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ONE OF THE MAJOR 2022 INITIATIVES at Pharmacy Times® is the Future of Pharmacy, where we tell the story—through articles and videos—of where the profession has been and where it is headed.

As we pass the midpoint of the year, we are proud of our coverage so far, which is housed on the Pharmacy Times® website at https://www.pharmacytimes.com/clinical/future-of-pharmacy. The Pharmacy Times® Future of Pharmacy Resource Center is a comprehensive source on the evolution of the pharmacy profession and the growing roles of pharmacists, pharmacy technicians, and support staff members.

So far this year, the initiative has focused on 4 key areas: the changes for pharmacists and pharmacies; the elevated role of technicians and support staff members; technology changes, including telehealth and scheduling platforms; and consumer expectations of pharmacies and pharmacists. Going into the second half of 2022, the initiative will focus on the following 4 areas: changes at pharmacy schools and to curricula in the wake of the COVID-19 pandemic; integrated health or what a pharmacy will look like in 5 years; creative ways to deal with burnout and stress among pharmacy professionals; and alternate career paths for pharmacists, such as administrative or in education. Be sure to check out our coverage!

Meanwhile, it is that time of year again when our editorial team begins putting together our editorial print calendars for 2023, and we will complete this process around the end of July. We will use the Future of Pharmacy content to inform our 2023 content, but please also feel free to reach out to our editorial team members with ideas for Cover Features, as well as topics for Rx Focus, Patient Focus, OTC Case Studies, Technician Focus, and Condition Watch articles. We will also need authors for these and other articles next year.

In this July 2022 issue of Pharmacy Times Health-System Edition™, our Cover Feature looks at how pharmacists can help slow the opioid crisis through monitoring programs, naloxone training, and patient education. Other coverage focuses on access to Clostridioides difficile treatments during transitions of care, SGLT2 inhibitors, and trilaciclib for chemotherapy-induced myelosuppression.

We hope you enjoy our comprehensive coverage as well as some much-earned vacation time this summer.

Thanks for reading!

MIKE HENNESSY JR
President & CEO
MJH Life Sciences®
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LAST YEAR IN this column, I expressed disappointment in the decision by the FDA to grant regulatory approval for the marketing of aducanumab (Aduhelm) for the treatment of patients with Alzheimer disease (AD) based on a surrogate end point that had not been clearly linked to clinical improvement or slowing of the disease.¹

At that time, most of the large commercial payers had decided to not cover the cost of treatment. The Centers for Medicare & Medicaid Services (CMS) stated that a national coverage determination (NCD) hearing was to be convened and it would take approximately 9 months for that process to be completed. Patient advocacy groups, most notably the Alzheimer’s Association, lauded the drug as a historic breakthrough therapy and were advocating for broad access to treatment.²

Several large health care systems said that they would not offer the treatment pending more data, a decision that was not overly brave, considering that there was essentially no way to get paid for providing this expensive therapy.

Having become a bit of a cynic in my later years, I feared that the necessary influences would be applied in the proper places, resulting in a shift of political and public opinion toward funding this treatment, despite controversial and sparse evidence of efficacy and definitive evidence of harm. So, what has developed in the past year regarding to antiamyloid monoclonal antibody treatments?

In the face of minimal sales and a huge financial fallout, Biogen/Eisai said in January 2022 that they would reduce the cost of aducanumab by 50% to an average of approximately $28,000 per year. This move did not lead to any appreciable increase in utilization, as major payers did not reconsider coverage and the CMS had not yet completed the NCD process. In April 2022, the CMS finalized Medicare coverage policy for monoclonal antibodies targeting amyloid for the treatment of AD. The coverage determination had 2 major elements:

Medicare will cover monoclonal antibodies targeting amyloid or plaque for the treatment of AD that receive traditional approval from the FDA under coverage with evidence development.

For drugs that the FDA has not determined to have shown a clinical benefit or that receive accelerated FDA approval, Medicare will cover in the case of FDA or National Institutes of Health approved trials. Under this NCD, the CMS will support the FDA by covering the drug and any related services, including, in some cases, PET scans if required by trial protocol for individuals with Medicare who are participating in these trials.³

This NCD is noteworthy for 2 reasons. First, it did not address just aducanumab but rather the...
entire drug class, which is important, given the number of agents in various stages of clinical development. Second, it signaled that the CMS was not going to broadly cover the treatment unless there was adequate evidence of efficacy and safety to warrant traditional FDA approval. This was a strong message to the pharmaceutical industry concerning the acceptable development pathway for these drugs.

In May 2022, Biogen said that its CEO would step down, along with most of the commercial Aduhelm marketing team. This essentially marked the end of the commercial development of aducanumab. Biogen failed to successfully introduce this therapy into broad clinical use, with less than $6 million in sales since Aduhelm’s approval.4,5 The partnership between Biogen and Eisai is shifting its attention to gaining approval for lecanemab, another antiamyloid monoclonal antibody, with suggestions that Eisai will lead the regulatory effort this time. The Clarity AD confirmatory trial (NCT03887455) of lecanemab is expected to have early data reported in fall 2022. Anticipating the final CMS policy decision, Eli Lilly announced delays in the development plan for its candidate, donanemab, so that larger clinical trials with efficacy and safety end points could be completed later in 2022. The company abandoned its plans to pursue accelerated approval based on surrogate end points.6

On June 15, 2022, Genentech announced that crenezumab was ineffective at preventing the development of cognitive decline in patients with autosomal dominant AD.7 This was a study of patients with a genetic predisposition to develop early AD who were enrolled prior to the onset of cognitive decline.

There were high hopes for this trial given the early introduction of treatment, which was hypothesized to be most effective prior to the onset of clinical signs and symptoms. Although the results from this unique subset of patients may not predict efficacy in typical AD, it is one more study that questions the validity of the amyloid theory as a treatment target for AD.

We all remain hopeful for a meaningful breakthrough in the treatment of AD, a disease that affects more than 6 million individuals in the United States, with devastating consequences for patients and families, but this saga reminds us that there are no shortcuts and that rushing treatments to market for business purposes is not ethical or helpful. The actions taken by CMS in this case should provide some reassurance that one governmental agency is willing to take an evidence-based position on policy, whereas another is not. Perhaps the system of checks and balances is still working. Health system pharmacists must remain cognizant of the evidence behind new drug approvals, contribute to decisions that are in the best interest of patients, and support responsible use of limited health care resources available in the community.

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Empagliflozin Cuts Risk of Hospitalization for Heart Failure for Adults With T2D

Empagliflozin (JARDIANCE; Boehringer Ingelheim, Eli Lilly and Company) was associated with a reduction in the risk of hospitalization for heart failure compared with 2 other classes of glucose-lowering therapies in adults with type 2 diabetes in routine care, according to 2 analyses from the EMPRISE study (NCT03363464).

“Heart failure is present in up to 30% of all people with type 2 diabetes. [so] it is critical that health care professionals treating this population have treatments that demonstrate cardiovascular effectiveness in routine care,” Elisabetta Pataro, MD, DrPH, associate epidemiologist of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women’s Hospital and an associate professor of Medicine at Harvard Medical School, both in Boston, Massachusetts, said in a statement. “These 5-year results from EMPRISE, showing empagliflozin was associated with a decreased risk of hospitalization for heart failure and for death, are encouraging data for adults with type 2 diabetes and their care team.”

Relative risk reductions were 50% with empagliflozin compared with DPP4 inhibitors and 30% compared with glucagon-like peptide 1 receptor agonists. Compared with DPP4 inhibitors, empagliflozin was also associated with a 40% reduction in relative risk of all-cause mortality in individuals who had Medicare coverage. In the overall population in the study, empagliflozin was associated with a 12% reduction in the risk of composite outcomes of myocardial infarction or stroke compared with DPP4 inhibitors.

The results were presented at the American Diabetes Association Scientific Sessions 2022 in New Orleans, Louisiana.—Ashley Gallagher

Omega-3 Fatty Acids Consumed Daily May Reduce Blood Pressure

Approximately 3 g of omega-3 fatty acids consumed in food or supplements is the optimal daily dose to help lower blood pressure (BP), according to the results of a research review published in the Journal of the American Heart Association.

Omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are typically found in fatty fish, including herring, oysters, salmon, sardines, trout, and tuna. Individuals also combined both acids in supplements.

The results of previous studies have suggested that omega-3 fatty acids could lower BP, but there never has been an optimal dosage pinpointed.

“According to our research, the average adult may have a modest blood pressure reduction from consuming about 3 g a day of these fatty acids,” Xinzhi Li, MD, PhD, assistant professor and program director of the School of Pharmacy at Macau University of Science and Technology in Macau, China, said in a statement.

Investigators analyzed the results of 71 clinical trials from around the world that were published between 1987 and 2020. The studies examined the relationship between BP and DHA and EPA, either combined or individually, in adults, with or without high BP or cholesterol disorders.

The study included 5000 individuals who were aged 22 to 86 years. Participants took dietary and/or prescription supplement sources of fatty acids for an average of 10 weeks.

Investigators found that, compared with individuals who did not consume DHA or EPA, those who consumed between 2 and 3 g daily of both acids had reduced diastolic and systolic BP by an average of 2 mm Hg. Additionally, they found that consuming more than 3 g of omega-3 fatty acids daily may have added BP-lowering benefits for adults with high BP or high blood lipids.—Ashley Gallagher

Study: Evusheld Offers Significant Prevention Against Severe COVID-19 Disease, Death

Detailed results from the TACKLE phase 3 outpatient treatment trial showed that tixagevimab and cilgavimab (Evusheld; AstraZeneca) provided clinically and statistically significant protection against progression to severe COVID-19 or death from any cause compared with the placebo, AstraZeneca said in a statement.

Additionally, the findings, published in Lancet Respiratory Medicine, showed that treatment with tixagevimab and cilgavimab earlier in the disease course led to more favorable outcomes.

“Despite the success of vaccines, many individuals such as older adults, individuals with comorbidities and those who are immunocompromised, remain at risk for poor outcomes from severe COVID-19. Additional options are needed to prevent disease progression and reduce the burden on health care systems, especially with the continued emergence of new variants,” Hugh Montgomery, MD, professor of intensive care medicine at University College London in the United Kingdom, said in the statement.

“The TACKLE results show that 1 intramuscular dose of [tixagevimab and cilgavimab] can prevent these individuals from progressing to severe COVID-19, with earlier treatment leading to even better results,” he said.

The TACKLE study (NCT04723394) was conducted in individuals with mild to moderate COVID-19 who were symptomatic for 7 days or fewer and were not hospitalized. Investigators reported that 90% of the individuals were at high risk of progression to severe COVID-19 because of age or comorbidities. In the study, a single 600-mg intramuscular dose of tixagevimab and cilgavimab significantly reduced the relative risk of progressing to severe COVID-19 or death, from any cause, by 50% through day 29 compared with placebo in individuals with mild to moderate COVID-19 who were symptomatic for 7 days or fewer and not hospitalized, which was the study’s primary end point.

In prespecified analyses of individuals who received treatment within 3 days of symptom onset, tixagevimab and cilgavimab reduced the risk of developing severe COVID-19 or death, from any cause, by 88% compared with placebo.—Ashley Gallagher
SECOND OPINION™

Frequently Asked Financial Questions
Tim Ulbrich, PharmD, and Tim Baker, CFP, RLP, discuss financial FAQs for health care professionals, including the decisions that must be made before retiring, how to manage student loan debt while saving for the long term, and the pros and cons of investing in real estate.

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Pharmacists Can Help Slow the Opioid Crisis
Patient Education, Naloxone Training, and Monitoring Programs Make a Difference
BY KHADIJA KHAN-CHAN AND DEEPALI DIXIT, PHARMD, BCPS, BCCCP, FCCM

Rates of problematic opioid use have been increasing since the 1990s, attributable in large part to rising life expectancy, the misuse of and surge in opioid prescriptions, and socioeconomic factors. As the opioid crisis continues, pharmacists can help alleviate and reduce the resulting morbidity and mortality.

As many as 25% of patients receiving long-term opioid therapy in a primary care setting have an addiction, and although sales of prescription opioids in the United States nearly quadrupled between 1999 and 2014, the amount of pain that Americans reported remained unchanged, according to the CDC.1

How Did We Get Here?
Although opiates have been used for more than 8000 years, the catalyst of the current opioid crisis can be traced to the late 20th century. In the 1980s, Purdue Pharma assured health care providers that their opiate drugs carried low addiction potential and were safe for chronic pain. In addition to drug coupons for patients and incentives for Purdue Pharma’s employees, the company recruited more than 5000 physicians to speak on its behalf. Policies were enacted protecting physicians against regulatory action for prescribing opioids. As a result, providers began prescribing OxyContin liberally, and Purdue Pharma’s profits jumped more than 20-fold between 1996 and 2001. By 2012, 259 million prescriptions for opioid pain medication had been written, and by 2015, deaths by overdose had almost tripled in less than 20 years.2,3

Pharmacist’s Role
In 2016, the CDC created a guideline for prescribing opioids for chronic pain, which included recommendations for addressing harm and assessing risks of opioid use; determining when to continue or initiate opioids for chronic pain; and detailing opioid selection, dosage, duration, follow-up, and discontinuation.4 Pharmacists are on the front lines and can directly educate patients about proper medication efficacy and safety.

However, barriers can hinder pharmacists’ ability to fight the opioid crisis. These include inadequate or no training, a lack of confidence, and most commonly, a lack of time. In addition, patients may not fully understand the role of pharmacist and do not seek proper help. Despite this, there have been multiple successful measures taken to address the opioid crisis. For instance, the Prescription Drug Monitoring Program (PDMP) is an electronic database that tracks controlled substance
prescriptions in each state. The PDMP improves opioid prescribing, informs clinical practice, and protects at-risk patients.

PDMPs have changed prescribing behavior and decreased substance use treatment admission and the use of multiple providers by patients, according to the CDC.³

A caveat to the PDMP program is that it often puts pharmacists in a difficult dual position in which they must both police patients and treat them.

Another intervention is medication-assisted treatment (MAT), which uses medications in combination with behavioral and counseling therapies to provide a patient-centered approach to the treatment of substance use disorders. Pharmacists are involved in community, inpatient, and outpatient settings to help prevent overdose mortality and provide education on the use of abuse-deterrent formulations of opioid analgesics. The MAT program uses FDA-approved medications to treat opioid dependence, such as buprenorphine, methadone, and naltrexone. The MAT program also uses naloxone (Narcan) to prevent opioid overdose by reversing the toxic effects of the overdose.⁶ Pharmacy schools are incorporating naloxone training into their curricula to prepare future pharmacists in the management of opioid overdose. The program has resulted in lower costs and a reduction in opioid overdoses. Pharmacists are the key to informing patients about these programs and making sure they adhere to these treatments.

In an inpatient setting, pharmacists are integral to managing patients’ pain. Clinical pharmacists review active medications, assess the need for opioids, and encourage deescalation or discontinuation of opioid treatment. Throughout the health care system, pharmacists are partnering with prescribers to ensure effective, optimal, and safe pain management for patients to prevent opioid use disorder (OUD) and overdose. The CDC Guideline for Prescribing Opioids for Chronic Pain emphasizes patient safety and encourages pharmacists and prescribers to collaborate in integrated pain management and team-based practice models. Pharmacists and prescribers should apply the guideline and work collaboratively to optimize pain management while preventing OUD and overdoses. This will improve patient outcomes.⁴ Through these efforts, pharmacists closely monitor for misuse by health care professionals and patients.

Pharmacists also have been at the front line of educating patients about overdose education and naloxone prescribing, distribution, and appropriate use. When pharmacists evaluate new prescription orders, they should assess for signs of OUD or medication diversion. Signs include altered or forged prescriptions, cash payment, early or inconsistent fills, multiple prescribers, or prescriptions originating from outside the immediate geographic area. Community pharmacists should verify customer identification and the prescriber’s United States Drug Enforcement Administration registration in addition to using tools such as the PDMP.

Some pharmacies provide an FDA-approved DisposeRx at-home medication disposal packet with each prescription, which is a convenient, effective, and simple way for patients to dispose of expired or unused medications. When the DisposeRx powder and water are added to a prescription vial and shaken, a polymer gel forms that traps the drugs. It can be used with capsules, liquids, pills, and powders, and it can be thrown away in the household trash.³ This is yet another way to lessen the potential for opioid addiction or overdose.

Conclusion
Evidence supports a collaborative and multifaceted approach to the opioid crisis. Pharmacists, both inpatient and outpatient, can help combat the opioid crisis through monitoring the PDMP, naloxone and opioid training and dispensing, and patient education. Pharmacists are essential to helping prevent opioid misuse.

REFERENCES
OPPORTUNITY FOR DIVERSION of controlled substances occurs at all steps in medication management. Health systems face many risks associated with diversion, including financial, legal, patient injury, and reputational. Affected parties include coworkers, patients, pharmacy staff members, and providers. To secure an effective diversion prevention program, pharmacy leaders should proactively engage essential interdisciplinary stakeholders, including individuals in charge of storing or disposing of controlled substances, the executive team, operating room staff, and patient care units. Input and shared decision-making with staff members should include discussions on decreased documentation burden, ways to lower diversion risk, peer oversight, and program value.

Risk Points
The American Society of Health-System Pharmacists (ASHP) Guidelines on Preventing Risk Diversion identify where in the supply chain diversion is most likely. These are the 5 essential phases where pharmacists should focus their efforts:

- **Drug procurement phase:** There is an opportunity for staff members to alter or delete records, gain unauthorized access to electronic controlled-substance ordering system and Drug Enforcement Administration (DEA) forms, or compromise a product container.
- **Preparation and dispensing phase:** Staff members might divert overfill, remove volume from a solution, replace one product with another, or replace a prepared drug with another product.
- **Prescribing phase:** Prescription pads could be targeted; prescribers might self-prescribe or prescribe controlled substances for family or friends. Issues with illegitimate or nonauthorized verbal orders may arise. Also, patients might alter written prescriptions. E-prescriptions have helped but do not eliminate risk.
- **Medication administration phase:** Products could be removed for a discharged patient, medications might be documented as administered but not provided to patients, or substitute drugs might be administered in place of the product.
- **Waste and removal phase:** Controlled-substance waste might be removed from unsecured waste containers, expired products might be diverted from holding areas, and waste in syringes might be replaced with saline.

Focusing on these risk points identified by the ASHP is important to ensure supply chain integrity. A comprehensive plan addressing all 5 phases with financial stewardship is important to assure adequate oversight.

Elements of a Good Prevention Program
First, administrative checks and balances help provide oversight and accountability. This includes the development of drug diversion teams. Teams should meet at set intervals to certify that controlled substance legal and regulatory requirements are met. Oversight should include general and random screens for handling of all controlled substances. The teams should ensure prompt audits and investigations, and results should be taken seriously. Automated intelligence provides teams with additional information with standard deviations to analyze efforts.

Second, teams should engage in health system-wide processes. This involves addressing components of human resources management (2 witnesses for medication waste), automation and technology
(appropriate policy and procedures, including sign-outs), ensuring prompt event reporting and investigation, proactive monitoring (including scheduled and random counts), and camera surveillance. A good program makes it difficult to divert controlled substances while ensuring patient care.

Third, pharmacists should establish adequate user competencies, oversight, and training around chain of administration, custody, disposal, internal pharmacy supply chain, prescribing, returns, security and storage, and waste. An avenue for providing feedback and shared decision-making for these processes should be used.

A culture of collaboration in team efforts should include a variety of departments, including anesthesiology, human resources, medicine, nursing, and pharmacy, with support from the executive team. Ensuring transparent communication, goals, and perceived value with other disciplines is crucial to efficient controlled-substance management.

**Medication Waste**

Diversion and waste are significant problems, especially in areas where there is high use of drug products. The more waste produced, the greater the prospect for medication diversion. Reducing waste reduces diversion risk. The Third Consensus Development Conference on the Safety of IV Delivery Systems has a list of 10 items to ensure safe handling and reduce waste of intravenous products. Best practices include competencies, formal education, interdisciplinary efforts, legislative and regulatory frameworks, standardizing packaging sizes, training, and use of automation and technology where possible with appropriate policy and oversight.

The DEA’s 2014 Final Rule on Disposal of Controlled Substances discusses disposal of a DEA registrant’s inventory. But it does not discuss disposal by health care facilities of partially administered syringes or single-dose vials (eg, medication waste) or how household users should handle waste disposal. The Environmental Protection Agency amended the Resource Conservation and Recovery Act in 2020 to require staff members to render wasted medication irretrievable. Product can no longer be poured down the sink into wastewater. This is now an added consideration.

**Conclusion**

Pharmacists should identify institutional practices supporting best practices, medication safety, and staff education to minimize drug diversion risks. Engaging key interdisciplinary stakeholders to gain support and improve the institution’s controlled-substance stewardship program are the goals essential to reducing the opportunity for diversion and ensuring a successful program.

**REFERENCES**


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SGLT2 Inhibitors Are Shown to Reduce HF Death and Hospitalization
Empagliflozin Also Was Associated With Improvement in Quality of Life
and Greater Reduction in Body Weight

BY DEEPA LI DIXIT, PHARMD, BCPS, BCCCP, FCCM

HEART FAILURE (HF) is one of the most common chronic diseases associated with substantial hospital readmission, morbidity, and mortality.¹ Patients hospitalized for acute HF experience a significant burden of symptoms that may lead to physical limitations and poor quality of life.

After hospital discharge, approximately 40% of these patients are readmitted within 6 months, and 1-year mortality post discharge is substantial.² Several randomized controlled trials have evaluated pharmacological interventions in patients hospitalized with acute HF. However, none of the therapies tested was associated with improved outcomes or readmission rates, emphasizing an urgent need to fill this gap. The sodium glucose cotransporter-2 (SGLT2) inhibitors dapagliflozin (Farxiga) and empagliflozin (Jardiance) have been shown to reduce the risk of cardiovascular death (CVD) or hospitalization for HF in patients with chronic heart failure (CHF) with a reduced left ventricular ejection fraction. Furthermore, empagliflozin has been shown to reduce the risk of CVD or hospitalization for HF in patients with CHF with a preserved left ventricular ejection fraction. The latest iteration of the heart failure guidelines include SGLT2 inhibitors for heart failure management.³ The combination of the SGLT1/2 inhibitor, sotagliflozin, has been associated with improved clinical outcomes in patients with diabetes and progressing HF. However, it was unknown whether empagliflozin provided clinical benefit in patients hospitalized for acute HF. During hospital admission for HF, therapies used to manage symptoms frequently led to considerable fluid and electrolyte shifts and hemodynamic changes. Providers often face limited available therapeutic options, and it has been uncertain whether it is safe to initiate treatment with an SGLT2 inhibitor during hospitalization.

Rationale
The phase 3 EMPULSE study (NCT04157751) assessed the clinical benefit and safety of empagliflozin compared with placebo in patients hospitalized with acute HF.⁴ EMPULSE evaluated the effects of empagliflozin on 3 central goals of care in hospitalized patients with acute HF: reduction of heart failure event (HFE), survival benefit, and symptom improvement.

This double-blind, international, multicenter, parallel-group, placebo-controlled, randomized study enrolled patients between June 2020 and February 2021. During the trial, 566 patients were screened, and 530 were randomly assigned to empagliflozin 10 mg daily (n = 265) or placebo (n = 265). To be included in the trial, patients had to have been hospitalized with acute HF, regardless of diabetes or ejection fraction status; have systolic blood pressure of 100 mm Hg or higher; have not needed an increase in intravenous (IV) diuretic dose within 6 hours; have had no symptoms of hypotension within 6 hours; have not needed an increase in intravenous (IV) diuretic dose within 6 hours; have not been on IV vasodilators, including nitrates, within 6 hours; and not have had IV inotropic drugs within 24 hours. Other criteria included N-terminal pro-B-type natriuretic peptide (NT-proBNP) of 1600 pg/mL or greater or BNP of 400 pg/mL or greater during hospitalization or within 72 hours prior to admission. The median age of participants was 71 years; 47% had diabetes, 78% were White, and 34% were women. The median time from hospital admission to
being randomly assigned was 3 days, with a 90-day duration of follow-up. The primary outcome was assessed using a stratified win ratio, defined as a composite numbers of death, number of HF events, time to first HF event, and change in Kansas City Cardiomyopathy Questionnaire-Total Symptom Score (KCCQ-TSS) from the baseline to 90 days. Clinical benefit occurred at a rate of 53.9% in the empagliflozin group compared with 39.7% in the placebo ($P = .005$) group. The empagliflozin effect on the primary efficacy outcome was consistent across prespecified subgroups. The secondary outcome of the incidence of cardiovascular death or HFE until the end-of-trial visit was 12.8% in the empagliflozin group and 18.5% in the placebo group. There was no major difference in the proportion of patients with a KCCQ-TSS improvement of 10 points or greater at day 90 between the 2 groups. Acute renal failure was observed in 7.7% of participants taking empagliflozin vs 12.1% in the placebo group. Furthermore, the empagliflozin group had a higher reduction in NT-proBNP concentration and body weight than patients in the placebo group.

Key Takeaways
The EMPULSE findings indicate that initiation of empagliflozin in patients hospitalized for acute HF was well tolerated and showed significant clinical benefit in the 90 days after initiating treatment. In terms of safety, adverse events were higher in the placebo arm. There were no cases of ketoacidosis reported in the study.

Conclusion
Among patients with acute decompensated HF, empagliflozin was associated with significant clinical benefit at 90 days. The EMPULSE study enrolled participants regardless of diabetes or ejection fraction, and there was no evidence for treatment interaction based on either of these variables. The benefit of empagliflozin was independent of symptomatic impairment at baseline. Empagliflozin vs placebo also was associated with fewer deaths, improvement in quality of life, and greater reduction in body weight without any safety concerns. To date, very few interventions have shown symptom improvement and functional status in the postdischarge period in patients hospitalized with acute HF. The results of the EMPULSE trial suggest that the initiation of empagliflozin will become the standard of care in eligible patients hospitalized for acute HF.

"Patients hospitalized for acute HF experience a significant burden of symptoms that may lead to physical limitations and poor quality of life."
Trilaciclib Protects Against Chemotherapy-Induced Myelosuppression
Treatment’s Approval Marks Exciting New Development for Patients
With ES-SCLC to Prevent CIM

BY BRYAN P. FITZGERALD, PHARMD, BCOP

MYELOSUPPRESSION IS ONE of the most common and dangerous dose-limiting toxicities of traditional chemotherapy.

Chemotherapy-induced myelosuppression (CIM) can cause clinically significant sequelae, including bleeding, fatigue, and potentially fatal infections. Historically, CIM has been managed with transfusions, chemotherapy dose delays, dose reductions, and drugs.

Pharmacologic management of CIM has consisted of administering growth factors, including erythropoietin-stimulating agents (ESAs) and granulocyte colony-stimulating factors (G-CSFs). By stimulating the production of erythrocytes and neutrophils, respectively, these agents promote bone marrow recovery after chemotherapy administration. Despite their proven clinical benefit, risks and toxicities exist, ranging from bone pain with G-CSFs to an increase in thrombotic events with ESAs. The risks of these agents must be weighed against their clinical benefits.

In 2021, the FDA approved trilaciclib (Cosela, G1 Therapeutics) to prevent CIM in patients with extensive-stage small cell lung cancer (ES-SCLC). Trilaciclib reversibly inhibits cyclin-dependent kinase (CDK) 4/6 and arrests hematopoietic stem cells (HSCs) in the G1 phase of the cell cycle.1 Contrary to growth factors that promote HSC production after chemotherapy, trilaciclib protects HSCs from the cytotoxic effects of chemotherapy during chemotherapy exposure. This mechanism has been used by other CDK 4/6 inhibitors, including abemaciclib (Verzenio), palbociclib (Ibrance), ribociclib (Kisqali) in the management of breast cancer. However, trilaciclib is the first CDK 4/6 inhibitor approved for a supportive-care indication.

Trilaciclib was approved to prevent CIM specifically in patients with ES-SCLC receiving chemotherapy regimens containing a platinum/etoposide or topotecan. These indications are based on results of 3 randomized phase 2 trials enrolling patients with ES-SCLC receiving treatment with 1 of 3 regimens: first-line carboplatin plus etoposide; first-line carboplatin plus etoposide plus atezolizumab; or second-line or third-line topotecan.2-4 In each trial, patients were randomly assigned to receive trilaciclib 240 mg/m² intravenously daily or a placebo, given prior to chemotherapy infusions. The primary end points in each trial were duration of severe neutropenia during cycle 1 of chemotherapy and percentage of patients with severe neutropenia during treatment. Severe neutropenia was defined as an absolute neutrophil count of less than 0.5 × 10⁹ cells/L, which is classified as a grade 4 toxicity by Common Terminology Criteria for Adverse Events version 4.03.1

Across the 3 trials, 242 patients were randomly assigned to receive either trilaciclib (n = 123) or placebo (n = 119) prior to chemotherapy. Patients receiving trilaciclib had significant improvements in both primary outcomes, with a lower percentage of patients experiencing severe neutropenia (11.4% vs 52.9%, \( P < .0001 \)) and a shorter mean duration of severe neutropenia during cycle 1 (0 days vs 4 days, \( P < .0001 \)).1 The trilaciclib group also had improved secondary outcomes, including improvements in the rates of grade 3 to 4 anemia, grade 3 to 4 thrombocytopenia, G-CSF administration, and ESA administration.1
The pooled safety analysis from the 3 trials showed that the majority of patients in both groups had at least 1 adverse event (AE): 94.3% with trilaciclib vs 96.6% with the placebo. The most common AEs reported with trilaciclib were aspartate aminotransferase elevation, fatigue, headache, hypocalcemia, hypokalemia, hypophosphatemia, and pneumonia. Less common but still-notable reactions in the trilaciclib group were injection site reactions (13.9% vs 2.5% in the placebo group), phlebitis or thrombophlebitis (9.0% vs 0.8%), and hypersensitivity reactions (4.1% vs 3.4%). Compared with 3 patients in the placebo group, 6 patients in the trilaciclib group had fatal AEs, including cerebrovascular accident, hemoptysis, pneumonia, and respiratory failure. The FDA approved trilaciclib with a warning for pulmonary toxicity, a warning that other CDK 4/6 inhibitors also carry in their labeling.

Because of its mechanism in arresting cell cycle progression, it is important to investigate any effects of trilaciclib on tumor response rates and concerns for tumor progression. Fortunately, the pooled analysis of the 3 trials suggested that tumor response rates were similar between trilaciclib and the placebo, with objective responses achieved in 49.1% of patients taking trilaciclib vs 51.8% of those taking the placebo. Median durations of response, overall survival, and progression-free survival also were considered to be similar between the 2 groups.

The choice of investigating the use of trilaciclib in patients with ES-SCLC was deliberate. Because of their loss of the retinoblastoma protein, SCLC tumor cells do not depend on CDK 4/6 for replication. Therefore, inhibition of the CDK 4/6 enzyme with trilaciclib would selectively arrest the replication of healthy cells and not affect SCLC tumor cells. Future studies investigating the use of trilaciclib to prevent CIM will require careful consideration in select tumor types that replicate outside of the CDK 4/6 pathway.

Trilaciclib was approved at the same dose investigated in the trials of 240 mg/m² as a 30-minute intravenous infusion prior to chemotherapy administration. Trilaciclib should be administered on each day that chemotherapy is given and must be completed within 4 hours prior to the start of chemotherapy infusion. An inline 0.2- or 0.22-µm filter is required during trilaciclib administration.

Conclusion
The approval of trilaciclib to prevent CIM marks an exciting new development for patients with ES-SCLC. However, data are limited to phase 2 trials. Therefore, larger, more robust phase 3 trials are needed to confirm these results and determine any clinical implications. Additionally, the benefit of trilaciclib is limited to patients with ES-SCLC because of the cells’ independence from the CDK4/6 pathway. Time will tell if any additional tumor types would be candidates for this novel therapy in preventing CIM.

References
Access to C. difficile Treatments Presents Challenges During Transitions of Care
This Inflammation of the Colon Poses a Substantial Burden to Patients and the Health Care System

BY EMILY DRWIEGA, PHARMD, BCIDP, BCPS, AAHIVP; AND MONIQUE R. BIDELL, PHARMD, BCPS

CLOSTRIDIODES DIFFICILE INFECTION (CDI) affects nearly 500,000 patients each year, costing the health care system several billion dollars. Infection is associated with substantial morbidity, including the risk of recurrent infection. Recurrent CDI (rCDI) occurs in approximately 10% to 30% of patients after a first episode, with the risk of recurrence increasing with subsequent episodes.

In 2021, the American College of Gastroenterology, the European Society of Clinical Microbiology and Infectious Diseases, and the Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHEA) all published guideline updates with increased emphasis on therapies that have been shown to decrease the risk of rCDI. Notable updates include preference for use of bezlotoxumab and fidaxomicin in patients at high risk for rCDI, as well as recommendations for fecal microbiota transplantation (FMT) in patients with multiple episodes of rCDI. Although these therapies are clinically beneficial, they are associated with several barriers that may affect patient access and successful transitions of care.

Perhaps the most widely appreciated barrier to CDI therapies is affordability. Medication delays related to economic barriers are associated with rCDI and rehospitalization. Although affordability is a concern, especially with fidaxomicin (the average wholesale price is approximately $5000 per treatment course), insurance coverage may be increasing since the 2021 IDSA/SHEA treatment guideline update. One small study of 15 patients discharged with fidaxomicin in 2021 identified successful acquisition of fidaxomicin in 12 cases (80%), with all prescriptions covered by commercial insurance. Most (93%) patients had insurance co-payments of less than or equal to $50. However, this was a small analysis, and investigators indicated that the number of successful discharge prescriptions with fidaxomicin was higher than anticipated.

Several best practices can be considered to improve access to fidaxomicin. In the days prior to hospital discharge, a patient’s fidaxomicin formulary status and prescription insurance policy should be determined to confirm affordability and coverage. In many cases, prior authorizations may be necessary. In instances when an insured patient has a high co-pay, coupons available on the manufacturer’s website may be helpful. Uninsured patients can use the manufacturer patient assistance program.

ABOUT THE AUTHORS
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Each of these efforts requires time for processing, which may delay patient access to treatment.

Similar access issues exist with bezlotoxumab in that predicting costs to the patient can be challenging. Patient assistance programs from the manufacturer are available but can delay time to administration, which is recommended to occur during antibiotic therapy. Coordination with outpatient infectious diseases providers can be beneficial to synchronize efforts with an outpatient infusion center and help manage the patient until time of bezlotoxumab administration.

Paired with cost challenges, availability of these therapies may be limited. Local pharmacies and postdischarge care facilities may not adequately stock fidaxomicin. Local pharmacies and postdischarge care facilities may be limited. Local pharmacies and postdischarge care facilities may not adequately stock fidaxomicin. Therefore, supply should be confirmed at the time of bezlotoxumab administration.

A final barrier that may be underappreciated is lack of provider familiarity with these therapies. Bezlotoxumab is often reserved for patients at high risk for rCDI and is preferentially administered in the outpatient setting for reimbursement purposes. Therefore, some providers may have limited experience with or knowledge of this agent. This may lead to missed opportunities to identify candidates who may benefit from this therapy. Similar barriers may exist surrounding FMT, as the processes often require a gastroenterologist or an infectious diseases specialist.

Conclusion

There are numerous barriers associated with CDI management, including clinical, patient-related, and systemic barriers. One comprehensive resource that addresses these barriers is a guide for transitions of care developed by an expert multidisciplinary committee, including a case manager, CDI patient representative, gastroenterologist, and primary care provider. This guide, published in 2019 by the National Transitions of Care Coalition, summarizes strategies to prevent primary CDI, reduce the risk of rCDI, and mitigate the risk of CDI-associated readmissions.U Pharmacist members of interdisciplinary care teams can play a variety of roles, including collaborative development of institutional treatment pathways, such as assisting with medication access, providing CDI-associated counseling, and considerations for transitions of care. A multidisciplinary approach with supportive infrastructure can help facilitate successful therapy access and transitions of care to patients.

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REFERENCES

Opinion: FDA Is in a Hole With MOU on Compounding Medications
The Drug Quality and Security Act Eliminated the Original Problem, so the Agency Should Stop Digging

BY SCOTT BRUNNER, CAE

When FDA lawyers conceded in US federal court this past February that the agency had not properly followed Congress’ instructions for creating a memorandum of understanding (MOU) with states regarding interstate distributions of compounded medications, they finally were heeding Will Rogers’ advice: “If you find yourself in a hole, stop digging.”

For the FDA, that hole is now 25 years deep. Its impetus was a directive from Congress in 1997, part of revisions made to the Food, Drug and Cosmetic Act, that the agency execute an MOU under which state boards of pharmacy would report to the FDA certain information about state-licensed compounding pharmacies that distributed a large percentage of their compounded preparations across state lines.

As Congress conceived it, the MOU would be voluntary, but the law would impose restrictions on pharmacies shipping compounded drugs from states that chose not to sign it. Congress intended it to be a consensus document, created via the formal rule-making process, with input and endorsement of the states. In other words, Congress expected the FDA to draft an MOU that states would be willing to sign.

But that is not what the agency did. Instead, it started digging. After several proposed iterations spanning 24 years, the FDA in 2020 finalized an MOU that:

• Conflated 2 important pharmacy law definitions: dispense” and “distribute
• Did not go through formal notice-and-comment rule making
• Failed to properly assess the economic impact on pharmacies and state boards of pharmacy

That resulted in a lawsuit against the agency by 7 compounding pharmacies, whose arguments resonated in part with a federal judge and led to the FDA conceding its failures in court in February 2022. Granted, the agency did not entirely abandon its shovel in that court appearance. Instead, it laid out plans for starting work on a new hole: proposing yet another version of the MOU, this time via the prescribed rule-making process it previously failed to follow.

But abandoning that MOU is precisely what the FDA ought to seek permission to do, because the specific problem the MOU was conceived in 1997 to address no longer exists.

To understand why the MOU as envisioned by Congress is out of date, let’s first return to those definitions mentioned earlier. Across federal and state pharmacy law, the terms dispense and distribute have remarkably consistent definitions.

Dispensing is patient-specific; it refers to a drug prepared for an individual patient pursuant to a prescription from a physician or other prescriber. Distributions, on the other hand, are not patient-specific; the term applies to batches of compounded medications prepared for in-clinic or in-hospital administration by a physician to a patient, and a prescription is not required.

Back in 1997 when Congress authorized creating the MOU, it was to address compounding and distribution by traditional compounding pharmacies of non–patient-specific medications intended for in-clinic administration. It was a practice generally allowed under most states’ laws at the time but was subsequently prohibited by Congress when it passed the Drug Quality and Security Act.
Across federal and state pharmacy lines, the terms dispense and distribute have remarkably consistent definitions.

Quality and Security Act (DQSA) in 2013. Under the DQSA, traditional compounders were forbidden from compounding drugs for in-clinic use without a prescription. Not only that, but a new category of compounding operation, called outsourcing facilities, was created. Those facilities would be allowed to distribute compounded medications to hospitals and clinics if they complied with current good manufacturing practices, much like the manufacturers of FDA-approved drugs do.

The DQSA eliminated the need for that 1997 MOU because traditional compounders could no longer do what the MOU was envisioned to illuminate. Still, the requirement for an MOU remained in the Food, Drug and Cosmetic Act, so the FDA decided to dig a little deeper.

The agency redrafted an MOU that applied to both distributions and dispensing of compounded medications, even though Congress had only authorized the MOU to cover distributions, and not patient-specific dispensing, the regulation of which has long been the purview of state boards of pharmacy. That overreach led to the aforementioned lawsuit against the agency by compounding pharmacies and that February court appearance where the FDA climbed out of one hole and announced it would start digging another.

Here’s the thing: Pharmacy compounders are not opposed to some level of reporting on shipments of compounded medications across state lines, even the shipping of patient-specific compounded drugs. Because it is not unusual in compounding that the pharmacy that makes that customized drug for a child, partner, or Aunt Sadie in a different state, it is reasonable for the FDA and state boards of pharmacy to want to know which pharmacies are shipping majorities of their compounded preparations out of state.

So instead of digging a new hole, the FDA should join with the compounding profession to change the law. Eliminate that out-of-date MOU requirement, an MOU that several states have already said they cannot sign, because of state law, or will not sign, because of the administrative burden.

In its place create a statutory regime for reporting shipping information to state boards of pharmacy, to be shared with the FDA. Perhaps also create a narrow but permanent pathway in the statute for compounding pharmacies to mitigate drug supply-chain problems by preparing urgent-use drugs in small batches for clinics and hospitals when those drugs are in national or regional shortage.

Stop digging, FDA, and let’s start building a new framework that provides the reporting you want and maintains patient access to safe, life-enhancing compounded medications.

FOR REFERENCES, GO TO PHARMACYTIMES.COM/PUBLICATIONS.
OR 6 YEARS, Lanh Dang, PharmD, BCACP, a clinical ambulatory care pharmacist in the University of Florida Health (UF Health) specialty pharmacy in Jacksonville, was a constant and reassuring presence in Gwendell Snead’s life.

Snead, a 63-year-old patient with Crohn disease, has dealt with the social isolation associated with the debilitating condition. “She’s my angel,” Snead said of Dang. “[Dang is] always there when I need her. If I’m feeling down, she’ll pick me up and fill me in on what I need to know and what I need to do. I would be lost if it wasn’t for her.”

Snead began having symptoms associated with Crohn disease when she was in her late 20s. Over time, the flare-ups got worse, resulting in frequent hospitalizations, preventing her from working for long periods of time, and keeping her confined to her home. Snead was not able to keep up with many of her favorite activities, such as attending church and going on outings with family and friends.

She met Dang during her initial visit to UF Health Gastroenterology–Jacksonville, an academic medical center within the UF Health system. Dang was part of the clinical team that evaluated Snead, developed a treatment plan for her, and provided follow-up care.

“I remember her saying in that first meeting, ‘If you ever need anything, just pick up the phone and call me.’ I knew right away that Lanh was the one I wanted to work with me,” Snead said.

Previously, 3 drug therapies for Crohn disease had failed to alleviate Snead’s symptoms. Dang and the UF Health team prescribed ustekinumab (Stelara; Janssen Biotech), an injectable treatment for Crohn disease, to be administered every 8 weeks. When that proved ineffective and the frequency had to be changed to every 4 weeks, Snead’s insurance company questioned the above-average dosage. Dang, working with Snead’s gastroenterology specialist, appealed successfully on Snead’s behalf, and the insurer agreed to keep paying for the higher dosage. The drug’s average wholesale price is $30,000 per pen.

On another occasion, when Snead confused the ustekinumab shot with another medication she was taking and injected ustekinumab too soon, Snead called Dang for help. Dang quickly connected with Snead’s physician and recommended an adjustment to the dosage to get her back on schedule.

HSSPs Untangle the Journey for Patients With Complex Specialty Diseases
Health System Specialty Pharmacies Help Remove Barriers to Care, Optimize Therapy, and Improve Outcomes
BY GARY HOPKINS

ABOUT THE AUTHOR
GARY HOPKINS is a principal with Blanco + Hopkins & Associates LLC, a health care public affairs firm based in La Canada, California.
Dang and the rest of the specialty pharmacy team at the clinic are an integral part of Snead’s care team, providing support by consulting with Snead’s providers on drug therapies, making sure she has all the information she needs about their medications, helping coordinate refills, guiding her through the insurance maze, and providing co-pay assistance and information when needed.

According to Snead, who says her condition has stabilized, having Dang on her care team has been critical to her recovery. “From the day I met her, she’s been wonderful,” Snead said. “I just thank God that I have her.”

**Integrating Specialty Pharmacy and the Patient Journey**

Patients who receive a diagnosis of a chronic, complex disease or condition that requires a specialty medication often face specific challenges: how to access the drug and how to get the help needed to manage therapy.

These medications are often expensive and typically require a high degree of ongoing patient assessment or case management to optimize therapy and prevent adverse effects, which can be resource-intensive for pharmacy care teams. In some cases, manufacturers and pharmacy benefit managers limit distribution of specialty drugs to a handful of specialty pharmacies or a single large commercial specialty pharmacy, requiring patients to go outside health systems to obtain treatment. This creates an additional care transition for patients, which may lead to delays or interruptions. For patients with a potentially terminal diagnosis who need to start their therapy in a timely manner, any delay in accessing their medication can be especially devastating, both emotionally and physically.

Specialty pharmacies were created to coordinate care for patients on these complex therapies, beginning with transplant patients at academic medical centers, according to Burnis Breland, PharmD, MS, FASHP. Breland, a longtime pharmacy educator and practitioner, is a regional account director with Acentrus Specialty, a national network of 133 health systems and large hospitals committed to providing specialty pharmacy care for patients.

With Acentrus, Breland is a strong advocate for integrating specialty pharmacy within health systems and hospitals. The specialty pharmacy space is dominated by large commercial specialty pharmacies and pharmacy benefit managers, which control approximately 87% of the specialty pharmaceutical prescription revenue market. Health system specialty pharmacies (HSSPs) and other noncommercial specialty pharmacies make up the remaining 13%.

“The specialty patient’s journey is a particularly challenging one. Integrated specialty pharmacies help health systems and hospitals meet these challenges so they can give total care to patients within their system and minimize the stress and concerns that these patients go through,” Breland said. “Working collaboratively with providers, specialty pharmacies within a health system or hospital can help ensure the best quality care, the best clinical outcomes, and the best patient satisfaction. This clinical patient management, including interaction between the specialty pharmacists and the specialty clinic providers, cannot be provided by pharmacists and pharmacies outside the health system who lack the same level of direct patient interaction as well as access to the patient’s medical records.”

Specialty pharmacy leaders from 4 major academic centers across the country—UAB Medicine in Birmingham, Alabama; UCSF Medical Center in San Francisco, California; UF Health Jacksonville in Florida; and UNC Medical Center in Chapel Hill, North Carolina—echoed Breland’s sentiments during a panel discussion at the Acentrus Specialty Pharmacy conference in San Diego, California, in April 2022. The panel members described how being included in the clinical care teams at their facilities allows them to anticipate and proactively address care coordination challenges patients may face.

During the discussion, the representatives from each academic center agreed that, as part of the care teams, specialty pharmacists can view information available in patients’ electronic health record (EHR) to better understand their condition and progress.

They can monitor for adverse interactions between patients’ specialty medications and any other drugs they may be taking, manage adverse events, get timely prior authorizations from insurers so patients can start therapies quickly,
handle appeals when necessary, and help patients obtain financial assistance to cover co-pays. Additionally, by documenting each step they take in the EHR, pharmacists update the entire care team on their patients’ progress from a pharmacy perspective.

Real-world Data to Improve Patient Outcomes

Advocates for HSSPs say that in addition to promoting better clinical management of patients, they also offer access to meaningful real-world data that improve treatment outcomes.

Unlike large commercial specialty pharmacies, which typically only have access to claims and pharmacy dispensing data, specialty pharmacies within a health system or hospital can access all the clinical data contained in the patient’s EHR.

“It’s impossible to perform meaningful outcomes studies from claims data and pharmacy dispensing data,” said Tom Renshaw, MBA, RPh, senior director of business solutions at Acentrus. “You need the full continuum-of-care data, the kind of robust clinical data you get from the EHR, to do this kind of work. The real-world evidence that comes from the unstructured EHR data, including the provider’s clinical notes, gives you a much deeper understanding of the patient journey than you can get from traditional data sources.”

HSSPs are already using their access to EHR data to connect the dots between the care they provide and patient outcomes. For example, an evaluation by Acentrus of clinical EHR data at 12 hospitals found that approximately 50% of patients with HER2-negative breast cancer who met the National Cancer Institute guidelines to receive palbociclib (Ibrance; Pfizer) or another drug in the cyclin-dependent kinase 4/6 inhibitor class were not being given the medication.

“When we went out and educated the providers and the specialty pharmacists about the results of our study, many of these patients were subsequently put on the medication,” Renshaw said. “This kind of retroactive analysis is a great way to improve care and ensure that guidelines are being followed.”

Additionally, there is another major initiative under way to use EHR data to measure, understand, and benchmark patient outcomes. In August 2021, Acentrus, in conjunction with Loopback Analytics, formed the Therapy Specific Outcomes Coalition, a collaborative, multisystem group of the nation’s leading HSSPs.

This coalition is designed to develop therapy-specific outcomes and identify best practices through clinical benchmarking between health systems on a standard platform. The coalition is actively identifying key outcome measures for 8 disease states specific to the specialty pharmacy space, including cystic fibrosis, multiple sclerosis, and oncology.

“The problem for many health systems is that although they may understand the effectiveness of a therapy on a single patient, they don’t have a clear understanding of its effectiveness on a patient population level. They don’t have the ability to connect the dots,” said Neesha Thakkar, PharmD, BCPS, a regional account director at Acentrus who is helping lead the coalition.

Therapy-specific dynamic dashboards will allow health systems to understand their clinical outcomes, benchmark against other health systems, and identify best practices.

In addition to helping health systems optimize patient care, the coalition aims to partner with manufacturers and payers to better understand how specialty drugs are being used and how effective they are.

“Our overarching goal is to demonstrate that patients treated in an integrated specialty pharmacy have superior clinical outcomes,” Thakkar said. “Ultimately, and most importantly, it’s the patient who should benefit.”

REFERENCE

The Role of Pharmacists in monitoring appropriate utilization of immunoglobulin (Ig) therapy in patients with primary immunodeficiency disorder (PID) is growing. In a session at the 2022 Asembia Specialty Pharmacy Summit titled “Intravenous and Subcutaneous Immunoglobulin in the Management of Primary Immunodeficiency Disorder: Updates for Specialty Pharmacists,” led by Bob Geng, MD; and Jonathan Ogurchak, PharmD, CSP, pharmacists gained insight into strategies to optimize patient outcomes with Ig therapy.

Dr Geng provided some background information on PID and its history. There are currently more than 400 PID syndromes, with more being discovered due to improvements in diagnostics and genetic testing. Individuals with PID generally present with antibody deficiencies. Dr Geng explained these deficiencies can be associated with frequent complications affecting several major organ systems and collectively termed these “inborn errors of immunology.”

Ig is the standard treatment for PIDs and is derived from plasma from human donors. A single lot can be pooled from the plasma of 10,000 to 50,000 donors. The plasma undergoes a rigorous screening process, and multiple steps are involved in the isolation, purification, and viral inactivation. Dr Geng detailed the differences between subcutaneous (SC) and intravenous (IV) formulations. Compared with IVIg, administration of SCIg allows for a slower release of Ig, which reduces systemic adverse effects (AEs). However, SCIg has been associated with more local AEs, such as injection-site pain.

Recent approaches in the management of Ig therapy have focused on individualizing treatment. Each patient may need a different IgG level to achieve infection control, and this level must be aligned across recommendations from payers and providers to prevent infections. As part of individualizing treatment, patients may be switched from IVIg to SCIg. Dr Geng reviewed quality-of-life improvements reported by patients with use of SCIg.

Dr Ogurchak dove deeper into available combination IVIg/SCIg products. He reminded pharmacists to consider formulary coverage and potential limitations of the patient’s insurance when switching or initiating Ig therapy. It is also important to be aware that Ig products may be approved for multiple indications and that dosing for each indication may vary. He reviewed safety and efficacy and discussed differing characteristics of Ig products, as some may use sodium or sugar as stabilizers and higher levels of these may exacerbate underlying conditions for patients.

Additionally, Dr Ogurchak reviewed the importance of titration according to patient response, which can be variable. There is a higher incidence of infection and hospitalization among patients who do not receive appropriate therapy management. It is estimated that appropriate management of Ig therapy in patients with PID could result in an overall 50% reduction in annual per-patient costs.

Dr Ogurchak ended the presentation with clinical pearls for managing patients with PID, especially the importance of vaccination. Other considerations pharmacists should keep in mind when counseling patients on route selection include whether the patient may have poor venous access, flexibility of schedule, or any conditions that would limit their ability to perform at-home SCIg administration. Teaching patients how to self-administer SCIg, providing tips to manage AEs, and emphasizing appropriate needle selection are points pharmacists should address during counseling.

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-SEMBIA-on-demand-programs
The activity is available through May 10, 2023.
New Treatments Are Essential to Reduce Challenges in Pediatric Atopic Dermatitis

THE PEDIATRIC PATIENT POPULATION is frequently affected by eczema, or atopic dermatitis (AD). In a session at the 2022 Asembia Specialty Pharmacy Summit titled “Overcoming the Challenges of Treating and Managing Moderate to Severe Atopic Dermatitis in Pediatric Patients,” Anna Fishbein, MD; and Allison Provine, PharmD, BCPS, BCPPS, discussed escalation of therapy and emerging treatments indicated specifically for this population. Several patient cases were shared throughout the presentation to evaluate the diagnostic criteria and determine appropriate diagnosis of AD as well as age-appropriate first-line therapies.

Dr Fishbein reviewed the essential diagnostic features of pediatric AD. Pruritus and chronic or relapsing history are essential in the diagnosis of AD, and other associated features that can confirm diagnosis include early age of onset and/or family history. Dr Fishbein reminded the audience that 60% of pediatric patients experience symptoms of AD within the first year of life, and the burden of AD continues to be substantial throughout the life span. There is an inflammatory loop in AD, in which breakdown of the skin barrier is stimulated by contact with inflammatory microbiota triggering release of cytokines, mast cells, and interleukins, and results in continuous disruption by scratching.

Goals of treatment are to reduce or eliminate rash, resolve itch, and improve quality of life. Dr Fishbein outlined how this can be achieved through stepwise management. Liberal and frequent use of moisturizers as well as daily lukewarm baths are important for patients with nonlesional or mild AD. Avoiding triggers or skin irritants, such as harsh soaps, specific clothing materials, or temperature extremes, can also alleviate symptoms. For patients with moderate disease, in addition to these basic management strategies, daily topical anti-inflammatory medications and maintenance with topical corticosteroids (TCS) or topical calcineurin inhibitors are recommended. Patients presenting with severe AD may require referral to a specialist, along with use of systemic immunosuppressants. When stepping up therapy, it is important to increase potency of TCS therapy and allow for adequate time to evaluate efficacy, usually over a 3-month period.

Dr Provine further discussed 2 recently approved and emerging biologic treatments for pediatric AD, dupilumab and upadacitinib. Whereas omalizumab is not currently approved for AD, it is approved in other indications and is under investigation for AD. Dupilumab is a monoclonal antibody that blocks interleukin-4 and -13 that is FDA approved in 2 formulations as a prefilled syringe for children 6 months and older and adults (as of June 2022) and as a prefilled pen for children 12 years and older as well as adults. Upadacitinib is an oral Janus kinase inhibitor that was approved in January 2022 for patients 12 years and older with refractory, moderate to severe AD with inadequate disease control despite use of other systemic drug products, including biologics.

To wrap up the discussion, Dr Provine shared important counseling points for patients and caregivers about general AD care. She emphasized the role of pharmacists in explaining regimens and reinforcing the liberal and frequent application of moisturizers and appropriate patient education for the newer agents used. In addition, pharmacists should explain how and when to use prescribed therapies to improve patient adherence as well as ask patients and caregivers to demonstrate the amount they are using. Worsening rash or intolerable adverse effects can be indicators that patients may need referral to an AD specialist, and pharmacist monitoring and involvement in care can significantly help improve quality of life for pediatric patients with AD.

“Pharmacists can be helpful partners with physicians in the recognition and management of pediatric atopic dermatitis and can provide patients and caregivers with comprehensive education about treatment plans and goals of therapies.”

—Allison Provine, PharmD, BCPS, BCPPS

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs
The activity is available through May 10, 2023.
John V. Bosso, MD, FAAAAI, FACAAI, FCPP; and Katharine Rimes, PharmD, BCACP, AAHIVP, CSP, delivered an informative presentation titled “The Role of Biologic Therapy for the Management of Chronic Rhinosinusitis With Nasal Polyps: Opportunities for Pharmacists” at the 2022 Asembia Specialty Pharmacy Summit. They detailed newly available treatments for chronic rhinosinusitis with nasal polyps (CRSwNP). This program featured a patient perspective interview, highlighting the experience of a patient who is also a health care worker receiving one of the newer treatments, dupilumab. She walked through her journey of challenges with receiving the diagnosis, followed by how helpful her health care team was in managing her CRSwNP and how significantly treatment has impacted her quality of life.

Dr Bosso began by describing the characteristics of CRSwNP, such as long-term facial pain, pressure, nasal obstruction or blockage, and nasal discharge. CRSwNP is often caused by an eosinophilic immune response, but can also be attributed to allergic fungal rhinosinusitis, aspirin-exacerbated respiratory disease, and central compartment atopic disease or environmental allergy. About 25% of patients with CRS present with nasal polyps and Dr Bosso reviewed the stages in their formation. Polyps are plentiful, noncancerous lesions that affect the lining of nasal sinuses and are generally formed due to epithelial breakdown. Importantly, 85% of patients with CRS also present with type 2 eosinophilic inflammation in which the epithelium breaks down and cytokines stimulate mast cells, ILC-2 cells to induce cytokines interleukin (IL)-4, IL-5, and IL-13, which are also involved in exacerbation of asthma symptoms.

The principles of management include reducing polyp size, providing symptomatic relief to improve quality of life, and preventing recurrence. However, adequately addressing symptoms of CRSwNP requires constant long-term management. Worrisome symptoms indicating more severe CRSwNP include ocular/neurologic symptoms, sepsis, bleeding, or severe headaches. Dr Bosso differentiated formulations of intranasal steroids, highlighting traditional nasal sprays do not deliver medication past the polyps and enhanced delivery system sprays are preferred as they penetrate medication deeper into the medial nasal cavity. In patients with CRS compounded by Staphylococcus aureus, both short-term and long-term treatment with antibiotic therapy can be used.

Dr Rimes then reviewed in more detail the pharmacologic properties of the currently FDA-approved biologics for CRSwNP, dupilumab (IL-4, IL-13), omalizumab (IgE), and mepolizumab (IL-5). Omalizumab requires weight-based dosing, whereas mepolizumab and dupilumab do not. Omalizumab and mepolizumab are available as either a vial for reconstitution or as a prefilled syringe requiring refrigeration. Dupilumab is available as a prefilled pen or syringe, and pharmacists should be aware of the different strengths, as just the 300-mg dose is currently approved for use in patients with CRSwNP. Benralizumab and reslizumab are currently under investigation for treatment of CRSwNP. Dr Rimes shared important counseling points for patients receiving omalizumab, mepolizumab, and dupilumab. Each medication has a black box warning for anaphylaxis, and in some instances this reaction can be delayed up to 4 days, so patients should be advised to seek immediate emergency care or keep access to epinephrine.

To conclude the session, Dr Rimes discussed the role of pharmacists in evaluating severity of patient symptoms, as this can be useful in determining efficacy of historical treatments as well as future treatment options for which the patient is eligible. Dr Rimes also touched on the role of specialty pharmacists in providing patients with options and support to access biologics approved for CRSwNP to optimize the care of these patients.

“Specialty pharmacies play a key role in access to care and helping patients navigate cost, and pharmacists in particular can provide counseling and education to prepare patients with CRSwNP to start biologic therapy if needed.”

— Katharine Rimes, PharmD, BCACP, AAHIVP, CSP

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs

The activity is available through May 18, 2023.
Pharmacists Can Help Little Patients Reduce Big Asthma Triggers With Biologics

Recent advancements in the biologic treatment landscape for moderate to severe pediatric asthma was a breath of fresh air for attendees at the 2022 Asembia Specialty Pharmacy Summit. In a panel discussion titled, “Effective Management of Moderate to Severe Pediatric Asthma: Applying Evidence-Based Case Reviews in Practice,” moderator Kelly Bridgers Short, PharmD, MBA, BCP-S, IgCP, led fellow panelists Carrie Gatzke, PharmD, CSP; and B. Louise Giles, MD, FRCPC, FAAP, through a discussion of recently updated indications of biologic therapies. Counseling videos detailing educational points pharmacists can provide to patients and caregivers of individuals with moderate to severe asthma were incorporated throughout the session.

The panelists discussed the clinical burden of moderate to severe asthma as well as signs and symptoms of severe asthma exacerbations in pediatric patients. Dr. Giles and Dr. Gatzke shared their experience in identifying patients with severe asthma exacerbations through cough, chest pain or tightness, and recurrent respiratory tract or viral infections leading to hospitalizations. Dr. Giles explained the importance of chronic airway inflammation and phenotypes in asthma diagnosis, especially atopic (Th2), genetic predisposition to immunoglobulin E (IgE) inflammation and the role of eosinophils in airway hyperresponsiveness.

Dr. Bridgers Short explained the significant health burdens and quality of life impact of severe asthma for pediatric patients, including missed school or inability to participate in activities with their peers. These patients utilize more doctors and have higher hospitalization rates. Pediatric indirect costs are higher than adult direct costs due to caregiver burden.

Current treatment recommendations for pediatric patients with moderate to severe asthma follow guidelines established by the Global Initiative for Asthma, and Dr. Gatzke reviewed the step-up process of selecting an initial treatment for individuals with asthma. Generally, treatment begins with an as-needed inhaled corticosteroid, with patients with severe disease escalating to higher doses as needed before considering the addition of biologic therapy. Pharmacists can have important roles in recognizing whether an individual is a candidate for therapy with biologics.

The panelists discussed approvals, outcomes, and administration considerations for dupilumab, mepolizumab, and omalizumab in the management of moderate to severe pediatric asthma. Dupilumab is indicated for treatment of eosinophilic phenotype asthma; it showed significant reduction in symptoms and improved lung function in the Liberty Asthma Voyage trial. After administration of a loading dose and training by a health care professional, maintenance doses of dupilumab can be self-administered. Mepolizumab is approved as add-on maintenance therapy and is administered as an injection every 4 weeks and its dosing is based on age. Omalizumab is approved for patients with uncontrolled symptoms despite inhaled corticosteroid therapy. Although there is limited evidence regarding its effect on improved lung function, evidence has shown decreased burden of asthma symptoms with use. Dr. Gatzke stressed that pharmacists should prioritize caregiver education on all available biologics because they will need to take an active role in ensuring proper injection of and adherence to biologics for pediatric patients.

Dr. Bridgers Short emphasized pharmacists should be actively engaged in the management plans of pediatric patients with asthma to establish effective asthma action plans and ensure patients are meeting treatment goals. The panelists agreed that simplifying communication, medication regimens, and explanations of how to use medications to accommodate patients and caregivers of all health literacy levels is of utmost importance. The panelists concluded the session with practical tips to overcoming caregiver hesitancy to administer injectable biologics and ensure adherence to therapy to optimize outcomes for pediatric patients with moderate to severe asthma.

“Pharmacists can play an important role in helping patients succeed on asthma therapies, especially through the active engagement of caregivers in the preparation and administration of biologics to pediatric patients.”

—Carrie Gatzke, PharmD, CSP

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs

The activity is available through May 10, 2023.
Pharmacists Can Improve Adherence in AMD and DME With Newer Agents

SEVERE VISION LOSS due to age-related macular degeneration (AMD) and diabetic macular edema (DME) can significantly impact quality of life for older patients. In a session at the 2022 Asembia Specialty Pharmacy Summit titled “Clinical and Practice Updates for Age-Related Macular Degeneration and Diabetic Macular Edema,” Joshua Mali, MD; and Alan Pannier, PharmD, MBA, discussed how pharmacists can make an impact in the management of therapies for patients with these conditions.

Dr Pannier explained that AMD is the leading cause of severe, irreversible vision impairment in the United States, with expected prevalence of 22 million by 2050. AMD can present as either dry or wet (neovascular); wet AMD is less prevalent but more severe and accounts for 90% of vision loss. It has been reported that 33% of individuals with diabetes will develop some form of diabetes-related eye damage or DME. Both conditions are characterized by growth of abnormal blood vessels causing edema, inflammation, and visual distortions that can progress rapidly.

The key in AMD and DME is maintaining vascular stability, and Dr Mali discussed the pathophysiology and angiopoietin (Ang)-2 and vascular endothelial growth factor (VEGF) pathways involved in disease. VEGF inhibitors are standard-of-care treatment options for both AMD and DME. These agents are administered as intravitreal injections, which present some complications, mainly the need for frequent in-office dosing. Dr Pannier outlined 2 newly approved treatments, faricimab, which is the first FDA-approved bispecific antibody for AMD that binds both VEGF-A and Ang-2, and the ranibizumab port delivery system, which is an ocular implant that provides 6 months of continuous release of ranibizumab. Additional agents still under investigation are OPT-302 and ONS-05010, which is an ophthalmic formulation of bevacizumab.

Dr Mali shared additional data for these treatment options and shared his clinical experiences with their use. He explained the goals of therapy with these treatments are to reverse vision loss and maintain visual acuity. However, the high injection burden with VEGF inhibitors contributes to high rates of discontinuation or nonadherence to treatment schedule, and it also conveys a significant burden for caregivers who need to take off work or spend time transporting patients to appointments. Dr Mali analyzed cost-effectiveness data for newly approved therapies for AMD and DME and reviewed real-world outcomes for the use of VEGF inhibitors, which have shown undertreatment among patients compared with protocols set in clinical trials.

The economic impact for AMD and DME is significant, with direct costs of outpatient services and prescription medications as well as indirect costs of lost productivity increasing the burden for patients, caregivers, and the health care system. Dr Pannier stated that pharmacists can be significant contributors to controlling costs for patients and the health care system. He emphasized that pharmacists can be essential in facilitating drug procurement through coordination of prior authorizations, step-therapy requirements, and pharmacy and medical benefits to ensure drug access for patients. The continued collaboration among pharmacists, retina specialists, and payers to assess dosing regimens in clinical practice and determine incentives and patient adherence will indicate drug preference and continue efforts to control cost of care for patients with AMD and DME.
CFTR Variants Are Essential in Determining Optimal Treatment of Patients With Cystic Fibrosis

IN A PRESENTATION at the 2022 Asembia Specialty Pharmacy Summit, Rebekah F. Brown, MD; and Alison G. Grisso, PharmD, BCPPS, reviewed the evolving landscape of cystic fibrosis (CF) care with recently approved CF transmembrane receptor (CFTR) modulators in a presentation titled “Integrating Best Practices and New Therapies in the Care of Cystic Fibrosis: The Role of Specialty and Managed Care Pharmacists.”

Dr Brown began the discussion by highlighting improvements in newborn screening rates across the United States, which have allowed approximately 70% of patients with CF to receive diagnosis earlier and have treatment initiated sooner. Dr Brown advocated for pharmacist involvement in newborn screening, as delayed diagnosis can negatively affect patient outcomes. Adult patients now outnumber children with CF, and this shift necessitates that pharmacists are familiar with approved therapies for all ages and are able to help patients navigate access to treatment. The presence of rarer CFTR mutations varies among individuals based on ethnicity and has led to disparities in the diagnosis and treatment of CF among minority groups.

Dr Brown reviewed treatments used for gastrointestinal (GI) and nutritional manifestations of CF as well as airway clearance devices and techniques before differentiating the classes of CFTR modulators. She defined correctors, which act on CFTR mutations that are not on cell surface or are abnormal, and potentiators, which act on CFTR mutations that are present on cell surfaces. Ivacaftor is a potentiator and a highly effective modulator therapy that is approved for individuals aged 4 months and older. The approval was based on data demonstrating decreased exacerbations requiring hospitalization, decreased use of antibiotics, and improved mucociliary clearance.

Correctors are used in combination with a potentiator and include lumacaftor/ivacaftor, tezacaftor/ivacaftor, and elegaftor/tezacaftor/ivacaftor (ETI). Lumacaftor/ivacaftor is approved for individuals aged 2 years and older; both tezacaftor/ivacaftor and ETI are approved for patients with CF aged 6 years and older. Lumacaftor/ivacaftor was approved in 2015 and has longer-term outcomes available in this patient population compared with the other CFTR modulator combinations. It has shown a decrease in rate of loss of lung function as well as in number of exacerbations by about one-third; however, up to 20% of patients discontinue therapy due to adverse effects (AEs). Tezacaftor/ivacaftor was approved in 2018 and has been associated with a lower risk of medication interactions compared with lumacaftor/ivacaftor. ETI was approved in 2019 as the first triple combination CFTR modulator, with data indicating fewer CF exacerbation visits and less antibiotic use among patients. Because of its significant impact on lung function and weight, it is considered a highly effective modulator therapy as well. As both tezacaftor/ivacaftor and ETI gained later approval, longer-term data for this population are not yet available.

Dr Grisso then discussed emerging CFTR modulators currently under investigation with the potential to reduce dosing frequency and limit AEs. She emphasized the importance of assessing CFTR modulator impact to reduce treatment burden for patients of all ages, but especially those with Medicare insurance, and reviewed an ongoing trial assessing use of ETI in pediatric patients aged 2 to 5 years.

Dr Grisso concluded the discussion by defining duties for CF pharmacists in providing education, conducting medication reviews, collaborating and advising on appropriate medication selection, monitoring for AEs and adherence, and directing formulary approvals. She highlighted clinical examples in which pharmacist-led interventions had direct benefits and improved outcomes for patients. Pharmacists can help address adherence by educating patients on the immediate effects of missing GI therapy or skipping airway clearance. Removing unnecessary barriers, such as step-therapy requirements, and being familiar with a patient’s CFTR mutation status and eligibility for therapies will be essential for pharmacists involved in the care of patients with CF in ensuring optimal use of medications.

“Specialty pharmacists are critical in mitigating treatment challenges for patients with CF because they have so much interaction not only with patients but also with medications.”
—Alison G. Grisso, PharmD, BCPPS

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs
The activity is available through May 10, 2023.
Approximately 60% of patients aged older than 65 years at the time of diagnosis with acute myeloid leukemia (AML). Not only does this group have a greater likelihood of poor tolerance to intensive therapy, they are also more likely to present with an adverse disease risk profile and less likely to receive treatment. In a presentation packed with clinical pearls, 2 experts provided solutions to overcome treatment challenges at the 2022 Asembia Specialty Pharmacy Summit in a presentation titled “Exploring Induction and Maintenance Regimens for Older Patients With AML.”

Anthony J. Perissinotti, PharmD, BCOP, explained that antileukemic therapy is recommended over supportive care for older adults with newly diagnosed AML who are candidates for such therapy. He illustrated National Comprehensive Cancer Network guideline recommendations for patients who are not eligible for intensive therapy include the following options: venetoclax plus a hypomethylating agent (HMA) or low-dose cytarabine; glasdegib plus low-dose cytarabine; gemtuzumab ozogamicin; ivosidenib in patients with an IDH1 mutation; enasidenib in patients with an IDH2 mutation; and an HMA combined with venetoclax or an FLT3 inhibitor in patients with an FLT3 mutation. The data for these regimens continue to be updated and nuances for individual patients should be considered for older adults who achieve remission after intensive antileukemic therapy and who are not candidates for stem cell transplantation. Dr Perissinotti explained that post-remission consolidation is recommended with the same regimens used for induction in patients ineligible for intensive therapy. Finally, he noted that maintenance therapy with a hypomethylating agent may improve overall survival. Oral azacitidine is the only agent currently approved for this indication. Videos of an interview with a patient receiving maintenance therapy for her AML were shared to offer a perspective of her treatment journey and challenges.

Megan Rees, PharmD, BCACP, CSP, shifted the focus to patient-specific challenges for older patients with AML, including:

- Functional status

“Although considered low-intensity therapy, toxicities still pose a challenge in older patients with AML.”

—Anthony J. Perissinotti, PharmD, BCOP

- Psychosocial issues
- Patients’ goals of care
- Cognitive performance
- Polypharmacy
- Caregiver availability
- Social support dynamics
- Patient frailty
- Financial well-being

Dr Rees explained that ideally at the pretreatment evaluation, providers discern which older adults are fit (ie, will tolerate and benefit from treatment in a similar fashion to a middle-aged person), versus vulnerable (ie, at risk for clinical or functional decline during or after treatment that may mitigate some of the treatment benefit) versus frail (ie, will have significant increased complications related to therapy). She suggested providers make use of tools to assess patient fitness including the Charlson comorbidity index, hematopoietic cell transplantation-specific comorbidity index, and/or Comprehensive Geriatric Assessment.

In the final portion of the presentation, Dr Rees illustrated the economic burden of caring for older patients with AML. She suggested use of clinical pathways to reduce costs while maintaining or improving quality of care. Lastly, Dr Rees highlighted the role of specialty pharmacists in management of older adults with AML, including:

- Streamlining transitions of care
- Alleviating barriers to medication access
- Medication optimization
- Multidisciplinary care involvement
- Adverse effect management
- Supporting palliative care
- Monitoring and facilitating adherence

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-assemblea-on-demand-programs. The activity is available through May 10, 2023.
Innovations in the Treatment of Immune Thrombocytopenia

 Destruction of platelets resulting in bleeding poses a significant burden to patients with immune thrombocytopenia (ITP) and negatively affects quality of life. Experts in adult and pediatric oncology teamed up to share the best practices in ITP at the 2022 Asembia Specialty Pharmacy Summit in a presentation titled “Immune Thrombocytopenia: The Role of Current and Emerging Therapies and Navigating Patient Care Opportunities for Pharmacists.”

Before delving into the clinical guidelines from the American Society of Hematology and International Consensus Report, Alexis Kuhn, PharmD, BCOP, emphasized that while the primary clinical manifestations of ITP (bleeding, ecchymoses, petechiae, and wet purpura) are related to thrombocytopenia, the primary nonhematologic symptom is fatigue. Definitions of ITP are based on the duration of low platelets and include newly diagnosed ITP, persistent ITP, and chronic ITP. Throughout the presentation, Dr Kuhn illustrated key differences between children and adults. She explained children typically have a duration of ITP less than 3 months; however, 70% of adults with ITP develop chronic ITP.

Dr Kuhn highlighted the role of thrombopoietin receptor agonists (TPO-RAs), rituximab, and fostamatinib in the management of adults with persistent/chronic ITP and stressed the importance of individualizing treatment to a patient’s needs and goals. Dr Kuhn wrapped up by reviewing clinical trial data for the 3 TPO-RAs (avatrombopag, eltrombopag, and romiplostim), rituximab, and fostamatinib.

In his portion of the presentation, Christopher Elder, PharmD, BCOP, narrowed in on the role of the pharmacist in supporting patients with ITP. He explained pharmacists play an essential role in the care of patients with ITP by:

- Recommending drug therapy selection
- Providing patient education
- Preventing and managing adverse effects
- Monitoring response and adjusting medication doses
- Supporting patient access

Dr Elder illustrated multiple differences in pharmacotherapy options for ITP based on dosing schedule, route of administration, adverse effect profile, monitoring guidelines, and predisposition for drug-drug interactions. He summarized the risk-to-benefit profile of options for chronic ITP before providing perspectives on appropriate therapies based on patient-specific treatment goals. Pharmacists should be aware of sequencing opportunities in treatment of ITP based on duration of ITP and response, as well as adverse effects with prior therapy. Dr Elder also touched on pharmacoeconomic studies of TPO-RAs highlighting approximately 17.5 life-years gained and lower costs per response compared with watch-and-rescue. He wrapped up the presentation with a treatment algorithm for persistent and chronic ITP, and summarized when to use a medication, and recommendations for monitoring and patient counseling.

“Pharmacists can play an integral role in the selection and monitoring of treatments for persistent and chronic ITP. They should consider patient-specific factors when evaluating recommended therapies, including the TPO-RAs avatrombopag, eltrombopag, and romiplostim, and rituximab for persistent ITP, as well as these and fostamatinib for chronic ITP.”

—Christopher Elder, PharmD, BCOP

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs

The activity is available through June 1, 2023.
Optimizing Ovarian Cancer Treatment

Two expert pharmacists reviewed the value of poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) in the treatment of ovarian cancer in a presentation titled “Evaluating the Utility of PARP Inhibitors in the Treatment of Ovarian Cancer” at the 2022 Asembia Specialty Pharmacy Summit.

Rachel Justus, PharmD, BCPS, BCOP, dove right into the National Comprehensive Cancer Network and American Society of Clinical Oncology guidelines for ovarian cancer, explaining niraparib is recommended as first-line maintenance therapy for platinum-sensitive patients regardless of BRCA or homologous repair deficiency (HRD) mutation status. In contrast, olaparib is recommended in patients with BRCA1 or BRCA2 mutations or HRD as first-line maintenance therapy; if patients received bevacizumab with initial chemotherapy, olaparib with bevacizumab may be used as first-line maintenance therapy. Patients who did not receive a PARPi as first-line maintenance may receive it as second-line maintenance regardless of mutational status, provided they achieve a complete or partial response to platinum chemotherapy. Dr Justus explained PARPi are recommended for patients with recurrent ovarian cancer with BRCA1 or BRCA2 mutations or HRD after 2 or 3 previous lines of therapy if patients are platinum sensitive and PARPi naïve.

Dr Justus highlighted key similarities and differences in pharmacology of the 3 PARPi (niraparib, olaparib, and rucaparib) FDA approved in ovarian cancer. She provided tips for management of drug class effects including gastrointestinal toxicity, nausea/vomiting, fatigue, and myelosuppression. She differentiated unique adverse effects with each agent, including hypertension with niraparib, pneumonitis with olaparib, and elevations in cholesterol and liver function tests with rucaparib. Wrapping up, Dr Justus reviewed the role of pharmacists in caring for patients with ovarian cancer, including:

- Therapy selection
- Patient education and consent
- Assessment of treatment plan
- Patient monitoring
- Drug interaction management
- Adherence assessment
- Provision of supportive care
- Health care team resource
- Management of financial toxicity

In her portion of the presentation, Megan Rees, PharmD, BCACP, CSP, focused on challenges to access and specialty pharmacy considerations for PARPi. She touched on disparities present in women experiencing financial toxicity during treatment for ovarian cancer, including age younger than 30 years, widowed/single/divorced, self-pay, and Hispanic or African American race. She emphasized that reducing disparities in ovarian cancer screening and treatment may aid in reducing overall mortality rates. Dr Rees highlighted approximately one-fourth of women are nonadherent to PARPi. She reviewed patient-specific, treatment-related, and system factors that impact medication adherence in women with ovarian cancer. She encouraged specialty pharmacies to work to improve access to care, mitigate financial toxicity, educate patients on therapy, and employ frequent touch points. Dr Rees underscored the effectiveness, toxicity, cost, and biomarker considerations must be balanced at the individual patient level to determine the right PARPi for the right patient at the right time.

“One in 4 females with ovarian cancer experiences financial toxicity and the combination of increasing drug prices and increased cost sharing makes patients more vulnerable to medication nonadherence.”

—Megan Rees, PharmD, BCACP, CSP

“The pharmacists’ role in adherence is key considering the role of maintenance therapy for ovarian cancer.”

—Rachel Justus, PharmD, BCPS, BCOP

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs

The activity is available through May 10, 2023.
Biomarkers Drive Therapy in Advanced Endometrial Cancer

Currently, immune checkpoint inhibitors and targeted therapies are employed in patients with advanced, recurrent endometrial cancer; however, ongoing phase 2 and 3 clinical trials have the potential to change that. A pair of excellent speakers discussed the current state and potential future role of biomarker-directed therapy in endometrial cancer at the 2022 Asembia Specialty Pharmacy Summit in a presentation titled “Exploring the Role of Novel Immunotherapy in the Treatment of Endometrial Cancers.”

Megan May, PharmD, BCOP, began with the basics and moved quickly to biomarkers used to guide therapy in endometrial cancer, including microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR); tumor mutational burden-high (TMB-H); polymerase epsilon (POLE)-mutated; neurotrophic tyrosine receptor kinase (NTRK) gene fusion; and human epidermal growth factor receptor 2 (HER2). She noted that biomarkers only play a role in first-line treatment for patients who are HER2-positive, where trastuzumab is added to carboplatin and paclitaxel. In contrast, emphasized Dr May, biomarkers guide therapy for second-line treatment. She outlined treatment recommendations for biomarker-directed systemic therapy in patients with recurrent endometrial cancer based on the National Comprehensive Cancer Network guidelines, including:

- Lenvatinib plus pembrolizumab (non-MSI-H/non-dMMR)
- Pembrolizumab (TMB-H or MSI-H/dMMR)
- Nivolumab (MSI-H/dMMR)
- Dostarlimab-gxly (MSI-H/dMMR)
- Avelumab (MSI-H/dMMR)
- Larotrectinib or entrectinib (NTRK+)
- Cabozantinib

After reviewing efficacy data for treatment recommendations in metastatic or recurrent endometrial cancer, Dr May shared guideline recommendations and clinical pearls for management of immune-related adverse events (irAEs). She emphasized that prompt identification and management of irAEs can minimize the impact on patient experience and mortality.

Laura R. Bobolts, PharmD, BCOP, went right to the heart of the matter about cancer disparities that affect women with endometrial cancer. Dr Bobolts emphasized managed care pharmacists play a key role in reducing health disparities in efforts to provide equitable, cost-effective, and high-quality care for patients with endometrial cancer. She encouraged pharmacists to engage in solutions to combat disparities in endometrial cancer by:

- Ensuring appropriate genetic testing
- Encouraging self-reporting of race and ethnicity
- Ensuring availability of culturally and linguistically appropriate services (CLAS)
- Conducting disparities research
- Educating on CLAS policies and practices
- Playing an active role in health policy and advocacy
- Ensuring continuity of care
- Referring patients to community health programs

Dr Bobolts suggested managed care pharmacists optimize endometrial cancer care by adopting evidence-based medicine guidelines and treatment selection guided by biomarker testing. She noted strategies to support cost-effective, high-quality care may include selection of a preferred PD-1/PD-L1 inhibitor, prior authorization, and toxicity management. Dr Bobolts offered patient education, patient outreach between clinic visits, digital health tools, rapid diagnosis and treatment, and leveraging real-world evidence as tools to more effectively manage toxicity in patients with endometrial cancer.

“The most important step in patients with advanced or recurrent endometrial cancer is molecular profiling, because 67% to 91% of patients have at least 1 therapeutically actionable genomic alteration.”

—Megan May, PharmD, BCOP

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs
The activity is available through May 10, 2023.
A Recently Approved Medication Offers a New Option for the Treatment of Hypertrophic Cardiomyopathy

The recent FDA approval of mavacamten was of particular interest to attendees at the 2022 Asembia Specialty Pharmacy Summit session titled, “Tackling the Unmet Needs in the Treatment of Hypertrophic Cardiomyopathy With Novel Targeted Therapies: A Review for Pharmacists.” In this presentation, Ty J. Gluckman, MD, MHA, FACC, FAHA; and John Lindsley, PharmD, BCPS, BCCCP, discussed the impact this new medication will have on the evolving role of pharmacists in the treatment and management of hypertrophic cardiomyopathy (HCM).

Dr Gluckman began by defining HCM as an inherited cardiovascular disorder characterized, in part, by abnormal cardiac muscle thickening. Consistent with current recommendations, genetic testing is recommended, with additional screening of asymptomatic family members. Beyond an increased risk for sudden cardiac death, patients with HCM often have limited physical functioning, which can be detrimental to their quality of life and mental health.

The main challenge Dr Gluckman identified with HCM is that, until recently, there were no current preventive or disease-modifying therapies available. In 2020, the American College of Cardiology and American Heart Association published updated guidelines on the management of HCM and recommended guideline-directed medical therapy to achieve treatment goals and provide symptomatic relief for patients. Dr Gluckman described lifestyle considerations and medications to avoid in this population before transitioning the discussion to Dr Lindsley for specific considerations about pharmacologic therapies.

Dr Lindsley led participants in a discussion about the current therapeutic options for HCM. β-blockers have been considered first-line therapy, with efficacy measured by symptom control. Non-dihydropyridine calcium channel blockers (CCBs) are considered second-line therapy; because of some vasodilating properties, however, they are less desirable in patients with a severe gradient and generally are not recommended for use in addition to β-blockers in the absence of hypertension. Disopyramide is an antiarrhythmic that traditionally has been recommended for patients with severe symptoms despite use of β-blockers and/or CCBs.

The FDA approval of mavacamten, a first-in-class cardiac myosin inhibitor, for obstructive HCM was announced just days before this program on April 28, 2022, and Dr Gluckman provided a timely review of key trial data underlying this. Improvement in functional status and symptoms from obstruction were observed in the phase 3 EXPLORER-HCM trial. He also highlighted results from the VALOR-HCM trial and made note of the MAVA-LTE trial, an ongoing 5-year extension study to assess outcomes of patients with HCM treated with mavacamten.

Another agent under investigation is aficamten, which has a shorter half-life than mavacamten. The phase 3 SEQUOIA-HCM trial is currently underway, assessing the potential of aficamten to improve symptoms and functional status in patients with HCM. Finally, Dr Gluckman highlighted other options with potential benefit, including gene therapy.

Dr Lindsley emphasized the importance of detailing treatment expectations and monitoring therapies for patients with HCM, especially in light of the recent approval of mavacamten. He discussed the requirements of the mavacamten REMS program, including the importance of screening for drug interactions and the patient’s needs for frequent echocardiograms. Dr Lindsley concluded the presentation with tactics for pharmacists to assist in determining the optimal place in therapy for mavacamten. By sharing drug information with both clinicians and patients, assessing costs, and establishing eligibility criteria for patients, the pharmacist’s role in the treatment and management of HCM will continue to grow.

“The recent approval of mavacamten is an important step in addressing unmet needs in the treatment of hypertrophic cardiomyopathy, and pharmacists will be essential in counseling patients and ensuring their access to this new agent.”

—John Lindsley, PharmD, BCPS, BCCCP

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs

The activity is available through May 10, 2023.
The Significance of S1P Receptor Modulators in the Treatment of Ulcerative Colitis

In a session at the 2022 Asembia Specialty Pharmacy Summit titled “Exploring the Promising Role of Sphingosine-1-Phosphate Receptor Modulators for the Treatment of Ulcerative Colitis: A Review for Specialty Pharmacists,” moderator Patty Taddei-Allen, PharmD, MBA, BCACP, BCGP, led fellow panelists Lopa Joshi, PharmD; and Joel Pekow, MD, in a discussion about the use of these agents in ulcerative colitis (UC). Throughout the discussion, panelists reviewed informative counseling videos providing examples of interactions specialty pharmacists may have with patients with UC regarding key education for the S1P receptor modulators.

Dr Taddei-Allen established the burden of UC, explaining that it is a continuous inflammation of the colon whereas Crohn disease (CD) can affect anywhere in the intestines. As the exact etiology of UC is unknown, Dr Joshi listed some contributing factors, including genetics, age, overactive immune system, ethnicity, and the potential for environmental factors such as processed foods. Dr Pekow built on the connection between pathophysiology of UC and the need for therapies to protect epithelial cell barrier to block the inflammatory responses in the intestines.

There is a significant financial burden for patients with UC as well, and Dr Taddei-Allen explained this population incurs approximately 3 times the annual costs as healthy patients. The panelists were all in agreement that proper management plans that incorporate specialty pharmacists can be key to reducing costs and promoting access to affordable treatments. Pharmacists can also help overcome challenges associated with delayed diagnosis by being informed of the symptoms of UC, which can include urgency, blood in the stool, or diarrhea; if left uncontrolled, these symptoms can negatively impact patient quality of life and increase cost of care. Dr Pekow emphasized the importance of defining treatment goals, regularly assessing the patient’s response to treatment, and the concept of “treat-to-target” of predefined goals, such as clinical remission or mucosal healing. Therapy decisions can then be adjusted or changed through discussion with clinicians and the patient, based on these parameters.

Dr Joshi then explained guideline-recommended medications for the treatment and management of UC. Pharmacists should be familiar with limitations and challenges of some medications, such as aminosalicylic acids, which are inappropriate for severe disease, or the delayed onset of action associated with corticosteroids and immunomodulators. Compared with immunomodulators, Janus kinase inhibitors have a faster onset of action but are associated with increased risk of infection. Biologics and anti-tumor necrosis factor agents are becoming first-line therapy, but previous exposure may indicate decreased response and some responders may also lose efficacy with longer treatment durations. Dr Pekow also cautioned that the heterogeneity of UC makes it difficult to predict how patients will respond to therapy, and concerns over clinical inertia with corticosteroids or current biologic therapies are why availability of new treatments, such as the sphingosine-1-phosphate (S1P) receptor modulators, are significant for this patient population.

Ozanimod was the first S1P receptor modulator to be approved for UC in the United States. Dr Joshi reviewed important patient counseling points, such as its oral dosing regimen and the importance of adhering to dose titration over the first 14 days of therapy, as well as the management of the minimal adverse effects due to its selectivity. Another highly selective S1P receptor modulator, etrasimod, is also currently under investigation for treatment of UC.

To conclude the discussion, the panelists shared recommendations for promoting patient adherence, such as setting reminders on a smartphone or physically marking a calendar. Additionally, cost, limited health literacy, or other challenges may prevent patients from being adherent to their medication regimens, and specialty pharmacists are well positioned to identify and help address these barriers.

“Specialty pharmacists can facilitate discussion with prescribers and should include patients’ input about their preferences when deciding which therapy to initiate for the treatment and management of ulcerative colitis.”

—Patty Taddei-Allen, PharmD, MBA, BCACP, BCGP

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs

The activity is available through May 10, 2023.
Oral Therapies Lay Foundation for the Management of CLL

Intravenous chemoimmunotherapy has been replaced by novel oral therapies in the management of chronic lymphocytic leukemia (CLL). Recent data show the 5-year overall survival for patients with CLL is almost 90%. Two expert pharmacists shared their perspectives on efficacy and toxicity of oral therapies in a presentation titled “Exploring Oral Therapies for the Treatment of Chronic Lymphocytic Leukemia: Adverse Effect Management Strategies for Specialty Pharmacists” at the 2022 Asembia Specialty Pharmacy Summit. Videos from an interview with a patient receiving treatment for CLL highlighted specific patient-focused challenges.

Kirollos S. Hanna, PharmD, BCPS, BCOP, reviewed the basics of CLL epidemiology, clinical presentation, staging, and prognostic risk assessment before delving into the clinical trial data for oral therapies. Dr Hanna presented the treatment pathway for first-line therapy of CLL based on the National Comprehensive Cancer Network guidelines. He emphasized preferred regimens for patients with or without del(17p)/TP53 mutation include acalabrutinib with or without obinutuzumab; ibrutinib; venetoclax plus obinutuzumab; and zanubrutinib. Dr Hanna illustrated the 2-year progression-free survival is approximately 90% among these options. He suggested weighing different factors when selecting therapies such as the need for indefinite therapy with BTK inhibitor monotherapy versus a fixed duration of therapy with venetoclax plus obinutuzumab; however, the latter regimen requires both intravenous and oral therapies. Other factors to consider include the potential for drug-drug interactions, nuances in the toxicity profiles, and data to support use of an alternative agent at progression.

“Myriad oral therapies have revolutionized the treatment of B-cell malignancies. The future is bright with exploration of finite treatments and use of combination therapies.” —Kirollos S. Hanna, PharmD, BCPS, BCOP

“Ibrutinib management by clinical pharmacists resulted in significant improvement in PFS and better tolerance than usual care. Every patient should have a pharmacist involved with their care.” —Jeff Reichard, PharmD, MS, BCOP

Dr Hanna explained that regimens recommended for second-line and subsequent therapy are very similar to first-line options, with the substitution of rituximab for obinutuzumab in combination with venetoclax, and the recommendation for acalabrutinib as monotherapy. The incidence of key toxicities varies among the oral therapies, illustrated Dr Hanna, but in general, toxicities to monitor include atrial fibrillation, hypertension, bleeding, tumor lysis syndrome, thrombocytopenia, and neutropenia.

Jeff Reichard, PharmD, MS, BCOP, brought to light key pillars in medication management patients benefit from while receiving oral therapies via a specialty pharmacy. He emphasized standardization of medication education with a focus on adherence and how to manage adverse effects. Dr Reichard highlighted a consistent process for monitoring laboratory values and completing medication reconciliation and adherence assessments. He explained that prescriptions are refilled after review of applicable labs and patient-reported outcomes. In addition, the value of the medication assistance team to perform timely benefits investigation, prior authorization, denial support, and secure co-pay assistance cannot be understated, emphasized Dr Reichard.

He underscored that while oral therapies for CLL may intuitively seem less toxic than intravenous chemoimmunotherapy, the adverse effects of oral therapies do impact outcomes. He highlighted the discontinuation rate with oral therapies ranges from 16% with venetoclax to 41% with ibrutinib. He shared tips for monitoring and managing adverse effects of oral therapies for CLL before wrapping up with examples of how to incorporate patient-reported outcomes into the electronic health record.

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs
The activity is available through May 10, 2023.
Pharmacists Are Integral to the Mindful Management of Patients With Alzheimer Disease

Pharmacists can promote awareness of Alzheimer disease (AD) and are well-positioned to recognize its early warning signs. During a session at the 2022 Asembia Specialty Pharmacy Summit titled “Novel Treatment Approaches for Alzheimer Disease: Considerations for Pharmacists Across Care Settings,” Mindy Roselli, PharmD, BCGP, CSP; and Gary Small, MD, discussed the advantages of early treatment interventions and emerging therapies for AD.

Dr Small explained that as the population of the United States ages, the prevalence of dementia and individuals with cognitive impairment will continue to increase. Alzheimer dementia is severe cognitive impairment that affects daily life and differs from normal cognitive decline associated with aging when individuals are able to maintain functional independence.

Dr Small then listed biomarkers used to track cognitive decline. Accumulation of amyloid plaques and deposits in the brain causing inflammation can begin 10 to 20 years before symptoms appear. Apolipoprotein E-4 (APOE-4) is a genetic risk for developing AD and has been identified in up to 40% of patients with AD. He reviewed additional risk factors associated with accelerated cognitive decline as well as approaches to maintain cognition in older adults. He stressed that early intervention is key to slow cognitive decline for patients as decreased cognition negatively affects patient quality of life, caregiver burden, and financial burden. Most direct costs of care in AD are attributed to care facilities for patients with severe cognitive impairment and indirect costs associated with caregivers’ lost productivity or inability to work.

Earlier diagnosis and treatment interventions can prepare caregivers and patients to plan for the future and implement better management strategies. However, Dr Small listed key barriers related to stigma of age-related cognitive decline, the uncertainty that surrounds diagnostic measures in AD, and lingering reluctance among clinicians to initiate therapy as current treatment strategies are associated with temporary benefits and high discontinuation rates. Current therapeutic options include anticholinesterase inhibitors, such as memantine, but Dr Small emphasized a need for new intervention strategies and disease-modifying therapies (DMTs) with additional indications for patients with different stages of AD.

The landscape of AD recently grew with the approval of aducanumab, an immunoglobulin (Ig) G1 monoclonal antibody, which showed reduction in amyloid plaques in AD. Dr Roselli listed other DMTs and treatments under investigation. She reviewed available clinical data for emerging IgG1 antibodies, including donanemab, gantenerumab, lecanemab, and solanezumab, which target amyloid accumulation. Ongoing clinical trials of interest focusing on small-molecule DMTs that target neuroinflammation include valitramiprosate, a cromolyn and ibuprofen combination (ALZT-OP1), and the oral tyrosine kinase inhibitor masitinib; TRx0237 (LMTM) is under investigation as a potential DMT targeting Tau protein.

Dr Roselli ended the session with a recap of the pharmacist’s role in AD treatment. They can be the first line of defense in identifying drug-disease and drug-drug interactions, as patients with AD are at high risk of polypharmacy that could exacerbate cognitive decline. Dr Roselli concluded the presentation with some tips for managed care pharmacists to participate in decreasing the cost burden of AD. She outlined specific strategies to improve medication compliance such as addressing forgetfulness by simplifying medication information that is explained to patients and caregivers as well as promoting utilization of medication alerts, pillboxes, or automatic refills.

“Pharmacists have a responsibility to improve health care outcomes for patients with AD and can do so by helping overcome adherence barriers and using clear and concise language to explain the need for therapy adherence.”

—Mindy Roselli, PharmD, BCGP, CSP

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs. The activity is available through May 16, 2023.
BCMA Brings Hope for Patients With Relapsed/Refractory Multiple Myeloma

At the 2022 Asembia Specialty Pharmacy Summit, 2 expert pharmacists and a patient provided perspectives on management of multiple myeloma (MM) in a presentation titled “Unprecedented Advances in Treating Multiple Myeloma With BCMA-Targeted Agents, Featuring a Patient Perspective.”

Sara Moran Smith, PharmD, BCOP, began by providing insight into clinical presentation, pathophysiology, and treatment of MM. She emphasized that MM is incurable and the disease course is characterized by periods of remission and relapse, with progressively shorter periods of remission as the disease progresses. She explained that overall survival (OS) correlates with the number of drug classes the patients’ disease is refractory to. Patients with triple-class refractory (TCR) MM have a median OS of 9.2 months and those with penta-class refractory MM have a median OS of 5.6 months. Dr. Smith then reviewed the role of B-cell maturation antigen (BCMA) in pathophysiology of MM and explained correlations between soluble BCMA levels and disease burden, response to therapy, and clinical outcomes. She provided an in-depth review of the 3 types of therapies targeting BCMA in MM: antibody-drug conjugate (belantamab mafodotin); chimeric antigen receptor (CAR) T-cell therapy (cilta-cabtagene autoleucel and idecabtagene vicleucel), and bispecific antibody investigational agents including teclistamab, elranatamab, CC-93269, and REGN5458.

Dr. Smith contrasted the adverse effect (AE) profile of the different BCMA-directed therapies, underscoring that the AE profile correlates with the mechanism of action rather than the BCMA target. She explained that key toxicities associated with belantamab mafodotin include infusion-related reactions, thrombocytopenia, and keratopathy and how to manage them. She noted BCMA-directed CAR T-cell therapies may cause cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) in addition to myelosuppression and infection. Lastly, she indicated that BCMA-directed bispecific antibodies may cause CRS and ICANS, though the incidence and severity of these AEs are under investigation. Both BCMA-directed CAR T-cell therapies and belantamab mafodotin have a Risk Evaluation and Management Strategy in place because of the risk for AEs.

The presentation incorporated video clips of an interview with a patient with multiple myeloma receiving BCMA-targeted therapy. The patient highlighted his challenges throughout his treatment journey and shared how grateful he was for the health care professionals who played a tremendous role to help improve his experience over the past few years.

In the second half of the presentation, Scott A. Soefje, PharmD, MBA, BCOP, FCCP, FHOPA, illustrated the cost of caring for patients with MM from multiple angles including phase of care, patients with disease that is responding or progressive, and for patients with or without stem cell transplant as part of their care plan. He presented quality-adjusted life-year (QALY) data for BCMA-directed CAR T-cell therapy and belantamab mafodotin, indicating the cost for CAR T-cell therapy would need to be lowered to meet commonly accepted QALY-based thresholds of less than $150,000 per QALY.

In the final portion of the presentation, Dr. Soefje offered potential solutions to provide cost-effective treatment of MM including the appropriate sequencing of MM therapies to maximize the overall outcomes of the patients, moving patients to lower cost sites of care, such as inpatient to outpatient treatments, whenever possible, and appropriately managing the AEs associated with these treatments.

“BCMA-targeting agents have led to significant improvements in outcomes for patients with refractory MM.”

—Sara Moran Smith, PharmD, BCOP

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs
The activity is available through May 10, 2023.
IN THE PAST DECADE, novel hormonal agents have moved from initiation in patients with metastatic, castration-resistant prostate cancer (CRPC) to use in patients with newly diagnosed, nonmetastatic or metastatic, castration-sensitive prostate cancer (CSPC). Two pharmacists teamed up with a social worker at the 2022 Asembia Specialty Pharmacy Summit to provide “A Primer for Specialty Pharmacists on Optimal Use of Anti-Androgen Therapies in Prostate Cancer.” Sherry L. Mori Vogt, PharmD, BCOP, illustrated the shift in therapy in prostate cancer followed by the data to back it up as outlined in the table below.

<table>
<thead>
<tr>
<th>Non-metastatic (M0)</th>
<th>CSPC</th>
<th>CRPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who: Localized disease</td>
<td>Treatment:</td>
<td>Treatment (PSADT &lt;10 months; continue ADT):</td>
</tr>
<tr>
<td>Localized disease</td>
<td>Surveillance</td>
<td>Apalutamide</td>
</tr>
<tr>
<td>Prostatectomy</td>
<td>EBR/ADT/abiraterone</td>
<td>Enzalutamide</td>
</tr>
<tr>
<td>EBRT/ADT/abiraterone</td>
<td>Enzalutamide</td>
<td>Darolutamide</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metastatic (M1)*</th>
<th>CSPC</th>
<th>CRPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who: “de novo” M1 disease, or develop M1 disease</td>
<td>Treatment:</td>
<td>Treatment (continue ADT):</td>
</tr>
<tr>
<td>Localized disease</td>
<td>ADT + “early” intervention</td>
<td>Enzalutamide</td>
</tr>
<tr>
<td>Prostatectomy</td>
<td>Docetaxel + abiraterone/ darolutamide</td>
<td>Abiraterone</td>
</tr>
<tr>
<td>EBRT/ADT/abiraterone</td>
<td>Abiraterone</td>
<td>Docetaxel</td>
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<tr>
<td>Enzalutamide</td>
<td>Enzalutamide</td>
<td>Cabazitaxel</td>
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<tr>
<td>Apalutamide</td>
<td>Apalutamide</td>
<td>Radium-223</td>
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</tbody>
</table>

ADT, androgen deprivation therapy; EBRT, external beam radiation therapy; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.

ADT does not include all potential treatment options. It focuses on the oral anti-androgens/abiraterone.

In the second portion of the presentation, Veronica Ajewole, PharmD, BCOP, highlighted bone health in men with prostate cancer. ADT increases the risk for osteoporosis and is associated with a 21% to 54% increase in fracture risk. She explained all men should receive screening and treatment based on normal population guidelines; bisphosphonates and denosumab may be indicated based on bone mineral density test results. Dr Ajewole emphasized patients with patients with CRPC and bone metastases should receive zoledronic acid or denosumab to prevent skeletal-related events.

Dr Ajewole summarized rates of drug therapy interruption, discontinuation, and nonadherence in patients with prostate cancer, noting that in most studies, nonadherence rates are less than 7%; however, in real life, these numbers may be much higher. She emphasized the need to support patients to ensure medication adherence and optimize treatment efficacy while minimizing disease progression, emergency department visits and hospitalization, medication waste, and financial burden.

Dr Ajewole reviewed specialty pharmacists’ roles in patient monitoring, promoting adherence, and mitigating toxicities in patients with prostate cancer. She emphasized a need for cultural sensitivity, having a proactive approach, prioritizing high-risk populations, and providing practical, patient-oriented measures. She shed light on a few of the disparities observed in prostate cancer including a mortality rate in Black patients more than double that of White patients. Dr Ajewole offered tools to combat disparities in prostate cancer care including communication, cultural sensitivity, support system, health literacy, clinical trial discussion, advocacy, and policy.

“Pharmacists are the most accessible health care providers and are uniquely positioned to address complexity of oral chemotherapy treatment and health disparities in prostate cancer.”

— Veronica Ajewole, PharmD, BCOP

“In the past decade, novel hormonal agents have moved from initiation in patients with metastatic, castration-resistant prostate cancer (CRPC) to use in patients with newly diagnosed, nonmetastatic or metastatic, castration-sensitive prostate cancer (CSPC).”

— Sherry L. Mori Vogt, PharmD, BCOP

Specialty Pharmacists Can Promote Safe Use of CTEPH Therapies

“Each patient presenting with CTEPH is unique, and it is the pharmacist’s responsibility to equip patients with the ideal medical therapy to help them succeed in their care journey.”

—Christopher Ogurchak, PharmD, MPBA, CSP

Specialty pharmacists are ingrained in the management of therapies for patients with chronic thromboembolic pulmonary hypertension (CTEPH). Dustin Fraidenburg, MD; and Christopher Ogurchak, PharmD, MPBA, CSP, reviewed the available and emerging therapies for CTEPH in a presentation titled, “The Evolving Treatment Landscape for Chronic Thromboembolic Pulmonary Hypertension (CTEPH): A Review for Specialty Pharmacists” at the 2022 Asembia Specialty Pharmacy Summit.

Dr Fraidenburg explained the complications of pulmonary embolism and the importance of pharmacist engagement in the timely resolution of thrombosis to prevent progression to CTEPH. He emphasized appropriate classification of patients into 1 of 5 pulmonary hypertension (PH) groups, in which group 4 consists primarily of patients with CTEPH that is classified by obstruction of pulmonary arteries and arteriopathy. A targeted screening approach is used to identify signs and symptoms of CTEPH, but other risk factors for CTEPH include age older than 60 years, presence of long-term or recurrent symptoms, and insufficient anticoagulation.

Treatment algorithms and practice guidelines for CTEPH have been developed to guide choice of therapy. Treatment decisions also hinge on whether the patient’s disease is operable or nonoperable. In patients with nonoperable CTEPH, pharmacologic therapy is then considered. Dr Fraidenburg discussed the need for lifelong anticoagulation to reduce risk of thrombosis and diuretics to control fluid overload, as well as supplemental oxygen. Due to overlapping pathophysiology, some medications approved for treatment of PH or pulmonary arterial hypertension are used off-label for CTEPH.

Dr Ogurchak then examined other treatment options and supportive therapies. Riociguat, a soluble guanylate cyclase stimulator, is the only medication currently approved with FDA labeling specific to CTEPH. He reviewed the 3 pathways—nitric oxide, endothelin receptor agonists, and prostaglandin pathways—that are targeted in CTEPH treatment by the investigational therapies macitentan, treprostinil, and selexipag. As Dr Ogurchak discussed the different medication classes and considerations regarding adherence to dose titration schedules, potential adverse effects, and drug-drug interactions, Dr Fraidenburg reviewed clinical trial results of each agent. Some dose-limiting adverse effects may limit patients from achieving the target dose and full therapeutic benefit, and this presents an important opportunity for pharmacists to mitigate adverse effects.

Dr Ogurchak also reviewed counseling pearls pharmacists can share with patients to promote safe use of these therapies. A best practice he shared to ensure continued patient safety is maintaining an accurate medication list for patients with polypharmacy, especially if patients are receiving medications from different pharmacies. Each agent discussed requires a Risk Evaluation and Mitigation Strategy program, and pharmacists should provide a medication guide and counseling to all patients about the risks of these medications, especially to females of reproductive potential.

The comprehensive role of pharmacists in the management of CTEPH should incorporate counseling about necessary immunizations, supportive care such as smoking cessation, and screening for quality of life impact and mental health support. CTEPH has been shown to have a huge impact on patients’ quality of life in areas of functional limitations, increased dyspnea and fatigue, and decreased work productivity. Because treatment cost for patients can exceed $100,000 per year, connecting patients with financial support can be an especially important service specialty pharmacists can provide. Dr Ogurchak concluded with a reminder to pharmacists of the importance of discussing adherence to therapy at each point of contact as well as knowing when to increase or change therapy for patients.

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs

The activity is available through May 10, 2023.
MANAGEMENT OF LOWER-RISK MYELODYSPLASTIC SYNDROME (MDS) has evolved from management with red blood cell transfusions to a complex algorithm based on presence of symptomatic cytopenias, genetic mutations, serum erythropoietin levels, and percentage of bone marrow blasts and ringed sideroblasts. Experts from the clinic and specialty pharmacy streamlined management of MDS at the 2022 Asembia Specialty Pharmacy Summit in a presentation titled “Evaluating the Important Advances in the Treatment of Lower-Risk Myelodysplastic Syndromes and the Specialty Pharmacist’s Role.”

In the first half of the presentation, Robert Mancini, PharmD, BCOP, FHOPA, reviewed treatment principles of lower-risk MDS. Following determination of low risk using the revised International Prognostic Scoring System (R-IPSS), treatment decisions are based on the presence of symptomatic cytopenias, serum erythropoietin levels, and genetic mutations, explained Dr Mancini. He highlighted hypomethylating agents (HMAs) as the treatment of choice in patients with thrombocytopenia/neutropenia. Dr Mancini identified lenalidomide as the preferred strategy for patients with symptomatic anemia with del5q. In contrast, patients with symptomatic anemia, without del5q, but with serum erythropoietin levels less than 500 mU/mL are candidates for erythropoiesis-stimulating agents with or without granulocyte colony-stimulating factor. Luspatercept is recommended for patients with at least 15% ring sideroblasts (or at least 5% if an SF3B1 mutation is present) with a serum erythropoietin level greater than 500 mU/mL, noted Dr Mancini. Lastly, patients with symptomatic anemia, without del5q, SF3B1, or ring sideroblasts less than 15%, with serum erythropoietin levels greater than 500 mU/mL, may benefit from HMAs, lenalidomide, or immunosuppressive therapy.

In the second half of the presentation, Gregory D. Wolfe, PharmD, BCOP, CSP, LSSGB, explained that different therapies for patients with MDS have specific dispensing requirements and considerations (eg, Risk Evaluation and Mitigation Strategies, white vs clear bagging, injection training, and cold chain procedures). He reviewed the unique ability for specialty pharmacy workflows to mitigate financial toxicity through preemptive financial assistance. He suggested proactive assessment for potential barriers to adherence or the safe and effective use of the therapy at the time of initial patient and treatment assessment. Lastly, he provided key counseling points for patients receiving therapy for MDS and emphasized monitoring for adherence, adverse effects, and response to treatment.

“Closed-loop communication regarding adherence, adverse effects, and treatment efficacy is key in a multidisciplinary approach to care of patients with lower-risk MDS.”

—Gregory D. Wolfe, PharmD, BCOP, CSP, LSSGB

Dr Mancini then delved into the potential for iron overload and adverse sequelae associated with red blood cell transfusions for symptomatic anemia. He highlighted a link between iron chelation and improvement in survival in patients with lower-risk MDS. The National Comprehensive Cancer Network guidelines recommend deferasirox and deferoxamine for iron chelation in patients with lower-risk MDS with a history of 20 to 30 red blood cell transfusions.

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs. The activity is available through May 10, 2023.
Caregiver Involvement, Pharmacist Collaboration Is Crucial to Successful Management of Patients With LC-FAODs

“...We are in a dynamic era in the treatment of long-chain fatty acid oxidation disorders, and a partnership is necessary among clinicians, specialty pharmacists, patients, and caregivers to tailor education and determine appropriate management strategies.”

—Jerry Vockley, MD, PhD

STRATEGIES TO ENHANCE THE QUALITY OF LIFE of patients with long-chain fatty acid oxidation disorders (LC-FAODs) was the focus of a session at the 2022 Asembia Specialty Pharmacy Summit titled “Exploring Long-Chain Fatty Acid Oxidation Disorders: Recognizing the Intricacies in Disease Management, the Available Agents in Treatment, and Considerations for Pharmacists Across Practice Settings.” Jerry Vockley, MD, PhD; and Richard J. Faris, PhD, MS, RPh, shared practice pearls associated with the use of new therapies and management strategies for patients with LC-FAODs. The program featured an interview with a caregiver who has a college-aged daughter living with LC-FAOD recalling their journey through diagnosis, complications, and usage of therapies.

Dr Vockley outlined the pathophysiology of LC-FAODs, explaining the serious errors in metabolism caused by defects in enzymes responsible for the transport of fatty acids to mitochondria. These defects cause difficulties with processing the enzymatic steps to get the maximum energy from a long-chain fatty acid molecule.

The incidence of LC-FAODs in the United States is approximately 1 in 9500 births. Although newborn screening has improved prognosis and significantly decreased early infant mortality, patients with LC-FAOD still experience metabolic complications including cardiomyopathy, hypoglycemia, and rhabdomyolysis that can lead to build-up of toxic metabolites and require frequent hospitalizations. These disease-related complications affect individuals differently depending on their age and type of FAOD mutation present. While more data are needed to account for the full scope of direct and indirect costs, specialty formulas and medications as well as hospitalizations for complications are significant cost contributors.

Symptoms of a metabolic crisis can be aggravated by increased energy requirements during times of fasting, illness, or physical or psychological stress. Dr Vockley emphasized the importance of meeting nutritional requirements despite dietary limitations and reviewed tips to share with caregivers and patients regarding dietary goals.

Triheptanoin is the first FDA-approved medium-chain triglyceride (MCT) oil for treatment of LC-FAODs and provides an alternative source of fatty acids. Whereas MCT oil provides only acetyl-coenzyme A (CoA), triheptanoin provides both acetyl-CoA and propionyl-CoA, which bypasses some enzymatic steps and facilitates energy production. Dr Vockley shared that triheptanoin improved cardiac function, significantly reduced total hospital-days per year, and was associated with fewer adverse effects in clinical trials. While gastrointestinal upset can occur, the symptoms usually resolve with dose reduction and slow titration to goal dose.

Dr Faris discussed the challenges in managing rare diseases and presented on the ongoing Odyssey registry, which aims to collect real-world data from more than 100 patients related to LC-FAOD progression and treatment. This information will be valuable to the limited amount of data currently available. He then explained the need for a collaborative approach involving specialty pharmacists in the management, administration, and access to therapies, including triheptanoin. Patients may express confusion or difficulties with storage of triheptanoin, as plastic containers must be avoided and glass containers are preferable.

Dr Faris also discussed the importance of continuous care and altering the information communicated to patients and caregivers about management of LC-FAOD, triheptanoin therapy requirements, and expectations for adverse effects that may change as patients age. He concluded the session with strategies for pharmacists to control specialty costs associated with new treatments. Pharmacist competency in reimbursement services, care management, and reporting/follow-up will be essential in reducing access barriers and establishing proactive approaches to successful treatment of LC-FAODs.
The population of patients with idiopathic pulmonary fibrosis (IPF) continues to grow due to improved diagnostic methods and disease recognition. At the 2022 Asembia Specialty Pharmacy Summit, Lisa H. Lancaster, MD; and Barbie Courtney, PharmD, BCACP, CSP, AAHIVP, reviewed the roles of specialty pharmacists in reducing IPF progression and ensuring treatment adherence in a session titled “Advancements in the Management of Idiopathic Pulmonary Fibrosis: A Review for Specialty Pharmacists.”

IPF is a progressive, fibrotic lung disease, with a median survival of 2 to 4 years. About 50% of patients present with familial or genetic etiology, and Dr. Lancaster emphasized the importance of obtaining a complete health history for patients and assessing risk factors. In some, inhaled environmental exposures, such as dust, viruses, aerosols, or cigarette smoke, can also contribute to development of disease. There are high rates of misdiagnosis associated with IPF due to nonspecific symptoms such as cough and shortness of breath. Early identification is necessary to improve prognosis and resolve comorbidities. Dr. Lancaster weaved a clinical case throughout the discussion, in which participants considered medical and social history as well as pulmonary test results of a patient to determine a diagnosis and appropriate course of therapy.

There are 2 antifibrotic therapies currently approved for management of IPF, pirfenidone and nintedanib. Dr. Courtney discussed long-term and real-world safety, efficacy, and tolerability of these therapies in patients with IPF. There have not yet been any head-to-head trials of these agents, so no significant benefit has been shown supporting use of one therapy over the other or in combination. Additionally, pooled data from clinical trials and observational studies have not indicated difference in cost or hospitalizations between nintedanib and pirfenidone. Dr. Courtney emphasized that treatment decisions should include assessment of comorbidities, management of adverse effects, and patient preference. Several emerging therapies for IPF are currently under investigation, which Dr. Courtney discussed.

Dr. Courtney concluded the session with practical recommendations for pharmacists to engage in active monitoring of worsening disease, managing adverse effects for each approved therapy, and ensuring patient compliance with medication regimens. Managing nonadherence through medication education is perhaps the most important role of pharmacists involved in the care of patients with IPF. Patients may assume that an increase in symptoms or decline in quality of life may indicate that the treatment is not effective. At each encounter, pharmacists should remind patients that the goal of IPF therapy is to slow disease progression, and it is essential that patients continue therapy to optimize IPF outcomes. Pharmacists must proactively set treatment expectations with patients and ensure they understand the progressive nature of IPF and the role of medications in reducing symptom progression.

“A collaborative effort between pharmacists and prescribers coupled with patient-focused educational counseling is fundamental for managing IPF and delaying disease progression to improve patient quality of life.”

—Barbie Courtney, PharmD, BCACP, CSP, AAHIVP
Emerging Therapies in IgA Nephropathy to Change the Trajectory of Disease Progression

In a presentation at the 2022 Asembia Specialty Pharmacy Summit titled, “Clinical Data on Newly Approved and Emerging IgA Nephropathy Treatments,” Neeta Bahal O’Mara, PharmD, BCPS; and Catherine Cooke, PharmD, MS, BCPS, PAHM, discussed strategies to curb chronic kidney disease (CKD) progression in patients with immunoglobulin (Ig) A nephropathy (IgAN) with a newly approved agent.

Dr O’Mara familiarized attendees with IgAN, defining it as an excessive collection of IgA antigen-antibody complex deposits in the glomeruli that leads to inflammation and damage to the kidneys. There is variability in both the presentation and clinical course of IgAN. In more than half of adults older than 30 years, clinical presentation is asymptomatic, which can complicate treatment. Often, by the time diagnosis is confirmed, patients have progressed to stage 3 CKD, and between 20% and 40% of patients develop kidney failure within 20 years after diagnosis.

Treatment for IgAN centers on optimizing supportive care through blood pressure management and dietary and lifestyle modifications. Dr O’Mara reviewed recommendations from Kidney Disease Improved Global Outcome (KDIGO) regarding the use of glucocorticoids in patients at high risk of progressive CKD. Glucocorticoids may be considered for a 6-month duration in this patient population, and Dr O’Mara reminded attendees of the importance in discussing potential for treatment-related toxicity with patients.

The first approved therapy for IgAN is an enteric-coated, delayed-release formulation of budesonide, which acts locally in the distal ileum of the small intestine, an important site of antigen recognition and secretion of IgA. In clinical trials, delayed-release budesonide demonstrated reduction in proteinuria. In December 2021 it was granted accelerated approval to reduce proteinuria in adults with IgAN at risk of rapid disease progression. Continued approval is contingent on results of ongoing trials to confirm clinical benefit.

“Pharmacists can support patient access to medications for supportive care and treatment of IgA nephropathy by assisting in the development of clear pathways through coordinated care efforts.”

—Catherine Cooke, PharmD, MS, BCPS, PAHM

Dr Cooke then reviewed the expansive pipeline for emerging agents for IgAN, such as sparsentan, which had a New Drug Application submitted in March 2022. Sparsentan is a selective antagonist of angiotensin receptor blocker II and endothelin A receptor that showed significant reduction in proteinuria in clinical trials. Therapies currently approved for other indications that have phase 3 studies in IgAN include bortezomib and the sodium glucose co-transporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin; the trial of empagliflozin was stopped early due to positive efficacy, though complete results were not yet available at the time of the presentation.

Understanding costs and managing access to therapies for IgAN will continue to be a priority for pharmacists. Dr Cooke shared that though there is limited information about the economic impact of IgAN, costs are compounded by hospitalizations as well as direct and indirect costs associated with treatment of CKD.

Dr Cooke concluded the session by outlining the importance of providing patient-centered communication and educational resources. She highlighted how pharmacists can be established on the multidisciplinary team and can use their position to assist in measuring patient progress, improving implementation of KDIGO practice guidelines, and overcoming barriers that may affect treatment decisions or patients’ access to care.
Meeting a Need: Targeted Therapies for Exon 20 Insertion Mutations in NSCLC

Two novel therapies were approved by the FDA in 2021 for patients with non–small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion (Ex20Ins) mutations, improving patient outcomes for patients with a historically poor prognosis. Two expert pharmacists reviewed all of the ins and outs of treatment in conjunction with the 2022 Asembia Specialty Pharmacy Summit in a virtual symposium titled “Caring for Patients With EGFR-Positive Non–Small Cell Lung Cancer: An Interactive Review of Drug Therapies Targeting Exon 20 Insertion Mutations.”

Whereas EGFR mutations are common in NSCLC, EGFR Ex20Ins mutations are present in just 2% of patients with NSCLC, explained Stefanie Houseknecht, PharmD, BCOP. She introduced amivantamab, an EGFR-MET bispecific antibody, and mobocertinib, an oral tyrosine kinase inhibitor (TKI) as 2 new options FDA approved for patients with EGFR Ex20Ins mutations whose NSCLC has progressed on or after platinum-based chemotherapy. Dr Houseknecht reported the overall response rate (ORR) was 40% in 81 patients treated with amivantamab after receiving a median of 2 prior therapies for NSCLC with EGFR Ex20Ins mutations. She noted the median duration of response (DOR) with amivantamab was 11.1 months. She described an ORR to mobocertinib of 28% in 114 patients with prior platinum therapy for NSCLC and a median DOR of 17.5 months.

Jeff Engle, PharmD, MS, provided specialty pharmacists with information needed to optimize care of patients receiving amivantamab and mobocertinib. Dr Engle highlighted infusion-related reactions, interstitial lung disease, and ocular and hepatic toxicity are reported with amivantamab in addition to dermatologic adverse effects (AEs) typical with EGFR-targeted medications. He reported 11% of patients discontinued amivantamab during the phase 1 trial.

Dr Engle explained mobocertinib is also associated with dermatologic AEs, interstitial lung disease, stomatitis, and diarrhea reported with other EGFR-targeted TKIs. Similarly, mobocertinib is a CYP3A4 major substrate and also a CYP3A4 inducer, explained Dr Engle. He indicated 17% of patients discontinued mobocertinib in the phase 1/2 study due to AEs.

Dr Engle reviewed strategies for managing toxicities with both medications and provided guidance about when to hold or dose-adjust therapy. He followed by contrasting the 2 therapies, noting the tradeoff between the need for infusion therapy in the clinic with amivantamab versus the need to ensure adherence to oral therapy at home with mobocertinib. Whereas amivantamab poses the risk for infusion-related reactions, mobocertinib increases the risk for drug-drug interactions and QTc prolongation. Patients may also have significant differences in out-of-pocket cost given amivantamab is billed through medical benefits and mobocertinib is billed through pharmacy benefits.

The panelists summarized recommendations by discussing 3 patient cases and highlighted their perspectives of pharmacists’ roles in the care of patients receiving these therapies by providing clinical and operational pearls.

“EGFR Ex20Ins mutations are defined by mutation heterogeneity and inherent resistance to first- and second-generation EGFR TKIs as well as the third-generation EGFR TKIs at standard doses.”

—Stefanie Houseknecht, PharmD, BCOP

“While effective, amivantamab and mobocertinib have significant toxicities leading to dose reductions in up to 15% and 25% of patients, respectively; thus, pharmacists play an important role in mitigating toxicity and facilitating medication adherence.”

—Jeff Engle, PharmD, MS

To view the on-demand CE session, please visit www.pharmacytimes.org/pages/2022-asembia-on-demand-programs
The activity is available through June 14, 2023.
A Multifaceted Approach to Resolving Itch in Prurigo Nodularis

UNCONTROLLABLE ITCHING CAN cause patients to experience sleep disturbances, anxiety, and diminished quality of life (QOL). In a live virtual symposium presented in conjunction with the 2022 Asembia Specialty Pharmacy Summit titled “Advances in the Management of Prurigo Nodularis: Updates for the Specialty Pharmacist,” Shawn Kwatra, MD; and Jamie L. McConaha, PharmD, NCTTP, BCACP, CDCES, familiarized the audience with the signs and symptoms of prurigo nodularis (PN) as well as emerging therapies for this debilitating dermatologic condition.

Dr Kwatra began the presentation with an overview of PN, drawing comparisons to other inflammatory skin diseases such as psoriasis and atopic dermatitis. PN is classified by a vicious itch-scratch cycle and presence of multiple areas of nodular lesions and chronic pruritus lasting longer than 6 weeks. An important differentiator is that individuals with PN have unique fibrotic and neurovascular dysregulation in addition to immunological dysfunction, which leads to a heightened neuroinflammatory response.

Several comorbidities are associated with PN, including chronic kidney disease, diabetes, and cardiometabolic diseases, as well as chronic hepatitis B/C virus and HIV infection. Dr Kwatra explained the presence of these comorbidities as a 2-way street; they can result from increased inflammation due to PN and PN can develop in patients with these conditions due to inflammation. Because sleep patterns can be disturbed in patients with PN due to the substantial itch burden, individuals can develop psychological comorbidities, such as mood disorders, substance use disorders, or engage in self harm. As a result, Dr Kwatra explained patients experience significant QOL impact.

Patients with uncontrolled disease may frequently seek health care services resulting in significant economic burden. There are currently no FDA-approved medications targeting PN, so use of off-label medications to relieve symptoms is common. Dr Kwatra explained typical treatment tiers are based on disease severity and can include topical or intralesional steroids for mild to moderate disease, and systemic immunosuppressives, biologics, or neuromodulating agents for moderate to severe disease. He explained goals of treatment should focus on reducing pruritus, interrupting the itch-scratch cycle, and healing PN lesions.

Several studies have focused on development of effective treatment options that target the pathogenesis of PN. Dr Kwatra first discussed dupilumab, which is approved for use in patients with atopic dermatitis and is being investigated in PN. In the PRIME trial, patients with PN receiving dupilumab experienced reduction in itch from baseline, improvement in nodules, and also improvements in overall health-related QOL and psychological symptoms. Nemolizumab is also under investigation for treatment of moderate to severe PN. Dr Kwatra discussed clinical data available for nemolizumab, which showed patient-reported reductions in itch rating as well as lesion severity. Other investigational therapies with potential in PN include vixarelimab, which is an oncostatin M β receptor antagonist, and nalbuphine, an oral dual-acting kappa-opioid receptor agonist/mu-opioid receptor antagonist.

Dr McConaha concluded the presentation with considerations for pharmacists managing treatments for PN. The role of the pharmacist starts with knowing disease characteristics in order to recognize patients with PN and should include appropriate counseling information on self-care measures, treatment recommendations, and investigational agents. Pharmacists can also share clinical pearls for emerging therapies with patients and provide counseling on storage, administration, and strategies to minimize adverse effects. Dr McConaha reminded the audience of the importance of supporting patients due to the emotional burden and significant QOL impact of PN. Without a treatment currently available for PN, nonpharmacologic counseling tips to resolve itch should be emphasized.

“Itch is the driver of prurigo nodularis, and the focus for pharmacists should be how to utilize emerging systemic therapies and treatment plans to help patients attain itch reduction.”

—Shawn Kwatra, MD
Optimizing Treatment Approaches for Iron Deficiency in Heart Failure

**EDUCATIONAL OBJECTIVES**

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

- Explain the pathophysiology, clinical manifestations, risk factors, and clinical burden of iron deficiency (ID) and iron deficiency anemia (IDA) in patients with heart failure (HF)
- Explore clinical guidelines for the treatment of ID/IDA in patients with HF using available iron formulations and emerging treatment strategies
- Identify the role of the pharmacist in the transitions of care for patients with ID and anemia in HF to ensure appropriate use and monitoring of parenteral iron

**TARGET AUDIENCE:** Pharmacists

**ACTIVITY TYPE:** Application

**RELEASE DATE:** May 27, 2022

**EXPIRATION DATE:** May 27, 2023

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

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

**INTRODUCTION**

Heart failure (HF) is a complex syndrome with multiple causes and effects. Patients often have many comorbidities that negatively impact their quality of life (QOL), reduce their ability to perform their normal daily activities, and increase their risk of hospitalization and death. Iron deficiency (ID) affects about half of all patients with HF and independently contributes to these negative effects. Over the past 2 decades, ID has been the focus of a growing area of research as clinicians seek to identify the role of various treatment modalities. The most recent HF treatment guidelines in the United States and Europe have included the treatment of ID in patients with HF as key updates with the aim of improving QOL and reducing morbidity and mortality in this patient population. Pharmacists in all practice areas have an opportunity to work within the interdisciplinary HF team to optimize treatment strategies for ID and provide education to patients on the importance of addressing this concomitant disease.

**Prevalence and Impact of Iron Deficiency in Heart Failure**

ID is a common, though often underappreciated, comorbidity in patients with HF. The reported prevalence in chronic HF varies based on definition and mode of diagnosis, from 21% in cases of newly diagnosed HF to 73% in a series of patients with HF diagnosed via bone marrow biopsy. More frequently, the rate of ID in the HF population is reported as approximately 40% to 50%. Though often associated with resultant anemia, ID is commonly present in nonanemic patients with HF. In one series, ID was reported in 61% of patients with HF and anemia (hemoglobin <12.0 g/dL for women and <13.0 g/dL for men) and 45% of patients without anemia. ID in patients hospitalized for acute HF has been documented to occur in as many as 50% to 80% of patients.

As with other chronic inflammatory conditions such as chronic kidney disease (CKD), cancer, and inflammatory bowel disease, patients with HF are at an increased risk for ID and should be evaluated for and treated as appropriate. Pharmacists can play a key role in the identification and management of ID in the HF population.

**REFERENCES**


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risk of ID relative to the general population. While classic ID risk factors such as young and old age as well as female sex, particularly while menstruating or pregnant, also play a role in the HF population, additional disease state-specific factors such as higher New York Heart Association (NYHA) symptom class, increased N-terminal pro-brain natriuretic peptide (NT-proBNP), and increased C-reactive protein have also been shown to increase risk.\(^3,7\)

ID in patients with HF stems from both absolute deficiency and inflammation. Volume overload, poor cardiac output, and resultant intestinal edema reduce gastrointestinal (GI) absorption of dietary iron. More importantly, the chronic inflammation associated with HF leads to an upregulation of hepcidin, a peptide hormone originating in the liver that regulates serum iron. In normal physiology, hepcidin plays a role in regulating GI absorption and sequestering excess iron in the liver and reticuloendothelial system. However, overactive hepcidin in patients with HF leads to a lack of functional iron by further limiting GI absorption and release of iron stores.\(^8,9\) A lack of available iron, whether through absolute or functional deficiency, results in worsened HF symptoms, as iron plays a foundational role in oxygen transport and cellular metabolism, particularly in myocardial and skeletal muscle.\(^10,11\) ID is frequently associated with anemia due to the reduction in erythropoiesis.

In a patient population already fraught with physical limitations and high morbidity and mortality, ID in HF substantially worsens a variety of clinical and surrogate outcomes. Both with or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia, ID has been shown to be an independent predictor of reduced exercise capacity with a lower or without concomitant anemia.\(^3,7\)

**Evaluation and Diagnosis**

Current HF guidelines define ID as a ferritin less than 100 ng/mL or ferritin 100 to 300 (or 299) ng/mL with transferrin saturation (TSAT) less than 20% (\textit{TABLE} 1\(^{16-19}\)).\(^{16,17}\) The definition was initially derived from an international consensus statement on ID in chronic inflammatory conditions and subsequently became accepted criteria for treatment initiation based on its use for inclusion in clinical trials.\(^{20,21}\) Due to the chronic inflammation in HF, these values are significantly higher than the World Health Organization’s diagnostic cutoff for the general population (ferritin <15 ng/mL).\(^22\)

According to the European Society of Cardiology (ESC) HF guidelines, “All patients with HF should be periodically screened for anemia and ID,” (Class 1, level of evidence [LOE] C: recommended/indicated based on consensus of expert opinion and/or small scale data) including those patients with new or suspected HF. Additionally, in light of recent literature updates, the ESC notes that assessment of iron status should occur before discharge in patients admitted for acute HF.\(^17,23\) The American guidelines give less specific direction but note that evaluation for anemia should be part of a “routine baseline assessment of all patients with HF.”\(^16\) Ongoing assessment, particularly following treatment of ID, is poorly defined in both guidelines.

For patients with adequate iron stores at initial check, it may be reasonable to reassess if any worsening in HF symptoms occurs or every 6 months at a minimum. Following intravenous (IV) iron supplementation, it has been suggested that repeat assessment would be reasonable between 3 and 12 months later.\(^5,7\)

Importantly, neither the American nor European HF guidelines list an Hb cutoff with the diagnostic criteria of ID but do group recommendations for ID and anemia together. In the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) Guideline for the Management of Heart Failure, all the recommendations for diagnosis and treatment of ID fall under the section heading “Management of Anemia or Iron Deficiency.”\(^16\) The ESC guideline highlights ID and anemia separately and in concert but specifically notes that ID can be present independently of anemia.\(^17\)

To estimate the degree of ID, the Ganzoni equation may be used to calculate the total iron deficit and inform dosing requirements to correct the ID using an ideal Hb of 15.0. In overweight/obese patients (body mass index >25 kg/m\(^2\)), ideal body weight should be
used rather than actual body weight. The 500 mg addition factors in repletion of iron stores, which Ganzoni’s equation does not otherwise address. See SIDEBAR for equation and example.7,24

**SIDEBAR. CALCULATING IRON DEFICIT7,24**

\[
\text{(body weight [kg]) \times (15 – Hb [g/dL]) \times 2.4} + 500 \text{ [mg]}
\]

Calculate the iron dose required for a 70-kg patient with an Hb of 11.5 mg/dL.

**Answer below.**

### TABLE 1. MANAGEMENT OF IRON DEFICIENCY PER CURRENT HEART FAILURE GUIDELINES16-19

<table>
<thead>
<tr>
<th>Screening</th>
<th>Diagnosis</th>
<th>Treatment recommendations</th>
<th>Class (level of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC ECDP on patients hospitalized with HF (2019)</td>
<td>Evaluate for underlying etiology of anemia</td>
<td>N/A</td>
<td>IV ferric carboxymaltose or non-dextran IV iron</td>
</tr>
<tr>
<td>ESC guidelines (2021)</td>
<td>Routine screening for comorbidities such as ID should occur in all patients</td>
<td>Ferritin &lt;100 ng/mL OR ferritin 100-299 ng/mL with TSAT &lt;20%</td>
<td>LVEF ≤45%. IV ferric carboxymaltose</td>
</tr>
<tr>
<td>All patients should be screened for ID before discharge from an AHF admission or at the first follow-up visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHA/ACC/HFSA guidelines (2022)</td>
<td>Anemia screening as routine baseline assessment for all patients</td>
<td>Ferritin &lt;100 ng/mL OR ferritin 100-300 ng/mL with TSAT &lt;20%</td>
<td>Intravenous iron (only data from ferric carboxymaltose trials are included)</td>
</tr>
</tbody>
</table>

ACC, American College of Cardiology; AHA, American Heart Association; AHF, acute heart failure; ECDP, Expert Consensus Decision Pathway; ESC, European Society of Cardiology; HF, heart failure; HFSA, Heart Failure Society of America; ID, iron deficiency; IV, intravenous; LVEF, left ventricular ejection fraction; RCT, randomized controlled trial; TSAT, transferrin saturation.

**Treatment Recommendations**

Given the negative impact of ID on functional capacity, QOL, and clinical outcomes in patients with HF, clinicians should seek to promptly identify patients with ID, with or without anemia, and initiate therapies that have demonstrated the ability to improve both clinical and surrogate outcomes. At present, 3 key HF guidance documents provide recommendations for diagnosis and treatment of ID in patients with HF (TABLE 1).16-19 In the United States, the recently published 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure builds on the 2017 ACC/AHA/HFSA Focused Update of the 2013 Guideline for the Management of Heart Failure based on growing clinical trial data published since the previous full guideline update in 2013.16,25,26 Treatment of ID in patients hospitalized for HF was also briefly addressed in the 2019 ACC Expert Consensus Decision Pathway (ECDP) on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized with Heart Failure.18 The 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure, however, provide the most thorough discussion and recommendation of ID treatment in patients with HF.17

In the current AHA/ACC/HFSA guidelines, IV iron replacement therapy is recommended as a reasonable consideration to improve functional capacity and QOL in patients with heart failure with reduced ejection fraction (HFrEF) and ID (ferritin less than 100 ng/mL or 100 to 300 ng/mL if TSAT is less than 20%) with or without anemia (Class 2a, LOE B-R: is reasonable based on moderate quality evidence from 1+ randomized trials/meta-analyses). Data from the FAIR-HF and CONFIRM-HF trials are referenced as the basis for the recommendation but are noted to have been underpowered to detect differences in hard clinical end points.27-28 However, this new guideline includes data from 2 meta-analyses and the AFFIRM-AHF trial, which demonstrate the positive impact of IV iron replacement on cardiovascular death and HF hospitalizations.29,30 Contrary to the 2017 ACC/AHA/HFSA Focused Update, which did not
address EF as a criterion for qualification, the 2022 AHA/ACC/HSFA Guideline specifically notes this recommendation is for patients with HFrEF but does cite the EF <50% criteria used for enrollment in AFFIRM-AHF. Additionally, though a specific IV iron product is not endorsed, ferric carboxymaltose (FCM) was used for the treatment arms in all referenced studies.

The 2019 ECDP for patients hospitalized for HF addresses ID/IDA more generally. Clinicians are first encouraged to address the underlying etiology. Both IV FCM and non-dextran products are specifically noted as options to be considered for iron replacement to improve functional capacity, even in cases where anemia is mild. In the most severe and symptomatic patients, blood transfusion should be considered. The document links to the 2013 Clinical Practice Guideline from the American College of Physicians for the Treatment of Anemia in Patients with Heart Disease, which notes low to moderate quality evidence supporting the use of IV iron to reduce cardiovascular (CV) events and improve exercise tolerance and QOL in patients with stable HF.

Several specific recommendations are made in the HF guideline update from ESC. Similar to the American guidelines, IV iron supplementation should be considered in symptomatic patients with ID (ferritin <100 ng/mL or ferritin 100-299 ng/mL with TSAT <20%) to improve exercise capacity and QOL (2a, LOE A: should be considered based on data derived from multiple randomized clinical trials/meta-analyses). However, FCM and an EF less than 45%, according to CONFIRM-HF, are each specifically included in the recommendation. Additionally, based on results from AFFIRM-AHF, FCM is recommended for consideration in symptomatic patients with HF who have been recently hospitalized for HF, have an EF less than 50%, and have ID to decrease the risk of subsequent rehospitalization (2a, LOE B: should be considered based on data derived from a single randomized trial). Furthermore, optimization of medical therapy while a patient is admitted for acute HF is discussed and includes addressing comorbidities such as ID that contribute to negative outcomes post discharge.

These guidelines are consistent in preferring IV iron replacement over oral iron, though specifics range from solely mentioning IV iron replacement, to noting that oral iron is not adequate to treat IDA in patients with HF, to explicitly recommending against oral iron therapy due to lack of efficacy. Both the American and European guidelines recommend against erythropoietin-stimulating agents in patients with HF and concomitant anemia outside scenarios where compelling indications exist due to a lack of data demonstrating benefit.

**Basis for Current Practice**

**Intravenous Iron in Chronic Heart Failure**

The research that has informed these guidelines began at the turn of the millennium and has steadily grown in scope and impact over the past 2 decades. The earliest report of IV iron therapy in patients with HF, published by Silverberg and the Tel Aviv group in 2000, evaluated combination erythropoietin and iron sucrose in patients with a reduced EF, refractory HF symptoms (NYHA class ≥3), and an Hb less than 12.0 g/dL despite 6 months of maximally tolerated HF therapy. Iron sucrose was dosed at 200 mg IV weekly until ferritin reached 400 ng/mL, TSAT reached 40%, or the Hb reached 12.0 g/dL, with subsequent maintenance therapy to maintain appropriate levels. Over an average duration of 7 months, the erythropoietin/iron sucrose combination therapy was associated with a significant reduction in NYHA functional class, improvement in left ventricular EF, resolution of anemia, and a 92% reduction in hospitalizations though there were no safety data provided.

During the 2000s, several smaller studies confirmed iron sucrose’s role in improving functional capacity and QOL. Bolger and colleagues assessed iron sucrose without concomitant erythropoietin in patients with stable HF and anemia and showed improvement in 6MWD, NYHA class, and MLHFQ score. These findings were followed up the next year in a randomized, placebo-controlled trial of patients with HF with anemia, ID, and CKD who received weekly iron sucrose infusions and saw improved Hb, renal function, and NT-proBNP levels in addition to better functional capacity and QOL scores and fewer hospitalizations. Both studies reported no safety concerns or adverse effects (AEs) associated with iron sucrose.

FERRIC-HF first introduced the definition of ID in HF still used in today’s guidelines (ferritin <100 ng/mL or 100-300 ng/mL with a TSAT <20%) and evaluated both anemic and non-anemic patients. Patients were randomized to receive iron sucrose 200 mg IV weekly until ferritin is greater than 500 ng/mL, then monthly thereafter or placebo. Improvements in exercise tolerance, NYHA class, and patient global assessment (PGA) scores were seen, but these benefits were driven almost exclusively by patients with concomitant anemia. All AEs were deemed to be unrelated or likely unrelated to treatment with iron sucrose.

The first large-scale trial to evaluate ID in HF, FAIR-HF, employed the newer FCM in patients with chronic stable HFrEF and ID. Those in the treatment arm received FCM 200 mg weekly to correct the iron deficit per Ganzoni’s formula then
every 4 weeks thereafter through the 24-week study period. For the self-reported PGA primary end point, significantly more patients in the FCM group reported feeling much or moderately improved at 24 weeks (improvement odds ratio [OR], 2.51; 95% CI, 1.75-3.61), and patients receiving FCM were more likely to achieve a NYHA class of 1 or 2 by week 24 compared with the placebo group (47% vs 30%; improvement OR, 2.40; 95% CI, 1.55-3.71). Though there was no difference in the rate of death or hospitalization, treatment with FCM resulted in clinically meaningful improvements in 6MWD and Kansas City Cardiomyopathy Questionnaire (KCCQ) score. Importantly, the benefit seen with FCM for the 2 primary end points was consistent in both anemic and non-anemic patients. In the FCM arm, injection-site discoloration and pain were reported in 4 and 2 patients, respectively, with no severe allergic reactions were reported.

In 2015, CONFIRM-HF sought to assess the benefit of FCM on QOL, functional capacity, and hospital admissions over a longer 52-week period. The trial enrolled 304 symptomatic patients with HF with a reduced EF (≤45%), ID, and elevated natriuretic peptides and randomized them to receive FCM or placebo. FCM was dosed between 500 and 2000 mg (based on patient weight and Hb) at initiation followed by 500 mg every 12 weeks, if needed for persistent ID, as a maintenance regimen. Improvement in 6MWD, the primary end point, was significant by 24 weeks and remained improved through the follow-up period. Similarly, PGA scores and NYHA functional class were improved by 24 weeks and to the end of study year. For the first time, treatment of ID in HF with IV iron led to a reduction in HF hospitalizations (HR, 0.39; 95% CI, 0.19-0.82). Similar to FAIR-HF, FCM’s impact on 6MWD was independent of baseline Hb, and AEs were limited to mild injection-site reactions without severe allergic reactions.

With most trials assessing IV iron being underpowered to detect differences in hard clinical outcomes, 2 meta-analyses aimed to elucidate the impact of IV iron replacement therapy on death and hospitalizations. Jankowska and colleagues assessed 5 trials in those with ID and HFpEF that included patients receiving either iron sucrose or FCM. While there was no appreciable impact on CV or all-cause death, HF hospitalizations were reduced by 72% (OR, 0.28; 95% CI, 0.16-0.50). Furthermore, the mean difference in 6MWD across the included studies was increased by nearly 31 meters (95% CI, +18.2-43.4). The benefits of IV iron therapy on QOL metrics (NYHA class, European Quality of Life-5 Dimensions score, KCCQ score, PGA, MLHQF score) were all significant. Treatment with FCM specifically across 4 studies was evaluated with similar results toward clinical end points. HF hospitalizations were significantly reduced (relative risk [RR], 0.41; 95% CI, 0.23-0.73), but there was no difference in CV or all-cause mortality. Across both evaluations, the benefits of IV iron replacement in ID was seen irrespective of the presence of anemia, and the lack of AE safety signals was confirmed in the larger cohort of patients.

### IV Iron in Acute Heart Failure

To expand beyond the solid foundation of evidence supporting IV iron supplementation in the chronic, stable HF setting, the AFFIRM-AHF study evaluated more than 1100 patients who had recently been stabilized from an acute, inpatient HF episode. Patients with ID and an EF less than 50% were randomized to receive IV FCM or placebo for as many as 24 weeks as determined by the degree of ID that was present. The primary composite end point included total HF hospitalizations and CV death at 1 year. Treatment with IV FCM led to a substantial reduction in the primary end point (57.2 events vs 72.5 events per 100 patient-years; rate ratio [RR], 0.79; 95% CI, 0.62-1.01; P = .059), though this difference did not reach statistical significance. In a key secondary evaluation, there was a statistically significant 26% relative risk reduction for total HF hospitalizations (95% CI, 0.58-0.94). Additionally, a COVID-19 sensitivity analysis that censored patients in each country on the date of the first reported COVID-19 case demonstrated a significant reduction in the primary end point (RR, 0.75; 95% CI, 0.59-0.96). Despite this being a potentially more tenuous patient population following admission for an acute HF event, there were no noted differences in overall AEs between the 2 arms. A post hoc analysis of AFFIRM-AHF also demonstrated that IV FCM improved HRQOL by week 4, which then persisted until week 24.

### Oral Iron

Conventional oral iron replacement therapy has failed to show meaningful benefit in patients with concomitant HF and ID. The IRON-HF trial attempted to compare oral ferrous sulfate with IV iron sucrose and placebo but was never fully enrolled. Nonetheless, an incremental increase of 3.5 mL/kg/min in peak VO2 at 3 months was seen in patients receiving IV iron sucrose, with no significant change in exercise capacity for the oral iron group. The IRONOUT-HF trial also sought to determine the potential role for oral iron replacement therapy in HF. Patients with HFpEF and ID (ferritin 15-100 ng/mL or 101-299 ng/mL with TSAT <20%) were randomized to
oral iron polysaccharide 150 mg twice daily or placebo. The primary end point was the change in peak VO$_2$ from baseline to 16 weeks; secondary end points assessed QOL and additional functional capacity end points. Oral iron polysaccharide failed to significantly improve peak VO$_2$, 6MWD, NT-proBNP levels, or KCCQ score, leading the authors to note that their data do not support the use of oral iron as an effective option to address ID in patients with HFrEF. 38

Recently, a single, non-randomized evaluation of oral sucrosomial iron in patients with HFrEF and ID demonstrated improvements in Hb, serum iron, and serum ferritin at 3 months. Sucrosomial iron is believed to have improved bioavailability and tolerability over conventional oral iron products. Overall, the novel product was well tolerated relative to the control arm though one patient did have drug-associated diarrhea that led to study drug discontinuation. Further randomized evaluations are necessary to confirm these findings and assess the impact of oral sucrosomial iron on HF hospitalizations and cardiovascular death. 39

Ongoing Clinical Trials

Currently, there are several key clinical trials ongoing that will further shape the treatment of this profound comorbidity in patients with HF. IRONMAN will randomize patients to ferric derisomaltose or placebo, with a primary composite end point of CV death or HF hospitalization. 40 IRONMAN is the first large-scale study that is evaluating a therapy other than iron sucrose or FCM. Both HEART-FID and FAIR-HF 2 will employ IV FCM in large (3014 and 1200 patients, respectively) randomized trials with hard clinical end points. 41-43 Lastly, patients with HFpEF (EF ≥45% with evidence of diastolic dysfunction) will be studied in FAIR-HFpEF, which will further shape the treatment of this profound comorbidity specifically randomized trials with hard clinical end points. 41-43 Notably, patients with HFpEF (EF ≥45% with evidence of diastolic dysfunction) will be studied in FAIR-HFpEF, which will assess the impact of IV FCM on 6MWD at 24 weeks. 44

Available Iron Products

With multiple iron supplementation products available in the United States, several factors should be considered when deciding among various treatment options for patients with concomitant ID/IDA and HF. As noted above, oral iron products have failed to show a benefit toward functional capacity, QOL, or even resolving anemia and are thus not recommended in patients with HF. 37,38 The vast majority of clinical data covering IV iron products is with iron sucrose and FCM. Nonetheless, the American guidelines fail to specifically mention any iron products, while the European guidelines recommend FCM. 17,25 The role for other IV iron products remains less clear.

There are currently 6 commercially available IV iron complexes (Table 2): FCM, ferric derisomaltose, ferumoxytol, iron dextran, iron sucrose, and sodium ferric gluconate. Chemically, the makeup of each complex differs by the iron (III)-oxyhydroxide/oxide core and the stabilizing carbohydrate. This difference in composition leads to clinical differences in the products’ pharmacokinetic and pharmacodynamic profiles in addition to the differences in molecular weight, stability, and iron content. Complexes with a higher molecular weight have greater stability. 52

Evaluations of FCM for ID/IDA in patients with HF consistently demonstrate that IV iron improves functional capacity, QOL, exercise tolerance, anemia, hematologic values, and hospitalization rates. 23,27-29,53 Furthermore, FCM is well tolerated in this potentially high-risk patient population. The meta-analysis by Anker and colleagues included 4 FCM placebo-controlled trials and showed a similarly low rate of AEs (105.4 vs 95.8 events per 100 patient-years) between patients receiving FCM and placebo, respectively. Across these trials, there were no serious or severe hypersensitivity reactions. 29 The AFFIRM-AHF broadens these findings in patients recently hospitalized for acute HF where there was also no difference in AEs. 23

Assessments of other commercially available iron products for ID in HF suggest potential benefit and tolerability as well as logistic advantages. Iron sucrose improved anemia, QOL scores, NYHA functional class, and exercise tolerance with no increased risk for AEs. 33,34,37 A single-center report of an accelerated sodium ferric gluconate regimen (250 mg twice daily until iron deficit was corrected or the patient discharged) showed improvements in anemia, ferritin, and TSAT and demonstrated that this rapid course was well tolerated. 31 A single infusion of ferric derisomaltose (650-1000 mg given over approximately 60 minutes) showed modest improvements in QOL and ID/IDA lab markers but was most notably free from infusion-related or anaphylactic reactions even without a test dose. 34

When considering patient populations beyond HF, anaphylactic reactions and other hypersensitivity-type reactions are a
<table>
<thead>
<tr>
<th>Product</th>
<th>FDA-approved indications</th>
<th>Typical adult dosing and administration</th>
<th>Key HF data/recommendations</th>
<th>Safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferric carboxymaltose (Injectafer)</td>
<td>Treatment of IDA in:</td>
<td></td>
<td>• Solely recommended product per ESC HF guidelines</td>
<td>• Well tolerated</td>
</tr>
<tr>
<td></td>
<td>• Adults and pediatric patients ≥1 year who have either intolerance to oral iron or an unsatisfactory response to oral iron</td>
<td>• ≥50 kg or more: 750 mg IV x 2 doses separated by ≥7 days</td>
<td>• Solely cited product per American HF guidelines</td>
<td>• Warnings for hypersensitivity reactions, symptomatic hyperphosphatemia, hypertension</td>
</tr>
<tr>
<td></td>
<td>• Adult patients who have non-dialysis-dependent CKD</td>
<td>• &lt;50 kg: 15 mg/kg IV x 2 doses separated by ≥7 days</td>
<td>• In large RCTs: improves functional capacity, QOL, 6MWD and reduces HF hospitalizations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May be given as a single-dose treatment (15 mg/kg, max 1000 mg) if weight ≥50 kg</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Slow IV push or infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferric derisomaltose (Monoferric)</td>
<td>Treatment of IDA in adult patients:</td>
<td></td>
<td>IRONMAN trial ongoing</td>
<td>Warnings for hypersensitivity reactions and iron overload</td>
</tr>
<tr>
<td></td>
<td>• Who have intolerance to oral iron or have had unsatisfactory response to oral iron</td>
<td>• ≥50 kg: 1000 mg IV x 1 dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Who have non-hemodialysis-dependent CKD</td>
<td>• &lt;50 kg: 20 mg/kg (actual body weight) x 1 dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• For patients weighing &lt;50 kg: administer ferric derisomaltose as 20 mg/kg actual body weight as an IV infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IV infusion over at least 20 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferric gluconate (Ferrlecit)</td>
<td>Treatment of IDA in adult patients and in pediatric patients ≥6 years with CKD receiving hemodialysis who are receiving supplemental epoetin therapy</td>
<td>• 125 mg each dialysis session until deficit corrected</td>
<td>Single center: improved Hb, ferritin, TSAT with rapid protocol</td>
<td>Warnings for hypersensitivity reactions, hypotension, and iron overload</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Administer diluted via infusion (1 hour) or undiluted via slow IV push (5 minutes)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Off-label accelerated course: up to 250 mg twice daily</td>
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<td></td>
</tr>
<tr>
<td>Ferumoxytol (Feraheme)</td>
<td>Treatment of IDA in adult patients:</td>
<td></td>
<td>None to date</td>
<td>BOXED WARNING: RISK FOR SERIOUS HYPERSENSITIVITY/ANAPHYLAXIS REACTIONS</td>
</tr>
<tr>
<td></td>
<td>• Who have intolerance to oral iron or have had unsatisfactory response to oral iron</td>
<td>• 510 mg x 2 doses separated by 3-8 days</td>
<td></td>
<td>(Patients must be observed for &gt;30 minutes following infusion for signs/symptoms of hypersensitivity)</td>
</tr>
<tr>
<td></td>
<td>• Who have CKD</td>
<td>• IV infusion over at least 15 minutes</td>
<td></td>
<td>Warnings for hypotension, iron overload, and interference with MRI</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; ESC, European Society of Cardiology; Hb, hemoglobin; HF, heart failure; ID, iron deficiency; IDA, iron deficiency anemia; IV, intravenous; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; 6MWD, 6-minute walk distance; RCT, randomized controlled trial; TSAT, transferrin saturation; QOL, quality of life.

Continued on next page
classic concern for IV iron administration. This risk has been tied almost exclusively to iron dextran, with the highest risk being in patients who receive higher molecular-weighted dextran formulations. Dextran-based products ferumoxytol and low-molecular weight iron dextran carry boxed warnings for anaphylactic reactions. Iron dextran continues to require a test dose before initiation of therapy, while ferumoxytol has been pulled from the market in the European Union. According to a retrospective analysis of Medicare beneficiaries, iron sucrose was associated with a lower risk of anaphylaxis than dextran-based products, ferumoxytol, and ferric gluconate, though a separate Medicare-based assessment found similar rates of adverse reactions among iron sucrose, sodium ferric gluconate, iron dextran, and ferumoxytol. Several reports support the safe use of iron sucrose in patients who have previously had infusion-related reactions with iron dextran products. Hyper-sensitivity reactions in patients receiving FCM were low (0.8% vs 2.4% in patients receiving iron dextran, sodium ferric gluconate, or iron sucrose).

As outlined above, FCM is currently the IV iron product with the most comprehensive data supporting its use for ID/IDA in HF. While IRONMAN (NCT02642562) with ferric derisomaltose will potentially provide additional information, it is important to remember that currently available literature for non-FCM products in patients with HF is limited. Product selection based on cost and convenience is an option to be considered but some caution against this approach, citing the potential impact of underlying inflammation that has a potentially unrealized impact on the body’s handling of different iron complexes in addition to the lack of data comparing products.

The Role of the Pharmacist in Managing Iron Deficiency in Heart Failure

The use of IV iron supplementation in patients with HF is not commensurate with the opportunity to address this consistently underaddressed comorbidity given its clear clinical benefits. Pharmacists in all practice settings have the opportunity to assist HF teams with leveraging this therapy to improve functional capacity and QOL in patients with HF while also reducing hospital admissions. Just as pharmacists have made substantial impacts in improving comprehensive care in HF, they should be involved with education to patients and providers, operational initiatives, and clinical optimization of iron utilization.

<table>
<thead>
<tr>
<th>TABLE 2. INTRAVENOUS IRON PRODUCTS</th>
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</thead>
<tbody>
<tr>
<td><strong>Iron dextran (INFeD)</strong></td>
<td>Treatment of adult and pediatric patients 4 months and older with documented ID who have intolerance to oral iron or an unsatisfactory response to oral iron</td>
</tr>
<tr>
<td>- Prior to the first dose, a 25 mg test dose should be given over ≥30 seconds; observe for at least 1 hour before administering the remainder of the dose</td>
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</tbody>
</table>
| - Total dose based on table in package insert or calculation of iron deficit until 
Hb is within normal range and iron stores replete |
| - Given as 2 mL (100 mg) daily until full dose administered |
| - Off-label fixed dose: 1000 mg x 1 dose |
| None to date | BOXED WARNING: RISK FOR ANALPHYLACTIC-TYPE REACTIONS |
| (Patients must be observed for signs/symptoms of anaphylactic-type reactions; limit use to patients confirmed to be iron deficient, not amenable to oral iron) |
| Warnings for delayed reactions with large doses, increased risk with certain conditions, and iron overload |
| **Iron sucrose (Venofer)** | Treatment of IDA in patients with CKD |
| - 100 to 400 mg via slow IV push or IV infusion |
| - Dose and rate of administration based on CKD/dialysis status |
| In small observation and randomized trials: improves functional capacity, QOL, LVEF |
| Warnings for hypersensitivity reactions, hypotension, and iron overload |

CKD, chronic kidney disease; ESC, European Society of Cardiology; Hb, hemoglobin; HF, heart failure; ID, iron deficiency; IDA, iron deficiency anemia; IV, intravenous; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; 6MWD, 6-minute walk distance; RCT, randomized controlled trial; TSAT, transferrin saturation; QOL, quality of life.
The pharmacists’ role in educating providers about iron supplementation has been previously reported in patient populations both with and without HF. Karl and colleagues demonstrated the impact of pharmacist-driven education for family medicine residents regarding monitoring for ID and appropriate treatment in patients with HF. Following this educational initiative, more patients with HF were screened for and diagnosed with ID, and the residents noted the pharmacists’ role in education had solidified their commitment to appropriately monitor for ID in patients with HF. Within oncology, pharmacists are noted to be primary resources to address underutilization of iron supplementation that often stems from prescribers’ safety misconceptions or discomfort with product selection.

Pharmacists have demonstrated operational value toward improving the use of iron supplementation as well. In a population of patients with advanced HF supported with left ventricular assist devices, a pharmacist-run IV FCM program led to resolution of anemia, reduced blood product utilization, and reduced hospital admissions and was found to be cost-effective across a mix of payers. Wall and Gilmartin have each led efforts to describe the role of clinical pharmacists addressing IDA in patients with CKD. They report on the substantial benefits associated with pharmacist-assisted dosing protocols and the general role of a pharmacist in an anemia clinic, respectively.

Within the community setting where pharmacists remain the most accessible health care providers, pharmacists should strive to empower patients to have conversations about iron replacement therapy with their health care teams. Relative to diabetes or gout, patients may see ID as a less important comorbid condition, but pharmacists can provide education on the significant risks of ID in patients with HF and the various treatment options available. For example, a community pharmacist filling HF medications for a patient who has also been prescribed oral iron tablets can highlight the lack of data supporting oral iron supplementation and encourage the patient to discuss the proven benefits of IV iron supplementation with their provider. An observation that a patient is purchasing iron supplementation, or laxatives to combat the associated GI AEs, over the counter creates a similar education opportunity.

Within the acute to chronic continuum of HF care, pharmacists share several responsibilities to ensure effective utilization of IV iron replacement. Given the high frequency and morbidity associated with ID in patients with HF, especially in those who have worsened to the point of hospitalization, assessment of ferritin and TSAT should be standard on inpatient order sets, similar to what is recommended by the 2021 ESC Guidelines. Inpatient pharmacists can advocate for this addition to clinical protocols and pathways, ensure labs are drawn and evaluated, and help facilitate IV iron therapy. Inpatient pharmacists should communicate the diagnosis of ID and any treatment that has been initiated to their outpatient counterparts to ensure continuity and completion of the iron replacement.

Pharmacists in ambulatory settings should play similar roles. However, there is an increased need for a clear process for when patients will be assessed for ID in the course of their chronic management. If a lab workup for ID was not completed during the hospitalization, this should occur at the early post-discharge visit. Outside of the hospital, selection of an IV iron product may be less limited by an institution’s formulary and more dependent on insurance coverage, group contracting, 340B eligibility, and overall reimbursement. Pharmacists may be required to complete prior authorizations and/or enroll patients in patient assistance programs sponsored by manufacturers or independent third parties. Pharmacists should also promote the avoidance of erythropoietin-stimulating agents in the HF population in patients who do not have other compelling indications.

Based on the calculated ID and the patient’s length of stay, the location of some or all of the iron replacement course can vary. Inpatient and outpatient pharmacists can work together to ensure that treatment courses are both completed and not unnecessarily repeated. The logistics of this process may lead to the selection and utilization of iron products that have total dose or accelerated course options. Alternatively, there may

**ADDITIONAL RESOURCES**


be scenarios where it makes the most sense to defer all iron treatment to the outpatient setting. Consider an institution that utilizes ferric gluconate as their inpatient formulary product and FCM in the outpatient setting:

A patient has a calculated iron deficit of 1500 mg. A total of 375 mg is administered during an inpatient admission via 3 doses of ferric gluconate 125 mg. To complete the additional 1125 mg needed to adequately address their ID, the patient receives 2 doses of FCM 750 mg in the outpatient clinic. In this scenario, the patient ultimately receives 1875 mg of iron replacement. Alternatively, had the entire course of iron replacement been deferred to the outpatient setting, the deficit could be addressed through administration of 2 doses of FCM 750 mg, and both the cost and the potential risks of inpatient ferric gluconate would be avoided. Considering the anticipated length of stay and optimizing transitions of care can therefore improve clinical, economic, and patient satisfaction outcomes.

Pharmacists should take a leadership role within the health care team to manage the many operational considerations of IV iron therapy. First, as mentioned above, the setting of infusion needs to be determined while considering the clinical course of each patient as well as financial/reimbursement factors. Outpatient administration may require additional prior authorization but may be advantageous financially when billed in a single clinic encounter. The specific facility for outpatient infusions may differ between health systems with some utilizing infusion centers and others handling in private or hospital-based clinics. Each IV iron product has its own set of administration instructions, and the duration of infusion, requirement of a test dose, or the need to monitor patients for an extended period of time all require adequate staffing. Furthermore, administration in a clinic setting is likely going to require the IV iron product to be prepared/diluted in a separate facility capable of sterile compounding. Pharmacists are typically best situated to serve as liaisons between the two, but they may also take the opportunity to implement a strategy using an undiluted product given as slow IV push (such as FCM).

In any direct patient care scenario, pharmacists may be called on to participate in the management of infusion-related reactions and other AEs. These reactions/events may range from itching and flushing in their milder form, to shortness of breath, tachycardia, and changes in blood pressure in a more moderate presentation, to sudden onset and rapidly progressive symptoms including cyanosis, loss of consciousness, and cardiac/respiratory arrest at their most severe. Though extensive discussion of this practice is beyond the scope of this article,

Rampton and colleagues have published guidelines on risk minimization and management. These guidelines emphasize patient considerations that warrant increased monitoring, quick identification of infusion-related events, and severity-based treatment interventions.71

At a higher level, pharmacists should be involved in the formulary management process within their institution/health system to identify the most appropriate IV iron products for inclusion in formularies and protocols. Decision making should take into consideration dosing strategies, safety, efficacy, guideline recommendations, cost, and product availability/shortages. Thereafter, pharmacists should lead drug use evaluations to ensure that treatment protocols are being appropriately followed, with special attention paid to instances where the total exposure to IV iron either fails to fully address or oversupplements a patient’s ID. Though newer IV iron products appear to be fairly safe, addressing AEs, such as infusion-related reactions, through a systematic process is also an important contribution for clinical pharmacists.

**STAR**

What are additional ways that pharmacists across all practice areas and specialties can contribute to the identification and optimal treatment of ID in patients with HF?

**Conclusion**

HF medication therapy continues to grow and evolve with many new agents and treatment approaches being integrated
into clinical practice. The impact of ID in this patient population is profound and can significantly limit QOL, functional capacity, and survival. IV iron therapy, especially with FCM, has demonstrated the ability to improve patient outcomes and has been included in the recent HF guideline updates that govern care in the United States and Europe. With challenging decisions on product selection and optimal treatment strategies, pharmacists in all practice settings should work with health systems, HF teams, and patients to optimally treat ID and effectively manage transitions of care through the many settings patients with HF find themselves receiving care.

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60. Aronoff GR, Bennett WM, Blumenthal S, et al; United States Iron Sucrose (Venofier) Clinical Trials Group. Iron sucrose in hemodialysis patients: safety of replacement and maintenance regi-
INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.

Go to www.pharmacytimes.org/ID-HF to access the online version of this activity.

Click “Proceed,” then complete the online pretest.

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

Complete the online posttest and activity evaluation form.

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

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POSTTEST QUESTIONS

1. Which of the following has been associated with an increased risk of iron deficiency (ID) in patients with heart failure (HF)?
   A. Sodium-glucose cotransporter-2 inhibitor therapy  
   B. Elevated N-terminal pro-brain natriuretic peptide levels  
   C. Ischemic etiology of HF  
   D. Male sex

2. You are serving as the clinical pharmacist in an outpatient HF clinic seeing patients at their post-discharge visit. Your patient AD is a 60-year-old man diagnosed with HF with reduced ejection fraction (HFrEF) approximately 1 year ago who has had 2 hospitalizations in the past 6 months. During the most recent admission, he was diagnosed with ID. AD is surprised by the diagnosis and hesitant to start therapy for his ID. Which of the following would be the most accurate discussion point to highlight the importance of addressing AD’s ID?
   A. ID leads to more frequent hospitalizations but should not otherwise affect his quality of life.  
   B. If AD’s hemoglobin (Hb) can be corrected to normal levels, his health-related quality of life will significantly improve regardless of his ID.  
   C. Failure to correct ID will reduce AD’s ability to tolerate guideline-directed medical therapy.  
   D. AD’s ID will decrease his exercise tolerance and increase his risk of further hospitalizations.

3. According to the most recent American HF guidelines (the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America Guideline for the Management of Heart Failure), which of the following would be diagnostic for ID in a patient with HF?
   A. Hb 14.2 g/dL, ferritin 145 ng/mL, transferrin saturation (TSAT) 18%  
   B. Hb 12.0 g/dL, ferritin 530 ng/mL, TSAT 25%  
   C. Hb 13.5 g/dL, ferritin 110 ng/mL, TSAT 22%  
   D. Hb 9.5 g/dL, ferritin 350 ng/mL, TSAT 18%

The following scenario should be used for questions 4 and 5.

SH is a 56-year-old man with HFrEF who is being seen in the outpatient HF clinic. His vitals/lab results are remarkable for: weight 85 kg, left ventricular EF 35%, serum creatinine 1.12 mg/dL, Hb 10.2 g/dL, ferritin 67 ng/mL, TSAT 20%, serum iron 100 mcg/dL.

4. Assuming a target Hb of 15.0 g/dL and the standard 500 mg addition for iron stores, what is SH’s calculated ID per the Ganzoni equation?
   A. 700 mg  
   B. 1240 mg  
   C. 1480 mg  
   D. 1680 mg

5. Based on current HF treatment guidelines from the United States and Europe, which of the following regimens would be the most appropriate to treat SH’s ID?
   A. Iron polysaccharide 150 mg by mouth twice daily  
   B. Iron sucrose 300 mg intravenous (IV) every 48 hours x 5 doses  
   C. Ferric gluconate 125 mg IV twice daily x 5 days  
   D. Ferric carboxymaltose (FCM) 750 mg IV weekly x 2 doses

The following scenario should be used for questions 6 and 7.

As a clinical pharmacist working with the HF team, you have been tasked to develop a protocol for screening for, diagnosing, and treating ID in patients who have been admitted to the hospital for acute HF events.

6. You have reviewed all of the available literature on treating ID in HF in both the inpatient and outpatient settings. Based on the _______ trial, you plan to include _______ as the preferred iron product in the protocol for patients currently admitted for acute HF events.
   A. AFFIRM-AHF; FCM  
   B. CONFIRM-HF; FCM  
   C. FERRIC-HF; iron sucrose  
   D. IRONMAN; ferric derisomaltose
POSTTEST QUESTIONS (continued)

7. Which of the following would be an important responsibility for you as the clinical pharmacist for patients who are receiving treatment per this new protocol?
   A. Discharge counseling on the likelihood of constipation with the new prescription oral iron polysaccharide that is included in the protocol for all patients
   B. Communicating with the outpatient HF pharmacist to ensure that a patient’s iron replacement course is appropriately completed in the clinic setting based on how much IV iron they received while admitted
   C. Educating nurses on the HF floor about the signs and symptoms of the common hypersensitivity reactions associated with the IV iron product you selected in question 6
   D. Ordering repeat iron studies including ferritin and TSAT to be drawn 1 week after the completion of the treatment course to ensure that the iron deficit was completely corrected

8. Which IV iron product has the highest risk of anaphylaxis and serious hypersensitivity reactions?
   A. Iron dextran
   B. Iron sucrose
   C. Ferric derisomaltose
   D. FCM

9. A group of cardiologists at your institution have asked that an IV iron product be added to formulary. Which of the following would be an accurate statement to include in your evaluation to present to the pharmacy and therapeutics committee who is considering this request?
   A. Though reports of their use in patients with HF are limited to smaller sample sizes, accelerated IV iron supplementation with sodium ferric gluconate or ferric derisomaltose may allow for more rapid correction of an iron deficit while a patient is admitted to the hospital.
   B. Current product labeling requires a test dose for iron dextran and ferumoxytol due to their boxed warnings for anaphylaxis and severe hypersensitivity reactions.
   C. Iron sucrose would allow for the most rapid correction of ID, as it can be given at up to 1000 mg per dose.
   D. FCM is the product of choice based on a number of retrospective reviews, but large randomized trials are ongoing to strengthen the level of evidence for this recommendation.

10. Which statement provides the most accurate description of the relationship between ID and anemia in patients with HF?
     A. Whereas ID often occurs without anemia, the benefits of IV iron replacement are limited to patients with associated anemia.
     B. Per the current American HF treatment guidelines, a diagnosis of ID requires an Hb less than 12.0 g/dL in women and less than 13.0 g/dL in men.
     C. Approximately half of all patients with HF, regardless of the presence of anemia, are iron deficient.
     D. The anemia associated with HF increases hepcidin, which reduces intestinal absorption of dietary iron, leading to ID.
Pharmacists have essential roles as identifiers, educators, and advocates for patients with or at risk of COVID-19 and related complications. This webinar curriculum series will focus on current management and preventive recommendations from the National Institutes of Health and Infectious Diseases Society of America, as well as other health organizations, regarding the treatment of COVID-19. The emergence of new viral genetic variants has greatly impacted existing knowledge on disease transmission and patient outcomes, and the evolving scope of information has led to continuous updates to treatment guidelines. As additional clinical data become available for treatment options for COVID-19, pharmacists must expand their knowledge of the efficacy and safety of the agents approved or authorized for treatment or prevention of COVID-19 infection as well as agents under investigation. This activity will focus on the importance of outpatient treatment and the role of pharmacists in minimizing the burden of COVID-19 through prompt evaluation and treatment of patients to minimize hospitalizations. The 3 webinars in this series will contextualize the currently recommended treatment guidelines and recent and ongoing studies and publications so pharmacists will be able to improve their clinical decision making and offer recommendations regarding the treatment of COVID-19 to reduce complications for patients. Additional components of this resource center will include an Ask the Expert activity and podcast, which will offer discussion on additional updates regarding the management of COVID-19. Participants who complete all 5 CE activities within this curriculum will receive a certificate of completion acknowledging their commitment to educating and advocating for patients during the COVID-19 pandemic.

Due to the evolving nature of COVID-19, information related to this topic is quickly changing. These activities included the most up-to-date information and available data at the time of the development of these webinars, but please continue to stay updated as information related to COVID-19 and associated therapies continues to change.
Non-Valvular Atrial Fibrillation, Obesity, and the Use of DOACs: Considerations for Pharmacists

Introduction
Atrial fibrillation (AF) is a common cardiac conduction disturbance wherein disorganized electrical activity in the atria results in loss of effective contraction. The prevalence of AF in the United States was estimated at 5.2 million in 2010 and is expected to rise to 12.1 million by 2030. AF poses significant burdens on both patients and the health care system. It is associated with increased risk of stroke, myocardial infarction, heart failure, cognitive decline, and mortality. AF is a leading cause of hospitalizations in the United States and has significant financial burden on the health care system. There are several major risk factors for the development of AF. While hypertension (HTN) is the highest population attributable fraction for AF, body mass index (BMI) greater than or equal to 25 is second highest, signifying the burden of elevated BMI and obesity on the prevalence of AF.

Obesity is considered an international epidemic, and rates continue to increase worldwide. In the United States, the prevalence of obesity was 42.4% in 2017-2018. Additionally, significant health disparities are present in obesity, including a higher percentage of Black and Mexican American individuals affected compared with White individuals and higher prevalence in less educated and lower-income groups. Obesity is a major risk for several diseases including cardiovascular disease (CVD), diabetes, musculoskeletal disorders, and some cancers. The World Health Organization defines obesity as a BMI greater than or equal to 30 kg/m². Obesity has been further subdivided into the following classes: class 1: BMI 30 to less than 35; class 2: BMI 35 to less than 40; and class 3: BMI of 40 and higher. Class 3 is often termed “severe” or

Interactive Simulation of Patient Cases
This article includes a unique and interactive patient simulation activity that will guide you through clinical decision making for patients with obesity who require use of DOACs. Access the simulation at www.pharmacytimes.org/NVAF
“morbid” obesity. While BMI is not a direct measurement of body fat, it is considered to be moderately correlated with body fat measurements obtained from methods such as skinfold thickness, bioelectrical impedance, underwater weighing, and dual energy x-ray absorptiometry.5

Physiologic disturbances and structural changes in obesity can lead to the development of AF. While atrial remodeling is a hallmark feature in all patients with AF, obesity independently contributes to structural changes secondary to increased blood volume, HTN, and epicardial adipose tissue.4 Inflammatory mediators are thought to play a direct role between epicardial adipose tissue and resulting AF through development of fibrosis and other cell signaling that affects conduction.4,5 Additionally, obesity is commonly associated with the development of other disease states that promote AF, such as HTN, diabetes, coronary artery disease, heart failure, and obstructive sleep apnea. Interestingly, obesity has been associated with lower rates of mortality, stroke, and bleeding in AF and CVD compared with the nonobese population. This phenomenon has been termed the “obesity paradox” and is well described in several studies.6,7 Despite obese patients developing disease earlier in life, living with it longer, and having a shorter life span than the general population, it is thought these factors may contribute to lower short-term risk of CVD states, and the earlier diagnosis and treatment may also confound outcome comparisons between populations.8

Given the large burden of obesity and its significant impact on the development of AF, it is important to consider how obesity might impact drug therapy for AF and associated outcomes. Direct oral anticoagulants (DOACs) have become the mainstay of treatment for prevention of stroke and systemic embolism (SSE) in AF. DOACs are recommended over warfarin due to faster gastric emptying time, increased gut wall permeability, and increased splanchic blood flow; however, these have often not equated to an increased oral bioavailability of drugs in obese patients.9 Volume of drug distribution can be significantly impacted in obese patients due to increased adipose tissue, increased lean mass, increased extracellular fluid volume, and alterations in plasma proteins.9,10 Drug-specific properties will determine the extent of alteration in distribution. For lipophilic drugs, volume of distribution will generally be increased due to the drug’s high affinity for adipose tissue. Hydrophilic drugs with small volumes of distribution can also be impacted by degree of obesity due to increases in lean body mass and extracellular fluid.9,10 However, volume of distribution is also impacted by drug ionization, protein binding, and tissue perfusion. Hepatic metabolism may be affected by the presence of nonalcoholic fatty liver disease, increased cardiac output, and increased blood volume in obese individuals.9 Various alterations in liver enzymatic activity have been described as well as increased hepatic clearance of certain drugs; however, this effect may be unpredictable. Additionally, obesity is associated with increased glomerular filtration rates and tubular secretion that primarily affects hydrophilic drugs that are renally eliminated.9,10

The PK profiles of the individual DOACs in healthy volunteers have been well described (TABLE 111-16). These parameters can be utilized to theorize potential alterations in volume of distribution and elimination in obese individuals. However, it is important to keep in mind that several physiochemical drug properties are responsible for the overall effect and can be unpredictable until directly evaluated. Dabigatran is a direct thrombin inhibitor and hydrophilic with low protein binding resulting in a high proportion of renal elimination that could result in increased drug clearance in obese patients.11,17 The factor Xa inhibitors are moderately lipophilic with octanol-
Water partition coefficient values of 0.67 for edoxaban, 2.18 for rivaroxaban, and 2.71 for apixaban. However, rivaroxaban and apixaban are also highly protein bound, thus limiting their volume of distribution and likelihood for alteration in obesity. For drugs that undergo renal elimination, such as the DOACs, estimation of renal function is important in determining maintenance dosing. The Cockcroft-Gault (CG) equation was utilized in DOAC clinical trials to determine drug dose adjustment. Concern has been raised regarding the accuracy of renal function estimation by the CG method compared with other estimation equations. In obese individuals, determination of the appropriate weight to use in the CG calculation is controversial. Total body weight (TBW) was used in the original CG study; however, obese and morbidly obese individuals were not included. TBW was also used for renal estimation in the DOAC clinical trials, which included some obese patients and very limited morbidly obese patients. There is legitimate concern that TBW could overestimate renal function in obese patients and risk overexposure in obese patients with concomitant renal dysfunction and/or advanced age. Nevertheless, because this was the method used in clinical trials in which the dose adjustments were assessed for safety and efficacy, the current recommendation is to use TBW in renal function estimation. Utilization of an ideal or adjusted body weight has not been studied and may have unintended consequences.

PK studies evaluating drug exposure in obese patients have been published for rivaroxaban and apixaban (Table 2). It is important to consider the weight range and BMI of the included study population when determining applicability to a clinical practice scenario. A single dose of rivaroxaban 10 mg resulted in similar peak concentrations and area under the concentration-time curve (AUC) in obese and nonobese individuals. Prothrombin time prolongation decreased significantly in the obese group, but AUC was similar. The authors concluded the effect of obesity on rivaroxaban PK and pharmacodynamic (PD) parameters was small. A single dose of apixaban 10 mg resulted in a mean peak and AUC that were 31% and 23% lower, respectively, in obese patients compared with nonobese patients. Similarly, there was a trend toward lower mean anti-factor Xa activity in the obese group. These changes were thought to be explained by the increase in volume of distribution and nonrenal clearance that was seen in the obese group. The authors concluded these effects to be modest and unlikely of clinical relevance. While direct PK studies in obesity are not published for dabigatran, these effects have been estimated by PK model simulation. PK data from the RE-LY trial was used for model simulation and demonstrated an increase in dabigatran volume of distribution with increasing body weight (Table 2). However, these simulations showed no impact of body weight on steady state AUC. PK studies assessing edoxaban exposure in obesity have not been published.

### Table 1. Dosing and Pharmacokinetic Profiles of DOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AF dosing</strong></td>
<td>150 mg BID; CrCl 15-30: 75 mg BID</td>
<td>20 mg daily; CrCl ≤50: 15 mg daily</td>
<td>5 mg BID; if meets 2 of the following: age ≥80, weight ≥60 kg, SCr ≥1.5: 2.5 mg BID</td>
<td>60 mg daily; CrCl 15-50: 30 mg daily; CrCl &gt;95: do not use</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>With or without food; do not open capsules, swallow whole</td>
<td>Take with evening meal; may be crushed</td>
<td>With or without food; may be crushed</td>
<td>With or without food; may be crushed</td>
</tr>
<tr>
<td><strong>Absorption</strong></td>
<td>3%-7% BA, C&lt;sub&gt;max&lt;/sub&gt; 1-3 hours</td>
<td>&gt;80% BA, C&lt;sub&gt;max&lt;/sub&gt; 2-4 hours</td>
<td>50% BA, C&lt;sub&gt;max&lt;/sub&gt; 3-4 hours</td>
<td>62% BA, C&lt;sub&gt;max&lt;/sub&gt; 1-2 hours</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>50-70 L, 35% protein bound</td>
<td>50 L, 92%-95% protein bound</td>
<td>≈21 L, 87% protein bound</td>
<td>107 L, 55% protein bound</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>12-14 hours</td>
<td>5-9 hours</td>
<td>12 hours</td>
<td>10-14 hours</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>20% biliary excretion</td>
<td>51% CYP3A4/5; CYP2J2; hydrolysis</td>
<td>≈25% Major: CYP3A4, Minor: CYP1A2, 2C8, 2C9, 2C19, 2J2</td>
<td>≈10% hydrolysis conjugation, CYP3A4</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>80% unchanged in urine</td>
<td>36% unchanged in urine; majority by tubular secretion via P-gp/BCRP</td>
<td>≈34% unchanged in feces; ≈21% unchanged in urine</td>
<td>≈40% biliary/intestinal secretion 50% unchanged in the urine</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; BA, bioavailability; BCRP, breast cancer resistance protein; BID, twice daily; C<sub>max</sub>, maximum concentration; CrCl, creatinine clearance; CYP, cytochrome P450; L, liter; P-gp, p-glycoprotein; SCr, serum creatinine.
**TABLE 2. DOAC PHARMACOKINETIC EVALUATIONS IN OBESITY**21-23

<table>
<thead>
<tr>
<th>Population Results</th>
<th>Nonobese group</th>
<th>Obese group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>BMI (kg/m²)</td>
<td>Weight (kg)</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese (n = 12)</td>
<td>74.0 ± 2.2</td>
<td>132.2 ± 9.9</td>
</tr>
<tr>
<td>Nonobese (n = 12)</td>
<td>(70-80)</td>
<td>(&gt;120)</td>
</tr>
<tr>
<td></td>
<td>24.3 ± 2.3</td>
<td>43.5 ± 4.2</td>
</tr>
<tr>
<td>• Similar peak and AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lower mean PT prolongation in obese patients (P &lt; .001), similar AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese (n = 19)</td>
<td>75 ± 5.5</td>
<td>137 ± 18.3</td>
</tr>
<tr>
<td>Nonobese (n = 18)</td>
<td>(67-84)</td>
<td>(120-175)</td>
</tr>
<tr>
<td></td>
<td>26.3 ± 2</td>
<td>42.6 ± 6</td>
</tr>
<tr>
<td>(22-30)</td>
<td>(32-54)</td>
<td></td>
</tr>
<tr>
<td>• 31% lower peak, 23% lower AUC in obese patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Inverse relationship between apixaban exposure and body weight (P &lt; .001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Increased Vd and nonrenal clearance in obese patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>Mean: 82.7 ± 19.5 kg</td>
<td></td>
</tr>
<tr>
<td>n = 9522</td>
<td>Range: 32.7-222.3 kg</td>
<td></td>
</tr>
<tr>
<td>• Each 1-kg increase above 80 kg resulted in 0.77% increase in Vd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No effect on steady state AUC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are displayed as mean ± standard deviation (range). AUC, area under concentration-time curve; BMI, body mass index; PT, prothrombin time; Vd, volume of distribution.

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**AF Clinical Outcomes in Obese Patients Receiving DOACs**

**Phase 3 Clinical Trials**

Phase 3 clinical trials evaluating the efficacy of DOACs for SSE prevention demonstrated similar or improved efficacy outcomes compared with warfarin and a reduction in intracranial hemorrhage.24-27 These trials included limited numbers of obese and morbidly obese patients for which a post hoc subgroup analysis was completed and is discussed in the following sections (TABLE 324-30). As previously described, an obesity paradox was observed wherein event rates were lower in patients with high body weight or obesity. Besides the general limitations of post hoc analysis, some of the data reported for weight and BMI had limited usefulness. For example, it is unclear how the described weight classifications were selected for grouping patients for analysis and these classifications varied across trials, limiting the ability to compare populations. BMI was not well described in all trials. Additionally, some of the ranges of BMIs overlapped overweight and obese individuals into the same group, limiting the usefulness in describing events in an obese population.

**Dabigatran**

In RE-LY, patients with AF and a CHADS2 score of 1 or higher were randomized to either dabigatran 150 mg or 110 mg twice daily, or warfarin.24 In the overall study population, dabigatran was noninferior to warfarin for prevention of SSE and dabigatran 150 mg met statistical significance for superiority compared with warfarin. Major bleeding was significantly reduced compared with warfarin in the dabigatran 110 mg group and similar to warfarin in the 150 mg group. The mean weight and standard deviation of the overall study population was 83 ± 19 kg and ranged up to 222 kg. Fifty percent of the population had a BMI greater than or equal to 28, but no further description was reported. The post hoc analysis found no interaction between weight or BMI on the primary outcome of SSE. Analyses of bleeding outcomes were not reported. Subsequently, further analysis of outcomes according to BMI was published in abstract form.31 Patients were divided into the bottom 10% of BMI (≤22.5 kg/m²), the middle 80% (22.5 to ≤36 kg/m²), and the upper 10% (>36 kg/m²). Consistent with the overall trial results, SSE was lower in patients who received dabigatran 150 mg compared with dabigatran 110 mg or warfarin in all BMI subgroups.

**Rivaroxaban**

In ROCKET-AF, patients with AF and a CHADS2 score of 2 or higher were randomized to rivaroxaban 20 mg daily or warfarin.25 In the overall study population, rivaroxaban
met noninferiority criteria for reduction in SSE compared with warfarin. The primary safety end point of major and nonmajor clinically relevant bleeding was similar between groups. The median weight of the study population was 73 kg (interquartile range [IQR], 65-78), and median BMI was 28 (IQR, 25-32). The post hoc analysis by weight category was not very insightful due to the weight cut points used (TABLE 3). Roughly 14% of the population had a BMI greater than 35. The post hoc analysis of efficacy and safety outcomes according to BMI was consistent with overall trial results and showed no significant interaction between BMI and treatment effect.

### Apixaban

In ARISTOTLE, patients with AF and a CHADS2 score of 1 or higher were randomized to apixaban 5 mg twice daily or warfarin. In the overall study population, apixaban significantly reduced the risk of SSE (P = .01 for superiority) and major bleeding compared with warfarin. The median weight of the overall study population was 82 kg (IQR, 70-96). Post hoc analyses categorized patients by weight and BMI to assess outcomes between groups. Patients were categorized as low weight (≤60 kg based on the dose-reduction criteria), high weight (>120 kg, based on the International Society of Thrombosis and Hemostasis [ISTH] cutoff for DOAC), and midrange weight (>60-120 kg). Efficacy outcomes were similar to overall trial results when comparing apixaban with warfarin across weight subgroups. There was a significant interaction between weight and major bleeding, with the risk of bleeding being higher in low and midrange body weight.

| Table 3. Outcomes According to Patient Weight or BMI from Phase 3 Clinical Trials |
|---------------------------------|-------------------------------------------------|---------------------------------|---------------------------------|
|                                 | Patients total number (%) | Stroke/systemic embolism | Major bleeding |
|                                 |                                | DOAC | VKA | P value | DOAC | VKA | P value |
| Re-Ly*                          |                                |      |     |         |      |     |         |
| BMI (kg/m²)                     |                                |      |     |         |      |     |         |
| <50 kg                          | 376 (2)                        | 2.24 | 5.04 | 0.42    | --   | --   | --      |
| 50-99 kg                        | 14,629 (81)                    | 1.14 | 1.77 | 0.04    | --   | --   | --      |
| ≥100 kg                         | 3099 (17)                      | 0.87 | 0.94 | --      | --   | --   | --      |
| ≥28                             | 9131 (50)                      | 1.17 | 2.01 | 0.21    | --   | --   | --      |
| ≥28                             | 8962 (49)                      | 1.04 | 1.34 |         | --   | --   |         |
| Rocket-AFb*                     |                                |      |     |         |      |     |         |
| BMI (kg/m²)                     |                                |      |     |         |      |     |         |
| <70 kg                          | 4025 (28)                      | 4.62 | 5.42 | 0.71    | 3.14 | 3.88 | 0.78    |
| 70-90 kg                        | 6166 (44)                      | 4.16 | 4.82 |         | 3.04 | 4.12 |         |
| >90 kg                          | 3977 (28)                      | 2.46 | 2.37 |         | 1.67 | 1.86 |         |
| ≥25                             | 3445 (24)                      | 4.25 | 5.6  | 0.54    | 2.91 | 4.3  | 0.69    |
| 25 to ≤35                       | 8826 (62)                      | 3.83 | 4.08 |         | 2.75 | 3.28 |         |
| >35                             | 1891 (14)                      | 2.88 | 2.94 |         | 1.96 | 2.4  |         |
| ARISTOTLEa                      |                                |      |     |         |      |     |         |
| BMI (kg/m²)                     |                                |      |     |         |      |     |         |
| ≤60 kg                          | 1985 (11)                      | 2.01 | 3.2  | 0.64    | 2.33 | 4.28 | 0.02    |
| 60-120 kg                       | 15,172 (84)                    | 1.23 | 1.44 |         | 2.15 | 3.02 |         |
| >120 kg                         | 982 (5)                        | 0.44 | 1.13 |         | 1.55 | 2.08 |         |
| ≥25                             | 4052 (22)                      | 1.65 | 2.36 | 0.41    | 2.22 | 4.70 | 0.006   |
| 25 to <25                       | 6702 (37)                      | 1.37 | 1.47 |         | 2.04 | 2.82 |         |
| ≥30                             | 7159 (39)                      | 0.97 | 1.28 |         | 2.12 | 2.51 |         |
| Engage-AFbc*                    |                                |      |     |         |      |     |         |
| BMI (kg/m²)                     |                                |      |     |         |      |     |         |
| ≤55 kg                          | 1082 (5)                       | 7.3  | 6.5  | 0.52    | 5.3  | 9.3  | 0.35    |
| 79.8-84 kg                      | 2153 (10)                      | 3.5  | 4.7  |         | 5.8  | 7.7  |         |
| ≥120 kg                         | 1093 (5)                       | 2.1  | 1.6  |         | 6.3  | 6.5  |         |
| ≥25                             | 4491 (21.4)                    | 2.1  | 2.1  | 0.16    | 3.2  | 3.7  | 0.81    |
| 25 to <30                       | 7903 (37.6)                    | 1.6  | 2.1  |         | 2.7  | 3.7  |         |
| ≥30                             | 5209 (24.8)                    | 1.3  | 1.8  |         | 3.0  | 3.3  |         |
| 35 to <40                       | 2099 (10)                      | 1.2  | 1.0  |         | 2.3  | 3.4  |         |
| ≥40                             | 1149 (5.5)                     | 0.8  | 0.5  |         | 2.9  | 3.5  |         |

BMI, body mass index; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

*Event rates are reported for the approved dose of DOACs.

% per year.

Total event rate, %.

Rate per 100 patients per year.

P value for interaction.
patients treated warfarin compared with apixaban, but similar risk between agents in patients greater than 120 kg. A small number of patients were more than 140 kg (1.4%), and event rates were so low in this population that a separate analysis was unable to be completed. If BMI information was available, patients were assessed by normal, overweight, or obese BMI (Table 3). Similar to the weight analysis, no treatment interaction was identified for SSE across BMI categories. Obese patients did not have the significant reduction in major bleeding that was seen in the normal and overweight populations with the use of apixaban.

**Edoxaban**

In ENGAGE-AF, patients with AF and a CHADS2 score of 2 or higher were randomized to either edoxaban 60 mg or 30 mg once daily, or warfarin. In the overall study population, both edoxaban doses met criteria for noninferiority in prevention of SSE compared with warfarin. Edoxaban 60 mg met statistical significance for superiority compared with warfarin and was selected for FDA approval based on the PK and clinical data. Major bleeding was significantly reduced in both edoxaban groups compared with warfarin. Post hoc subanalyses for the primary efficacy and safety end points were completed according to BMI and body weight. Of the total of approximately 21,000 patients included in the trial, roughly 40% were classified as obese (BMI ≥30) and 5.5% of the total population were morbidly obese (BMI ≥40). In warfarin patients, time in therapeutic range increased as BMI increased, driven by a lower median time in therapeutic range in underweight patients. In patients receiving edoxaban, median trough concentrations at 1 month were similar across BMI groups. When comparing outcomes between the edoxaban 60 mg and warfarin groups, there was no significant interaction according to BMI category for the primary efficacy or safety outcomes. However, there was a higher rate of ischemic SSE in the edoxaban group compared with warfarin for patients with a BMI greater than or equal to 40 (P = .047). These data should be interpreted with caution given the low overall event rate in this BMI category (10 events). Outcomes were also evaluated according to weight class: low body weight (≤55 kg, bottom 5th percentile), middle body weight (79.8-84 kg, 45-55th percentile), and high body weight (≥120 kg, top 5th percentile). The risks of SSE and major bleeding were similar between edoxaban 60 mg and warfarin for each of the 3 groups.

An additional consideration in obese patients is the impact of the renal restrictions in the FDA labeling. Avoidance of edoxaban is recommended in patients with an estimated creatinine clearance (CrCl) greater than 95 mL/min. In ENGAGE-AF, patients with high body weight (≥120 kg) had a median CrCl of 129 mL/min (IQR, 105.6-157.7 mL/min), which would prohibit use per FDA labeling. Although the necessity of this restriction has been questioned based on the discordant results from the obese and renal subgroup analyses, it will nonetheless limit use of edoxaban in the obese population.

**Real-World Experience**

Despite limited prospective data for the use of DOACs in obese and morbidly obese patients, real-world utilization in this population expanded due to increasing frequency with which obesity is encountered in the AF population and the known advantages of DOACs in the general population. Real-world, observational studies have been published that describe DOAC-associated outcomes in obese and morbidly obese patients with AF. While observational studies have several limitations, such as potential for selection bias and confounders to impact results, they can share valuable insights into real-world practices and into patient populations that may not be evaluated in randomized controlled trials.

There are many published observational cohort studies describing the use of DOACs in the obese population. These studies range in size from fewer than 100 patients to large registry analyses. Details for some of the larger, recently published cohort studies are described in Table 4. Many of the studies evaluated outcomes in the morbidly obese population (BMI ≥40) where data from phase 3 trials are lacking. Some limitations of the cohort data include method of identification of the study population (ie, billing codes vs patient level data), inability to confirm appropriate DOAC dosing, and potential for underlying prescribing bias and other confounders not able to be accounted for in an adjusted analysis. Therefore, it is important to reflect on the collective data as a whole and associations that were identified in multiple datasets. The majority of cohort studies associated DOAC use with similar or improved efficacy outcomes in the obese and morbidly obese populations compared with the use of warfarin in these patients or compared with nonobese populations. Generally, a reduction in bleeding outcomes was also associated with DOAC use. Additionally, several meta-analyses and systematic reviews utilizing clinical trial data and/or cohort data have not associated the use of DOAC with efficacy or safety concerns in obese or morbidly obese patients.
Few studies compared outcomes among DOACs and there are not enough data to clearly hypothesize the preference of one over another in this population. Substantial numbers of patients received rivaroxaban, apixaban, or dabigatran in the real-world data, and 3 large analyses solely evaluated rivaroxaban or dabigatran. Edoxaban is the least well described in the observational data, likely due to its late market appearance and low overall use in the general population. The limited data for use and restriction in patients with CrCl greater than 95 mL/min make edoxaban less suitable for selection in this population compared with the other agents, especially in the morbidly obese. Overall, most cohort studies did not describe the BMI distribution nor the BMI range that was captured in the patient populations greater than or equal to 40 kg/m². It is possible that patients with more severely elevated BMI, such as greater than 55 kg/m², remain underrepresented in these cohort studies and caution may need to be exercised in these patients.

### STAR

Describe the efficacy and safety outcomes associated with DOACs in obese and morbidly obese patients.

### Current Guideline Recommendations

Few guidelines specifically address the use of DOACs in the obese population. In 2016, the ISTH published a guidance statement that recommended avoiding DOACs for SSE prevention in AF and venous thromboembolism (VTE) prevention and treatment in patients with a BMI greater than 40 kg/m² or a weight greater than 120 kg based on the limited clinical data and PK/PD data suggesting reduced exposure and shorter half-lives with increasing weight. Furthermore, if DOACs were used in this population, they suggested obtaining drug-specific peak and trough levels to confirm they fell within the expected on-treatment ranges. DOAC use in

### Table 4. Select Observational Cohort Studies Evaluating AF Outcomes in Obese Patients on DOACs

<table>
<thead>
<tr>
<th>BARAKAT 2021</th>
<th>Population*, n (%)</th>
<th>DOAC, n (%)</th>
<th>Comparator, n</th>
<th>Results: DOAC vs comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5: 455 (1.3)</td>
<td>A: 8899 (48)</td>
<td>W: 17,640</td>
<td>• Reduced risk of stroke (all BMI groups)</td>
<td></td>
</tr>
<tr>
<td>18.5 to &lt;30: 18,339 (50.8)</td>
<td>R: 6834 (37)</td>
<td>• Reduced risk of bleeding (morbidly obese group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 to &lt;40: 13,376 (37.1)</td>
<td>D: 2700 (15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥40: 3924 (10.9)</td>
<td>E: 21 (0.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| COATES 2021 | ≤120 kg: 3522 | D: >120 kg | No difference in composite of stroke/SE, clinically relevant bleeding, all-cause mortality |
| 120 kg: 777 | |

| O’KANE 2021 | <30: 296 | A: 181 | Similar rates of stroke and major bleeding |
| ≥50: 299 | R: 118 | |
| Median BMI: 54.8 | BMI <30 | |
| BMI range: 50-97.8 | BMI ≥30 | |

| BRIASOULIS 2020 | ≥120 kg: 28,011 | A: 4471 (41) | • D and R similar risk of stroke; A, increased risk of stroke |
| Subgroup: | R: 3246 (29) | • All reduced risk of major bleeding |
| BMI >40: 16,426 | R: 5299 (30) | |
| W: 10,338 | • Similar risk of stroke |
| • Reduced risk of major bleeding |

| COSTA 2020 | ≥30: 34,174 | R: 35,613 | • Reduced risk of stroke/SE and major bleeding |
| 35 to <40: 19,017 (27) | R: 35,613 | Results consistent for all BMI groups |
| ≥40: 18,034 (25) | W: matched 1:1 | |

| DEITELZWEIG 2020 | ≥30: 88,461 | R: 22,053 (47) | • R and A reduced risk of stroke/SE; D, similar risk of stroke/SE |
| 35 to <40: 61,417 (73) | A: 18,181 (39) | • A and D reduced risk of major bleeding; R, similar risk of major bleeding |
| ≥40: 18,034 (25) | D: 6646 (14) | W: matched 1:1 |

| PETERSON 2019 | ≥40: 7126 | R: 3563 | • No difference in stroke/SE or major bleeding |

A, apixaban; BMI, body mass index; D, dabigatran; E, edoxaban; R, rivaroxaban; SE, systemic embolism; W, warfarin

*BMI expressed as kg/m².
obese patients up to a BMI of 40 kg/m² or weight of 120 kg was considered appropriate. This guidance predates a majority of the published large, real-world, registry analyses. Similar guidance was also incorporated into American and European AF treatment guidelines. In 2018, the European Heart Rhythm Association updated their practical guide for the use of DOACs in patients with AF. Consistent with the ISTH recommendations, they suggest use of vitamin K antagonists in patients with a BMI greater than or equal to 40 kg/m² or weight greater than 120 kg due to the limited data for DOACs. In 2019, the American Heart Association/American College of Cardiology/Heart Rhythm Society released a focused update to the AF treatment guidelines. While they make no recommendation for or against DOACs in the morbidly obese population, they state DOAC drug levels may be indicated for evaluation of drug absorption in severely obese patients (BMI >35 or weight >120 kg).

Most recently in 2021, the ISTH updated their 2016 guidance for DOAC use in obesity, specific to VTE prevention and treatment. For patients with a BMI greater than 40 kg/m² or weight greater than 120 kg, they now suggest rivaroxaban or apixaban are among appropriate options for VTE treatment, regardless of high BMI and weight. They suggest against the use of dabigatran or edoxaban for VTE treatment in this population based on “unconvincing” data for dabigatran and lack of data for edoxaban. They also suggest against regularly following peak or trough drug-specific DOAC levels because there are insufficient data to influence management decisions. It is important to note that this guidance is specifically for VTE treatment based on the scope of the literature review that was conducted for that statement. However, these updated recommendations demonstrate the incorporation of cohort data and meta-analyses to guide use of these agents in an area otherwise lacking clinical trial data. Similar, if not more, data are available in the AF population and a similar update would be expected that included the use of rivaroxaban, apixaban, or dabigatran in morbidly obese patients with AF. Use of edoxaban in the morbidly obese will likely remain limited due to lack of data.

Role of the Pharmacist
The pharmacist plays an integral role in ensuring the safe and efficacious use of anticoagulation therapy through drug therapy selection, dosing, education, and follow-up. The pharmacist can guide appropriate drug therapy selection by integrating critical appraisal of the literature with patient-centered care. While the benefits of DOAC over warfarin are well recognized in the general population, expanded use into special populations, such as obesity, requires weighing available options and utilizing available data and experience to determine if expanded use is acceptable. This includes incorporation of additional patient characteristics into drug selection, such as end-organ function, age, concomitant drug therapies, and other comorbidities that may impact bleeding risk, thrombosis risk, or drug effect. As a trusted and accessible medical professional, the pharmacist can also engage the patient to take an active role in their health and medication decisions and management. The patient should discuss their preferences for a given medication, lifestyle factors that may impact adherence and follow-up, and medication affordability.

If a DOAC is selected, the pharmacist should ensure an appropriate dose is prescribed based on approved labeling and appropriate calculation of renal function (eg, CG formula using total body weight and actual serum creatinine). Several observational studies have described inappropriate, off-label DOAC dosing in the general population and its potential association with poor outcomes, including increased bleeding and stroke risk. Inappropriate dosing by a provider may be an intentional effort to balance perceived risks of therapy or may be an unintentional misunderstanding of labeled dosing or renal function estimation. The pharmacist should address all inappropriate dosing through direct provider education and should be involved with implementation of tools, such as order sets and alerts, that help direct appropriate prescribing throughout the health care system. The pharmacist is also responsible for patient education to facilitate appropriate administration, knowledge and self-monitoring of adverse effects, and compliance. Patient education should include discussion of the following: (1) bleeding risk including specific examples of common or life-threatening bleeding and appropriate patient response (eg, nose bleeding, gastrointestinal bleeding, intracranial hemorrhage, and when to engage emergency services), (2) ischemic stroke risk (eg, signs and symptoms of stroke, and the need to promptly engage emergency services), (3) appropriate timing and drug administration technique (TABLE 1), (4) the potential for drug interactions including specific examples of over-the-counter medications to avoid, (5) avoidance of high-risk activities that may cause bleeding (eg, contact sports), and (6) the importance of compliance and follow-up.

As advised in major guidelines, routine assessment of DOAC drug activity levels should be discouraged, including in most obese individuals. The “on-treatment” drug level ranges observed
in phase 2/3 clinical trials were wide, demonstrating high inter-
individual variability in drug exposure. A therapeutic range
has not been identified nor studied in a prospective, controlled
manner. Comparison of an individual’s peak and trough levels
with “on-treatment” values may mislead the clinician, as they
cannot be expected to yield similar bleeding and thrombotic
outcomes if the baseline risk of the patient differs from the
lower complexity patients included in the trials. Furthermore,
post hoc analysis has identified patient-specific factors, in addition
to or instead of drug exposure, to have strong associations
with outcomes (eg, anemia, history of bleeding, antiplatelet
use). It is the pharmacist’s role to educate providers on this
information and the limited circumstances in which DOAC drug
activity levels may be considered. This could include assessment
for drug reversal, clearance before major surgery, or, rarely, for
continuation of long-term therapy where multiple factors may
influence drug effect or absorption. In the latter circumstance,
department should be emphasized that off-label dose adjustment based
on drug activity levels cannot be supported and selection of
alternative therapy would be warranted for undesirable levels.
Despite the lack of drug level monitoring, pharmacists can have
an important role in patient follow-up, including frequency
and assessment of monitoring parameters that affect dosing
(ie, renal function assessment every 6-12 months), screening
for drug interactions, assessment and management of adverse
effects, and periprocedural management.

**Conclusion**

Despite PK uncertainty and case reports of DOAC drug
failure in obese patients, large observational cohort studies
and meta-analyses describe overall acceptable efficacy and
safety outcomes in obese patients with AF treated with
DOACs. This has included the use of dabigatran, rivarox-
aban, or apixaban. Data for the use of edoxaban in morbidly
obese patients remain limited. Given the unlikelihood of
large, randomized trials being completed in this patient
population, pharmacists must determine if the current body
of literature provides enough support to proceed with use.
The known benefits of DOACs over warfarin in the general
population implore the clinician to find a balance between
cautious avoidance when there is lack of data or demonstr-
ated harm and unnecessary avoidance when harm has not
been identified. This is evidenced in the recent updates made
to the ISTH clinical guidance on the use of DOACs in the
obese population. The pharmacist plays a key role in patient
and drug selection, dosing, education, and follow-up. Obese
patients prescribed DOACs should be routinely reassessed
for safety or efficacy concerns and changes in parameters that
may impact drug dosing.

**REFERENCES**


**ADDITIONAL RESOURCES**


INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.

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Click “Proceed,” then complete the online pretest.

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

Complete the online posttest and activity evaluation form.

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POSTTEST QUESTIONS

1. In morbidly obese patients, which body weight should be used to calculate creatinine clearance for dosing direct oral anticoagulants (DOACs)?
   A. Ideal body weight
   B. Lean body weight
   C. Adjusted body weight
   D. Total body weight

2. Which statement is true regarding physiologic alterations in obese patients that could impact the pharmacokinetics of DOACs?
   A. There is a reduction in volume of distribution of hydrophilic drugs that could lead to reduced efficacy.
   B. There is a reduction in volume of distribution of lipophilic drugs that could lead to reduced efficacy.
   C. There is an increase in glomerular filtration rate that could lead to reduced efficacy of renally eliminated drugs.
   D. There is a decrease in glomerular filtration rate that could lead to reduced efficacy of renally eliminated drugs.

3. Which DOAC has the least published data describing its use in the morbidly obese population for prevention of stroke and systemic embolism in atrial fibrillation?
   A. Apixaban
   B. Dabigatran
   C. Edoxaban
   D. Rivaroxaban

A 60-year-old woman (weight 118 kg, height 5'2") with a history of heart failure and hypertension is diagnosed with new atrial fibrillation. Her laboratory results include a serum creatinine level of 1.1 mg/dL and hemoglobin of 11.3 mg/dL. Her medications are lisinopril 20 mg daily and spironolactone 25 mg daily. You engage the patient in a discussion regarding anticoagulation therapies. The patient travels a lot for work and expresses concern with laboratory monitoring and taking medications multiple times per day.

4. Which of the following is appropriate to share with the patient and physician regarding the use of DOACs in patients with morbid obesity?
   A. There are no available data for the use of DOACs in morbidly obese patients.
   B. DOACs are associated with harm when used in morbidly obese patients.
   C. Obese and morbidly obese patients were excluded from phase 3 clinical trials.
   D. Large, real-world studies have not signaled concern with the use of DOACs in morbidly obese patients compared with warfarin.

5. Based on clinical data, patient characteristics, and patient preferences, which of the following is most appropriate for the pharmacist to recommend for this patient?
   A. Warfarin 5 mg daily
   B. Edoxaban 60 mg daily
   C. Rivaroxaban 20 mg daily
   D. Apixaban 5 mg twice daily
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