisms in CTD-PAH do not differ significantly from idiopathic PAH (IPAH) but may have differing magnitudes of impact on disease progression. Endothelial dysfunction occurs as a result of endothelin-1 (ET-1) overexpression, coupled with deficiencies in both nitric oxide (NO) and prostacyclin. In SSc- and SLE-PAH, this ET-1 overexpression is inversely related to survival, and other data suggest that antibodies targeting ETα receptors are also more common in CTD-PAH and may predict prognosis in SSc-PAH. The role of autoimmunity and inflammation may be more pronounced as well, particularly in forms other than SSc-PAH. Histopathology suggests the presence of several autoantibodies, immune complexes, and proinflammatory cytokines that may contribute to arteriopathy, and there are data to suggest a possible link between inflammation and RV dysfunction.

Current data supporting the use of targeted pharmacologic therapies in the management of PH are overwhelmingly in the PAH (group I) population. However, earlier data suggest worsened prognosis and the magnitude of effect in the CTD-PAH population is difficult to ascertain given limited enrollment in randomized controlled trials. Despite improvements in overall mortality, death from PH in the CTD population has increased over time and represents a leading cause of mortality.

TABLE 1. ESC/ERS RISK ASSESSMENT TOOL FOR PULMONARY ARTERIAL HYPERTENSION: 1-YEAR MORTALITY

<table>
<thead>
<tr>
<th>Risk Determinant</th>
<th>Low (&lt;5%)</th>
<th>Intermediate (5%-10%)</th>
<th>High (&gt;10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs of RV failure</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Symptom progression</td>
<td>No</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Syncope</td>
<td>None</td>
<td>Yes, occasional</td>
<td>Yes, multiple</td>
</tr>
<tr>
<td>WHO-FC</td>
<td>I, II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6MWD (meters)</td>
<td>&gt;440</td>
<td>165-440</td>
<td>&lt;165</td>
</tr>
<tr>
<td>Peak VO2 on CPET</td>
<td>&gt;15 mL/min/kg (&gt;65% predicted)</td>
<td>11-15 mL/min/kg (&lt;35%-65% predicted)</td>
<td>&lt;11 mL/min/kg (&lt;35% predicted)</td>
</tr>
<tr>
<td>Biomarkers (ng/L)</td>
<td>NT-proBNP &lt;300 BNP &lt;50</td>
<td>NT-proBNP 300-1400 BNP 50-300</td>
<td>NT-proBNP &gt;1400 BNP &gt;300</td>
</tr>
<tr>
<td>Imaging</td>
<td>RA area &lt;18 cm²; no pericardial effusion</td>
<td>RA area 18-26 cm²; no/minimal pericardial effusion</td>
<td>RA area &gt;26 cm²; pericardial effusion present</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP &lt;8 mm Hg Cl ≥2.5 L/min/m² SvO2 &gt;65%</td>
<td>RAP 8-14 mm Hg Cl 2-2.4 L/min/m² SvO2 60%-65%</td>
<td>RAP &gt;14 mm Hg Cl &lt;2 L/min/m² SvO2 &lt;60%</td>
</tr>
</tbody>
</table>

6MWD, 6-minute walk distance; BNP, brain natriuretic peptide; Cl, cardiac index; CPET, cardiopulmonary exercise testing; ESC/ERS, European Society of Cardiology/European Respiratory Society; NT-proBNP, N terminal-pro brain natriuretic peptide; RA, right atrium; RAP, right atrial pressure; RV, right ventricle; SvO2, mixed venous oxygen saturation; WHO-FC, World Health Organization functional class.

What are the screening recommendations for PAH in patients with various types of CTDs?

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

Screening/Early Detection

Given the predominance of SSc in the CTD-PAH population, this is where the bulk of the data on screening comes from. Those with...
advanced disease are known to have poor response to therapy and data support early recognition to detect those with milder disease associated with improved survival.\textsuperscript{10} Despite this, there has been insufficient progress in early recognition of CTD-PAH, prompting the World Symposium on Pulmonary Hypertension to recommend annual screening for PAH in asymptomatic patients with SSc spectrum disorders and a diffusing capacity for carbon monoxide (DLCO) less than 80% of predicted to determine the need for diagnostic right heart catheterization. Tools may include the two-step DETECT algorithm, biomarkers, and/or transthoracic echocardiogram (TTE) or pulmonary function tests (PFTs) as recommended by the 2015 European guidelines.\textsuperscript{5,11,12} DETECT is suggested in those with more than 3 years of disease, and for PFTs the use of forced vital capacity/DLCO ratio greater than 1.6 in combination with N-terminal-pro hormone B-type natriuretic peptide (NT-proBNP) greater than 2 times the upper limit of normal are recommended cutoffs to prompt further diagnostic testing. Given the paucity of data in other forms of CTD-PAH, screening recommendations support echocardiography for symptomatic patients.\textsuperscript{5}

**Treatment Landscape**

**Guideline Recommendations and Goals of Therapy**

Despite the differences outlined in the CTD-PAH population, current guidelines support use of the same algorithmic approach as the overall group I PAH population.\textsuperscript{5,13,14} Once a diagnosis of PAH is confirmed by an expert center and supportive care is initiated, an estimation of 1-year mortality risk via the use of a comprehensive, multiparametric tool must be undertaken. The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines proposed stratifying patients into low (<5%), intermediate (5%-10%), or high (>10%) risk to guide
treatment decisions based on a number of signs, symptoms, and objective parameters. The goal of treatment is to reach a low (or lower) risk profile that requires this assessment to occur not only at baseline to determine upfront therapy in the treatment naïve, but also serial reassessment to guide need for intensification of treatment. The importance of targeting this low-risk profile is underscored by data showing that both lower risk status at baseline and improvement in risk in the first 12 months of therapy predicts future survival.\textsuperscript{15,16}

There are several tools available to estimate risk based on a varying number of parameters; however, none have been validated specifically for the CTD-PAH subset. The ESC/ERS risk assessment tool includes 12 variables, with categorization based on where the majority of parameters fall (see TABLE 1).\textsuperscript{5} This tool has been independently validated and retains accuracy with use of as little as 4 variables. Additionally, patients who attain 3 or 4 low-risk criteria have been found to have 1-year mortality of 1% or lower, as compared with 13% to 30% with zero low-risk criteria.\textsuperscript{5,15,18,19} The downfall of this tool and this low-risk goal is that the minority of patients treated will achieve it and the use of combination therapy in the validation cohorts was very low. Ultimately, there is a need to prospectively evaluate these ambitious treatment targets.

Another commonly used risk assessment tool comes from the US REVEAL registry, developed in attempts to predict both mortality and clinical worsening.\textsuperscript{20} The initial score used 12 variables with modification and expansion to include recent hospitalization and renal dysfunction in the more recent 2.0 version. Key differences with the ESC tool include consideration for the subgroup of PAH (including CTD-PAH differentiation from heritable-PAH [HPAH]), demographics (men >60 years), renal dysfunction, baseline vital signs (systolic blood pressure and heart rate), and need for hospitalization within 6 months. REVEAL was found to have better risk discrimination in comparison to some of the abbreviated tools, but there are benefits and drawbacks to all available scoring systems and a lack of data regarding how risk should translate to treatment strategy for patients in terms of improvements in outcomes. However, given that patients at higher risk do more poorly, and those who achieve a low or lower risk profile have improved outcomes, the approach to being more aggressive with upfront therapy in the highest risk and escalating therapy in those who do not attain that is a reasonable approach.

**FIGURE 1**\textsuperscript{13} outlines the recommended approach to pharmacologic treatment of PAH, including those with CTD-PAH. An important difference in the CTD-PAH subgroup is that vasoreactivity testing is not indicated before proceeding with risk assessment and directed pharmacologic therapy, and calcium channel blocker use is also not recommended.\textsuperscript{13} In the high-risk population with greater than 10% risk of 1-year mortality, management is more aggressive with upfront triple combination therapy with an intravenous (IV) prostacyclin being one of the agents. Patients who are either low or intermediate risk (<5 or 5%-10%), should be considered for upfront oral combination therapy targeting different pathways. Once an initial strategy is selected, it is important to evaluate achievement of the goal of improving risk status with evaluation after 3 to 6 months. For those patients on treatment for at least that duration meeting the low-risk goal, no change is warranted, and the patient should be followed up for continued clinical response. However, in those that remain at intermediate or high risk, therapeutic intensification is warranted. For those patients on dual therapy, a third agent should be added from a complementary pathway (sequential combination therapy) with re-evaluation in 3 to 6 months and further escalation to triple therapy including a parenteral prostacyclin if disease progression continues. These guidelines do not support the use of specific agent(s) in the pathway as head-to-head comparisons between agents are generally lacking.

**General and Supportive Measures**

Once a diagnosis has been confirmed, treatment should first begin with consideration for general health measures in addition to supportive therapies.\textsuperscript{15} Pregnancy avoidance is recommended due to high maternal mortality rates and concerns with teratogenicity associated with several therapeutic options. Females of childbearing potential should be instructed regarding the use of combination contraception with 2 methods, with specific considerations to comply with Risk Evaluation and Mitigation Strategy (REMS) requirements for selected agents.\textsuperscript{2} Standard immunization against influenza and pneumococcal infection are recommended, with support from the Pulmonary Hypertension Association for COVID-19 vaccination as recommended by the Centers for Disease Control and Prevention (currently all patients aged 12 years or older).\textsuperscript{21} Support and evaluation of adherence to complex medication regimens are also keys for success for both the physical and psychological health of the PAH population. Supportive therapies for PAH include considerations for anticoagulation therapy, diuretic and digoxin use, as well as considerations for anemia and hypoxemia. Anticoagulation is not recommended in the CTD-PAH population in absence of a concomitant indication given concerns regarding lack of benefit and increased bleeding and mortality in retrospective registry analyses.\textsuperscript{22,23} The use of loop diuretics is recommended for management of symptoms associated with volume overload, supported by clinical experience and
extrapolation for the left-sided heart failure population. Similarly, oxygen supplementation is recommended in those with arterial O₂ saturation less than 90% largely on expert opinion. Digoxin provides no long-term benefit in the management of CTD-PAH but is considered safe for use as required. Finally, as iron deficiency is prevalent in PAH with potential for adverse effects (AEs) on exercise capacity, it is reasonable to screen for and correct with IV iron, given potential concerns for reduced oral absorption.

**Pharmacologic Therapies: Endothelin Receptor Antagonists (ERAs)**

The known excess of ET-1 produced by endothelial cells is targeted by the ERAs which block the vasoconstrictive and hyperproliferative effects at the ETₐ and ETₐ receptors (see FIGURE 2). There are 3 agents available within this class with slight differences in receptor selectivity. Bosentan (Tracleer) and macitentan (Opsumit) block both ETₐ and ETₐ receptors, while ambrisentan (Letairis) acts only at the ETₐ receptor.

Bosentan was the first oral agent approved for the treatment of PAH and is indicated to improve exercise capacity and decrease clinical worsening (CW) in patients with PAH with WHO-FC II-IV symptoms. Treatment starts at 62.5 mg by mouth twice daily for 4 weeks before titration to the target dose of 125 mg twice daily for patients greater than 40 kg. The pivotal trials leading to its approval evaluated the effects of bosentan (62.5 mg twice daily for 4 weeks titrated to 125-250 mg twice daily) compared
with placebo for a total of 12 (Study 351) or 16 (BREATHE-1) weeks on 6MWD.\textsuperscript{26,27} Of the 245 patients enrolled in these trials, 66 (44 treated with bosentan) had a confirmed diagnosis of CTD along with PAH. Denton and colleagues pooled patient-level data to evaluate the effects of bosentan in this CTD-PAH subgroup both at the end of the double-blind phase and after the open-label long-term extension where all patients were treated with bosentan.\textsuperscript{28} The intervention group was older (mean, 58 vs 49 years; \(P = .02\)) with numerically more females (86% vs 77%) and those with SSc subtype (84% vs 68%). Despite similar baseline WHO-FC, the intervention group had other markers of increased disease severity with shorter 6MWD (312 m vs 361 m; \(P = .01\)) and higher pulmonary vascular resistance (10 Wood units vs 9 Wood units). Bosentan was associated with a stabilizing effect on 6MWD (absolute difference, 22.1 m; 95% CI, –32 to 76) and delayed time to clinical worsening (TTCW) (95% vs 91% at 12 weeks; 90% vs 86% at 16 weeks) with no significant differences in tolerability. The long-term extension included 64 patients treated for a mean of 1.8 years, of which 40 remained on bosentan monotherapy. Treatment was associated with improvement in WHO-FC in one-quarter of the population and improved 6MWD (15 m), with survival rates of 86% and 74% at 1 and 2 years, respectively. While the short-term 6MWD effects were attenuated in comparison to the overall trial population, the absolute difference is in line with the minimal clinically important difference of 24 m for the CTD-PAH population and meta-analyses showing the ability of a difference of 26 m to predict outcomes.\textsuperscript{29,30} These survival data were also improvements from historical reports in CTD-PAH (45% and 35% at 1 and 2 years, respectively). The small sample size, changes in treatment of PAH in comparison with older cohorts, and differences in disease characteristics in the bosentan-treated group make it difficult to conclude the full treatment effect of bosentan in the CTD-PAH population. Nonetheless, these data are encouraging in terms of clinical deterioration, prognosis, and tolerability of bosentan.

Ambrisentan is also indicated to improve exercise ability and delay TTCW in patients with FC II-III PAH, with the additional indication for upfront combination with tadalafil to reduce disease progression, PAH hospitalizations, and improve exercise capacity. Treatment starts at 5 mg by mouth once daily with titration to target dose of 10 mg once daily after 4 weeks.\textsuperscript{31} ARIESE-C (including ARIESE-1 and -2 studies) evaluated the effects of ambrisentan at doses of 2.5, 5, and 10 mg once daily compared with placebo over 12 weeks on 6MWD.\textsuperscript{32} Of the 394 patients randomized in these trials, 383 participants elected to continue in the extension study of open-label treatment with ambrisentan, including 124 individuals with CTD-PAH.\textsuperscript{33} The outcomes of this subset of patients were described as part of prespecified post hoc analyses.\textsuperscript{34} These patients were predominantly diagnosed with SSc spectrum (over 80%) with 81 randomized to ambrisentan. At 12 weeks, those patients randomized to the 2 higher doses (5 or 10 mg) of ambrisentan improved 6MWD by 17 and 22 m, respectively. These effects waned over time during the extension phase. When evaluating categorical improvements in 6MWD, however, nearly three-quarters of this higher dose group had improvement at 12 weeks, and in the pooled ambrisentan group improvements remained above 50% at the 3-year mark. Benefits on WHO-FC were also durable, and TTCW was comparable in comparison to patients with IPAH (64% by 3 years). Survival rates were higher than what was previously summarized for bosentan, with 1-, 2-, and 3-year rates of 90%, 80%, and 76%, respectively. Baseline WHO-FC, 6MWD, female sex, and CTD-PAH subgroup were found to be significant predictors of survival, with the SLE subgroup at increased risk, although a small percentage of the overall CTD population. Specifically looking at 6MWD, both the change at 12 weeks and maintenance of an absolute value over 222 m were prognostic for survival. These data strengthened the support for ERAs in the CTD-PAH subset.

Macitentan represents the newest agent to the ERA class and the first to demonstrate improvements in a long-term event-driven trial. It is indicated to reduce the risk of disease progression and PAH hospitalization in WHO-FC II-IV PAH at a dose of 10 mg by mouth once daily.\textsuperscript{35} The SERAPHIN trial evaluated the effects of macitentan (3 and 10 mg) compared with placebo on the time to first PAH event or death in 742 patients, of whom nearly a third (224) had CTD-PAH.\textsuperscript{36} About two-thirds of the population were on background therapy (predominantly phosphodiesterase type-5 inhibitors [PDE5i]) and those on parenteral prostanoids were excluded. The approved 10-mg dose was associated with a 45% reduction in the primary outcome (HR, 0.55; 95% CI, 0.32–0.76), driven mainly by a reduction in PAH hospitalizations over the 36-month follow-up and was associated with improvements in 6MWD (+22 m) and WHO-FC at 6 months. While discrete data are not available for the CTD-PAH subgroup, the effects were consistent with those of the overall cohort, and these data further solidify macitentan’s place in therapy.

Tolerability is comparable but variable across this class with vasodilatory AEs predominating, and with anemia and teratogenicity as a class effect. Bosentan is additionally associated with hepatotoxicity and requires baseline and monthly monitoring of liver function tests. Ambrisentan does not carry the same risk for hepatotoxicity; however, it is associated with significantly more peripheral edema and should be avoided in patients with concomitant idiopathic pulmonary fibrosis. No AEs were found to be significantly different in the CTD-PAH population as compared
with the overall cohort, but numerically there were increased reports of dizziness, edema, and fatigue. ERAs are available only through REMS programs from certified prescribers and pharmacies with unique laboratory and contraception requirements. All 3 agents are CYP substrates, and bosentan induces CYP 3A4 and 2C9, which makes drug–drug interaction (DDI) screening essential.

Pharmacologic Therapies: PDE5 Inhibitors
Two PDE5 inhibitors, sildenafil (Revatio) and tadalafil (Adcirca), target the deficiency of nitric oxide (NO) and the NO pathway by preventing the breakdown of cyclic guanosine monophosphate (cGMP), resulting in relaxation of pulmonary vascular smooth muscle and vasodilation, in addition to antiproliferative effects (see FIGURE 2').

Sildenafil is indicated to improve exercise capacity and delay CW in WHO-FC II-III PAH at a dose of 20 mg by mouth 3 times daily, and has an IV formulation available for use. The SUPER-1 trial evaluated the effects of sildenafil (20, 40, or 80 mg thrice daily) compared with placebo on 6MWD at 12 weeks. Results from the CTD-PAH subgroup (84 of 278 patients) have been reported as a post hoc analysis by Badesch and colleagues. Scleroderma represented nearly half of the cases, with most patients enrolled with WHO-FC II (38%) or III (61%) symptoms at baseline. All doses of sildenafil were associated with improved 6MWD (mean increase of 55 m in the 20-mg group) and improvement by at least 1 WHO-FC (29% in the 20-mg group) at 12 weeks. These results were comparable to the overall population, supporting sildenafil’s use in the CTD-PAH population.

Tadalafil is indicated to improve exercise capacity in WHO-FC II-III PAH with the advantage of being dosed once daily (40 mg once/day). The PHIRST trial treated 405 patients with or without background bosentan, randomized in equal numbers to increasing doses of tadalafil (2.5 through 40 mg) or placebo for 16 weeks, with 357 patients continuing on the highest doses of 20 or 40 mg once daily in the 52-week extension (PHIRST-2). Galiè and colleagues performed a post hoc descriptive analysis comparing outcomes in CTD-PAH compared with heritable/idiopathic (H/I)-PAH who were randomized to placebo, tadalafil 20 or 40 mg and completed the PHIRST-1 trial with subsequent enrolled in PHIRST-2. Fifty-six patients with CTD-PAH and 150 patients with H/I-PAH were included in the 16-week analysis and demonstrated improvements associated with tadalafil treatment in 6MWD in both cohorts. The CTD-PAH cohort had numerically higher rates of worsening WHO-FC (13% vs 7%) and CW (14% vs 11%) overall, but regardless of etiology, tadalafil 40 mg performed better in terms of WHO-FC. In the evaluable patients from the extension (CTD-PAH, n = 78; I/H-PAH, n = 223), 6MWD improvements were maintained regardless of etiology but were attenuated in those initially randomized to placebo or lower doses of tadalafil. WHO-FC worsening remained more common in CTD-PAH at the 40-mg dose (15% vs 7%); however, regardless of etiology, the 40-mg dose performed more favorably. CW and TTCW were more favorable in the I/H-PAH cohort over the entire 68-week duration. While these data are exploratory, they do support a benefit of tadalafil in the CTD-PAH population regardless of concomitant ERA therapy.

Tolerability is also comparable in this class with overlapping vasodilatory effects including headache and flushing, but also associated with myalgias and visual and auditory alterations. The post hoc analyses described comparable rates of these AEs in the CTD-PAH population, apart from slightly numerically higher incidence of serious AEs in tadalafil-treated patients compared with those with I/H-PAH, but the statistical and clinical significance is unknown given the small sample size and retrospective nature of these data. In addition to contraindication with concomitant nitrates and soluble guanylate cyclase (sGC) stimulators, both agents are substrates of CYP3A4, prompting the need for DDI screening with concomitant inducers or inhibitors.

Pharmacologic Therapies: sGC Stimulators
sGC stimulators also target the NO pathway by acting both in synergy with endogenous NO and directly stimulating sGC independently to increase cyclic guanosine monophosphate and reduce proliferation, fibrosis, vascular tone, and inflammation (see FIGURE 2). Riociguat (Adempas) is the only drug in this class approved for the treatment of PAH, indicated to improve exercise capacity and WHO-FC in those with FC II-III symptoms. Dosing is initiated at 1 mg by mouth thrice daily with titration, as tolerated, to a maximum of 2.5 mg thrice daily. The PATENT-1 trial evaluated the effects of riociguat at maximum doses of 1.5 or 2.5 mg thrice daily compared with placebo on 6MWD at 12 weeks in 443 patients with PAH, with optional continuation in the open-label extension trial at a maximum dose of 2.5 mg thrice daily. A prespecified analysis of patients with CTD-PAH with exploratory evaluation of response differences within CTD subtypes at both the 12-week (n = 111) and 2-year (n = 84) timepoints have been reported by Humbert and colleagues. Nearly two-thirds of the population were treated with background therapy, predominantly ERAs (over half), and SSc represented 59% of the CTD subtypes. At 12 weeks, riociguat improved 6MWD by 28 m, with the treatment effect driven by a larger worsening in the SSc subtype assigned to placebo. This was shorter than the overall PATENT-1 trial (39 m) but was maintained at 2 years. The effect on WHO-FC was comparable in all subtypes and to the overall population, and efficacy was comparable regard-
less of concomitant background therapy. Survival at 2 years was 93% matching that of the I/H-PAH population.

Vasodilatatory AEs are similar to the PDE5 inhibitors, but dyspepsia is very common. It appears that tolerability was comparable in the CTD-PAH population and among subtypes but may be more pronounced in comparison with the overall PAH population.\textsuperscript{54} In addition to contraindication with concomitant nitrates or PDE5 inhibitors, riociguat is a substrate of P-glycoprotein, breast cancer resistance protein, and various CYP isoenzymes. Smoking and antacid use are also important considerations for dosing as they are associated with reduced drug exposure.\textsuperscript{46} A REMS program is also in place for female patients with requirement for pregnancy testing and contraception requirements similar to the ERAs.\textsuperscript{49}

**Pharmacologic Therapies: Prostanoids**

Prostacyclin analogues offer the widest array of administration options at the expense of increased complexity. These agents act on the prostacyclin pathway to promote vasodilation and inhibit both platelet aggregation and smooth muscle cell proliferation by stimulating the prostacyclin receptor (see FIGURE 2\textsuperscript{24}). Injectable agents include epoprostenol (Flolan, Veletri) and treprostinil (Remodulin), administered by continuous IV infusion due to short half-lives.\textsuperscript{50,51} Treprostinil is also available for subcutaneous (SC) infusion, as well as both inhaled (Tyvaso) and oral (Orenitram) routes.\textsuperscript{51-53} Iloprost (Ventavis) is available only as an inhaled agent in the United States.\textsuperscript{54}

Injectable prostanoids have comparable tolerability, with vasodilatory effects as outlined with previously discussed agents. Unique AEs of this class include jaw pain, nausea/vomiting, and musculoskeletal pain. Additional distinctive AEs include thrombocytopenia (epoprostenol); gram negative bacteremia (IV treprostinil); and dose- and treatment-limiting infusion site pain/erythema (SC treprostinil). Dosing is in ng/kg/min with initiation at low doses (1.25-2 ng/kg/min) and titration based on tolerability and response. All injectable agents require continuous infusion without interruption via a dedicated line with sterile preparation. These agents are contraindicated with concomitant left-sided heart failure due to increased mortality noted with IV epoprostenol.\textsuperscript{55} These agents are available only through specialty pharmacy and require significant teaching and investment by the patient and caregivers to ensure success with drug admixture, administration, and maintenance of the infusion pump and access site.

**Epoprostenol**

Epoprostenol preparations are indicated to improve exercise capacity in WHO-FC III-IV PAH. IV epoprostenol remains the only agent associated with improved mortality in this population.\textsuperscript{56} Improvements in 6MWD and hemodynamics have also been demonstrated. The initial formulation (Flolan) was not stable at room temperature and required use of ice packs as well as a special diluent for stability. A newer thermostable formulation (Veletri) is available and, while not bioequivalent, is preferred from a logistical perspective. Branded Flolan is now stable at room temperature using a pH 12 diluent, while the generic formulation still requires a unique diluent but is only stable 8 hours at room temperature so requires ice packs during infusion.\textsuperscript{50,57}

The only randomized, prospective study of epoprostenol in CTD-PAH involved 111 patients with scleroderma spectrum of disease treated in an open-label manner with IV epoprostenol or conventional therapy.\textsuperscript{58} Over 12 weeks, epoprostenol was associated with improvements in 6MWD (108 m) as well as hemodynamics (mean pulmonary arterial pressure, pulmonary vascular resistance, right atrial pressure, cardiac index, mixed venous oxygen saturation). AEs associated with epoprostenol were similar to those previously discussed, with gastrointestinal (GI) effects and jaw pain predominating. The outcomes are difficult to interpret in the modern era given the significant advances in treatment; however, these data do support the use of epoprostenol in the CTD-PAH population.

**Treprostinil**

Parenteral treprostinil is indicated to reduce exercise symptoms in WHO-FC II-IV PAH, and in patients receiving epoprostenol who require transition to reduce the rate of deterioration.\textsuperscript{51} Treprostinil has a longer half-life than epoprostenol and more data exist for SC administration with dose-related increases in 6MWD and hemodynamics and is preferred to IV administration.\textsuperscript{51,59} The efficacy and safety of SC treprostinil was evaluated over 12 weeks in 470 patients, of whom 90 had CTD-PAH.\textsuperscript{60} In a retrospective analysis, treprostinil (1.25 ng/kg/min titrated to mean 8.4 ng/kg/min over 12 weeks in the active treatment arm) was associated with a 21 m increase in mean 6MWD and improvements in dyspnea rating, and those who tolerated a higher dose (>9 ng/kg/min) tended to have longer 6MWD, in line with the overall study population. Tolerability was similar to epoprostenol in this population; however, infusion site pain was very common (70%) and led to limitations of dose titration in the active treatment group as well as discontinuation of therapy. Although retrospective with a limited sample size, these data support the safety and tolerability of SC-administered treprostinil in the CTD-PAH population.

Oral treprostinil is indicated to delay disease progression and improve exercise capacity in WHO-FC II-III PAH.\textsuperscript{53} The overall
Inhaled Prostacyclins

Iloprost and treprostinil represent the currently available inhaled agents for the treatment of PAH. Discrete data on the clinical effects in the CTD-PAH population are more limited, as are long-term outcomes data, but the CTD-PAH population did compose nearly a third of the studied populations leading to approval of these agents. Iloprost is improved to improve the composite of exercise tolerance, WHO-FC, and lack of deterioration in WHO-FC III-IV PAH. Treprostinil is similarly indicated to improve exercise capacity in WHO-FC III PAH. Given the long and frequent administration times associated with iloprost (dosed 6-9 times/day, at least 2 hours apart during waking hours), it has largely been replaced by treprostinil in practice, which is dosed in breaths (6 mcg/breath) 4 times daily. Both agents are associated with the systemic AEs of the prostacyclin class, with the addition of cough and throat irritation. Agent-specific nebulizers are required for administration and both agents are available only through specialty pharmacies.

Selexipag

Selexipag (Uptravi) targets the prostacyclin pathway by selectively stimulating the PI receptor to promote vasodilation and antiproliferation (see FIGURE 2). It is indicated to delay disease progression and reduce hospitalization risk in WHO-FC II-III PAH. Dosing is initiated at 200 mcg by mouth twice daily and titrated at weekly intervals to a maximum dose of 1600 mcg twice daily based on tolerability, and now has an IV formulation available. The GRIPHON trial evaluated the effects of selexipag (200 mcg titrated to maximum 1600 mcg twice daily as tolerated) compared with placebo on the time to death or PAH complication in 1156 patients, of whom 334 had CTD-PAH (SSc = 170, SLE = 82) and nearly 80% were on background therapy with one or more agent. Selexipag was associated with a 41% reduction in the primary outcome (HR, 0.59; 95% CI, 0.41-0.85), driven mainly by reductions in PAH hospitalizations and disease progression over the more than 40-month follow-up despite modest improvements in 6MWD (+12 m). The effects were consistent across CTD subtypes, background therapies, dose achieved, and in comparison to the overall PAH population. This represents the largest cohort of patients with CTD-PAH and, unlike those data previously discussed, supports a similar benefit in this population. These outcomes are supported by real-world data from the SPHERE registry of newly initiated patients receiving selexipag, 132 of whom had CTD-PAH and had similar outcomes to patients with IPAH.

Many AEs are similar to those outlined with the prostacyclins (including jaw pain) with headache and GI concerns predominating. The incidence was similar in the CTD-PAH population from GRIPHON but were reported more frequently during dose titration and led to numerically higher discontinuation rates (19% vs 14% overall). Selexipag is a substrate of CYP2C8 and is contraindicated with concomitant gemfibrozil.

Clinical Benefits of Combination Therapy

Combination therapy has emerged as a first-line option for the majority of the PAH population, with selection of agents dependent on disease severity and risk assessment, as previously discussed. Data support upfront triple combination therapy consisting of IV epoprostenol with oral bosentan and sildenafil in a small high-risk population. Improvements included WHO-FC, 6MWD, and several hemodynamic parameters from baseline, with survival better than expected. Data on the benefits of combination therapy in the non-high-risk population have come predominantly from analysis of outcomes in the treatment-naïve versus pretreated patients enrolled in placebo-controlled add-on therapy trials (sequential combination therapy). Macitentan-treated patients in SERAPHIN had similar benefit regardless of background treatment (64% of overall population, mostly PDE5 inhibitors). Likewise, selexipag-treated patients in GRIPHON on either single or dual background therapy (80% on single, nearly a third on combination PDE5i inhibitor + ERA) had similar benefit to the overall population. The previously summarized analyses in the CTD-PAH population do not alone afford a fair evaluation of the benefits of sequential combination therapy in this population in comparison with the overall PAH population but are generally considered to be supportive of this approach.
The effects of upfront combination versus monotherapy on time to clinical failure was evaluated in 500 treatment-naïve patients in the AMBITION trial. Patients were randomized to oral combination therapy with ambrisentan 10 mg and tadalafil 40 mg daily versus monotherapy with either agent. A post hoc analysis of 187 patients with CTD-PAH (118 with SSc) was reported by Coghlan and colleagues. Combination therapy was associated with a 57% reduction in the primary outcome over a mean of 517 days in comparison with the pooled mono-therapy arm, driven by hospitalizations, and was consistent with the overall event rates in the trial and in comparison with the I/H-PAH subgroup. Tolerability appeared to be worse in the CTD-PAH subgroup, with peripheral edema and headache predominating and higher rates of discontinuation for AEs. These data solidify the upfront combination therapy approach in the CTD-PAH subgroup even in a low to intermediate risk category.

**STAR**

What roles can the pharmacist play in ensuring the safe and effective treatment of PAH in the CTD population?

Opportunities for Intervention by Pharmacists

Pharmacists can provide education on sterile technique for parenteral therapies with inclusion of family members and other caregivers in the process, and education for others regarding the resources available in case of emergencies through specialty pharmacies such as Accredo (toll free 24 hours, 866-FIGHT-PH). Additionally, considering the data identifying underrecognition of CTD-PAH and the adverse consequences of starting therapy in more advanced disease, pharmacists can advocate for increased awareness of the potential for PAH in the vulnerable CTD population with colleagues and local providers in the primary care space.

Given the complexity of parenteral prostacyclin preparation and administration, these agents are included on the high alert medication list of the Institute for Safe Medication Practices. Survey data from US PH centers suggest that most institutions have experienced errors somewhere in the medication ordering and administration process with severity ranging from minor to cases of fatality. These can be addressed through the creation of standardized order sets for order entry, policy development, and implementation of training and regular competencies for nursing and pharmacy personnel involved with order verification, preparation, and administration. Additional pharmacy-led initiatives to consider may include independent double checks of any calculations in the compounding process in addition to verification of the home dosing regimen with the patient’s specialty pharmacy.

Formulary management is another essential consideration for pharmacists. Considerations include a lack of data to support therapeutic interchange of agents within a class, differing REMS requirements/enrollment, administration differences, and need for continuous access is imperative. Evaluation of institutional needs and resources available to ensure safe, consistent involvement, as well as expected frequency of use, prescriber experience,

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**TABLE 2. REMS PROGRAM REQUIREMENTS**

<table>
<thead>
<tr>
<th></th>
<th><strong>Bosentan</strong></th>
<th><strong>Ambrisentan, Macitentan, and Riociguat</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participant enrollment</strong></td>
<td>Prescriber, pharmacy, hospital, ALL patients</td>
<td>Prescriber, pharmacy, hospital, FEMALE patients</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Baseline and monthly LFTs (all); pregnancy test (FRP)</td>
<td>Baseline and monthly pregnancy test (FRP)</td>
</tr>
<tr>
<td><strong>Required document(s)</strong></td>
<td>Medication guide</td>
<td>Medication guide (FRP, pre-pubertal); program guide (FRP)</td>
</tr>
<tr>
<td><strong>Acceptable contraception</strong></td>
<td>IUD or tubal sterilization alone; hormonal PLUS barrier; partner vasectomy PLUS hormonal or barrier</td>
<td>Same as bosentan; can also have progesterone implant as lone method</td>
</tr>
<tr>
<td><strong>Inpatient dispensing</strong></td>
<td>Hospital may only dispense ≤15-day supply on discharge; medication guide</td>
<td>Maximum 30-day supply; medication guide; confirm pregnancy test completed, prescriber enrolled</td>
</tr>
<tr>
<td><strong>Outpatient dispensing</strong></td>
<td>Maximum 30-day supply; medication guide; confirm labs completed, prescriber enrolled; document reason for stopping therapy</td>
<td>Maximum 30-day supply; medication guide; confirm pregnancy test completed, prescriber enrolled</td>
</tr>
</tbody>
</table>

FRP, females of reproductive potential; IUD, intrauterine device; LFT, liver function test.
2. Only noted for FRP and/or pre-pubertal females.
and cost must also be involved in this multidisciplinary decision. Given the infrequent prevalence in the overall population, it may be sporadic and infrequent for a given center to encounter patients requiring these medications, which further complicate the ordering and storage of multiple medications from an inventory perspective and potential for expiration prior to use. The use of patients’ own medication or emergency acquisition through specialty pharmacies should be considered in these situations.

Regulatory requirements are important formulary considerations but also represent an area for pharmacist involvement for the ERAs and riociguat. Requirements are similar but slightly differ for each of the agents and can be found in Table 2.\textsuperscript{27,39,50} These requirements apply for both inpatient and outpatient use, and for new initiation and continuation of therapy. The use of order sets to capture these requirements as part of the ordering process may aid in consistent compliance, in addition to appropriate staff education and training.

Pharmacist involvement in managing treatment cannot be understated, and should include AE management, DDI screening, initiation and titration guidance, and assistance with transitions of care. There is significant overlap in AE profiles due to the vasodilatory effects of these agents with several classes also associated with peripheral edema and significant GI distress. Prostacyclin initiation and titration is a particularly important area for discussion of AEs with patients as titration is limited by patient tolerability. Starting at appropriate doses (1-2 ng/kg/min) with titration only once tolerance has been confirmed with the patient, while educating the patient on what to expect, may help to ensure success. Many AEs (myalgias, nausea/vomiting/diarrhea, refractory dizziness/hypotension) are dose related and may respond to slower titration or dose reductions.\textsuperscript{72} Jaw pain is unique and can be significant, but should not necessitate dose alteration, and may be minimized by instructing the patient to take slow bites/sips or suck on a saltine cracker or candy before eating. Headaches and myalgias should be treated with nonopioid analgesics with acetaminophen first line and consideration for pretreatment before dose escalation. The unique site pain with SC treprostinil can be particularly problematic and can be aided by catheter-related considerations, including keeping the catheter in place as long as possible, avoidance of stretch marks/scar tissue, and pre-placing the next site to allow for healing before use. Management should include the use of topical treatments such as ice packs, capsaicin, and topical anesthetics or corticosteroids. If these are insufficient, nonnarcotic analgesics may be considered, but it is important to note that this is not responsive to dose reduction. Diarrhea and nausea can be controlled with antiemetics, with consideration for pretreatment before dose titration. Facial flushing also requires patient reassurance that tolerance will develop and may be improved with the use of a fan and/or cold packs. Given the overlap in AEs, additional considerations to improve tolerance when initiating combination therapy may include staggered initiation of combination therapy to avoid initiation on the same day (eg, starting PDE5 inhibitor and ensuring tolerance before adding on ERA therapy) or initiation of both agents at a lower dose with titration to target doses after 2 to 4 weeks (eg, start ambrisentan 5 mg daily plus tadalafil 20 mg daily, increase at 4-week intervals to target dose of both agents) as was done in AMBITION.\textsuperscript{68,73}

Given the aggressive treatment goals and significant burden associated with many therapies, monitoring response and compliance is another important consideration for pharmacists. These are not unique to PAH, but considerations include the number and frequency of medications and overall pill burden as well as a potential lack of short-term consequence conceived by the patient of missing a dose. Nonadherence has the potential to lead to a host of untoward effects, including unnecessary/inappropriate escalation of therapy, which can compound the problem. Additionally, patients may require increased oxygen or experience a rebound of symptoms or clinical deterioration leading to emergency department visits that may ultimately result in hospitalization or death.

Access to these costly medications and necessary supplies is increasingly complex, with special consideration for patients who require hospitalization for initiation as with parenteral prostacyclins. This includes submission or assistance with the prior authorization process and co-pay assistance or charitable funds; ensuring patients have the supplies and equipment they need in addition to just the drugs themselves; and compliance with REMS programs previously outlined.

Transitions between the inpatient and outpatient settings introduce another potential area for medication errors, making coordination of care to ensure continuous access and accurate dosing crucial in this population. Considerations include inpatient access to continue therapy, coordination with specialty pharmacy, discharge planning and communication with outpatient providers (both PH providers as well as primary care), and confirmation of home delivery and infusion pump access for parenteral agents. For those patients who are critically ill and require care in the intensive care unit or are unable to take medications by mouth, methods (crushing/suspensions for administration via tube) or alternative routes (IV availability, inhaled agents in ventilated patients) of administration must be considered. These may be aided by development of standard protocols and procedures for such scenarios with careful coordination through each step of the
process. Screening for DDIs should also take place in each phase of care given the predominance of CYP contribution to metabolism of many agents. Notably, the PDE5 inhibitors, ERAs, treprostinil, riociguat, and selexipag all have CYP interactions to consider that may require dose alteration or entire avoidance. Within the PAH target therapies, it is important to avoid multiple agents from the same pathway when combining therapy, and the concomitant use of PDE5 inhibitors and riociguat is contraindicated.

**Conclusion**

PAH is a rare disease with significant impact in the CTD population that remains underrecognized. Earlier data reported worse outcomes in the CTD-PAH subgroup; however, more contemporary data from the targeted treatment era with earlier diagnosis and treatment suggest similar outcomes. Approach to treatment is largely similar in CTD-PAH with careful discussion regarding risks and benefits, education, and safety monitoring. Risk assessment is crucial to appropriate therapeutic intervention and assessment of response. Pharmacists are uniquely positioned to aid in the safe and effective use of targeted therapies throughout the spectrum of the health care setting.

**ADDITIONAL RESOURCES**

| World Symposia on Pulmonary Hypertension Association | www.wsphassociation.org |
| Pulmonary Hypertension Association | phassociation.org |
| Accredited PH Care Centers | phassociation.org/phcarecenters/accredited-centers |
| phaware Global Association | phaware.global/resources |
| CHEST Foundation (patient information) | foundation.chetnet.org/lung-health-a-z/pulmonary-arterial-hypertension-pah/ |
| Proceedings of the 6th World Symposium on Pulmonary Hypertension | erj.ersjournals.com/collections/WSPH?survey=1 |

**REFERENCES**

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POSTTEST QUESTIONS

1. Which statement is true regarding connective tissue disease (CTD)-associated pulmonary arterial hypertension (PAH)?
   A. CTD-PAH is more common than idiopathic or heritable PAH.
   B. Patients with CTD-PAH have improved treatment outcomes.
   C. There are significant differences in the pathophysiology of CTD-PAH.
   D. Systemic sclerosis (SSc) is the most common cause of CTD-PAH.

2. JP is a 65-year-old woman with SSc diagnosed 2 years ago, hypertension, and diabetes presenting for annual wellness screen. Her most recent pulmonary function test revealed a diffusing capacity of carbon monoxide (DLCO) 75% predicted, but she does not have any complaints today. Which of the following screening tests should be performed as a first step for JP to evaluate for PAH?
   A. No further screening is warranted as JP is asymptomatic.
   B. N-terminal-pro hormone B-type natriuretic peptide (NT-proBNP) level
   C. Transthoracic echocardiogram
   D. DETECT algorithm assessment

3. Which of the following is true regarding PAH targeted therapies in the CTD-PAH population?
   A. Patients with CTD-PAH have shown to have better tolerability than PAH overall.
   B. CTD-PAH has consistently been shown to be associated with less response to treatment.
   C. PAH-related mortality has increased over time and has been worse than predicted in CTD-PAH.
   D. Contemporary data support the use of targeted therapies for CTD-PAH.

Use the following case to answer questions 4 and 5.

RD is a 62-year-old man with systemic lupus erythematosus (SLE) recently diagnosed with PAH. He complains of lower extremity edema, shortness of breath with activities of daily living causing severe limitation, and fatigue. His symptoms are consistent with World Health Organization Functional Class (WHO-RC) III. His medications include aspirin 81 mg daily, prednisone 5 mg daily, isosorbide mononitrate 30 mg daily, and chlorthalidone 25 mg daily. He lives alone, and has issues with dexterity in his hands.

4. Based on the European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk assessment, RD is deemed to be at intermediate risk of 1-year mortality. Which of the following treatment regimens would be most appropriate to initiate?
   A. Tadalafil 40 mg daily plus ambrisentan 10 mg daily
   B. Bosentan 250 mg twice daily plus riociguat 1 mg titrated to 2.5 mg thrice daily as tolerated
   C. Macitentan 10 mg daily plus selexipag 200 mg titrated to 1600 mg twice daily as tolerated
   D. Sildenafil 20 mg thrice daily plus IV epoprostenol 2 ng/kg/min titrated based on tolerability

5. Which treatment goal is a reasonable expectation to discuss with RD?
   A. Achieve a low-risk status within 12 weeks
   B. Improvement to WHO-FC I symptoms within 6 months
   C. Improvement in 6-minute walk distance (6MWD) within 12 months
   D. Reduced risk of death from PAH within 12 months

6. A patient returns to clinic with complaints of weakness and is found on laboratory analysis to be anemic. Which of the following PAH medications is associated with anemia?
   A. Macitentan
   B. Tadalafil
   C. Riociguat
   D. Selexipag
POSTTEST QUESTIONS (continued)

7. CW is a 62-year-old woman with SSc-PAH presenting with progressive PAH symptoms and high risk of mortality despite treatment with ambrisentan 10 mg daily plus tadalafil 40 mg daily for the past 3 months. Which of the following is the most appropriate therapeutic intervention at this time?
   A. Schedule hospital admission for initiation of IV epoprostenol
   B. Discontinue tadalafil and add riociguat 1 mg titrated as tolerated to maximum 2.5 mg thrice daily
   C. Add selexipag 200 mcg titrated as tolerated to maximum 1600 mcg twice daily
   D. No change in therapy, re-evaluate in 3 months

8. Which of the following is the most appropriate recommendation to address adverse effects (AEs) associated with parenteral prostacyclin therapy?
   A. Discontinue oral agents with overlapping vasodilatory effects prior to initiation to maximize chances for tolerability
   B. Pretreat with acetaminophen prior to dose increases if headaches are experienced
   C. Titrate the dose up quickly to achieve a fast time to steady state and reduce AEs
   D. Slow dose titration or reduce the dose if patients exhibit site pain with subcutaneous treprostinil

9. You are asked to evaluate the addition of macitentan and riociguat to your formulary. Which one of the following would most likely bar the addition of either agent?
   A. Contraindications for both agents with concomitant PDE5 inhibitor or nitrate
   B. Inability to enforce necessary regulatory REMS requirements
   C. Cost of stocking and administering these medications
   D. Nursing unfamiliarity with administration

10. Which of the following supportive/general care recommendations are appropriate to recommend for patients with CTD-PAH?
    A. Avoidance of male patients fathering a child
    B. Routine anticoagulation
    C. Diuretics for symptoms of volume overload
    D. Calcium channel blocker use
Opzelura Cream 1.5%
Manufactured by Incyte
Opzelura cream 1.5% is indicated for topical short-term and noncontinuous chronic treatment of mild to moderate atopic dermatitis in patients 12 years and older who are not immunocompromised and whose disease is not fully controlled with topical prescription therapies. It can be applied to affected skin up to 20% of body surface area, including sensitive skin. In clinical trials, the most common adverse reactions included nasopharyngitis, diarrhea, bronchitis, ear infection, eosinophil count increase, urticaria, folliculitis, tonsillitis, and rhinorrhea.

FOR MORE INFORMATION:
opzelurahcp.com

Aimovig Injection
Manufactured by Amgen and Novartis
With a new Pharmacy Times® video series designed to help pharmacists support patients with migraine, Aimovig offers a preventive approach to treatment. As a once-monthly injection, Aimovig is a convenient option for patients with chronic migraine. In safety analysis of clinical trial patients who received at least 1 dose, the most common adverse reactions were constipation and injection site effects.

FOR MORE INFORMATION:
aimovig.com

Shingrix
Manufactured by GlaxoSmithKline
Indicated for prevention of herpes zoster in adults aged 50 and older, the Shingrix vaccine is an essential preventive care service for older adults. According to CDC data, 99.5% of individuals aged 50 and older are infected with the varicella-zoster virus, and one-third of those will experience virus reactivation and shingles. When administering a COVID-19 or flu vaccine, pharmacists can ask whether eligible patients have received the shingles vaccine. Solicited local adverse reactions included pain, redness, and swelling; general adverse reactions included myalgia, fatigue, headache, shivering, fever, and gastrointestinal symptoms.

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