CONTINUING EDUCATION: TREATMENT APPROACHES FOR IRON DEFICIENCY IN HEART FAILURE | BIOSIMILAR INSULIN IN THE PHARMACY: UPDATES ON INTERCHANGEABILITY

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PRACTICAL INFORMATION FOR TODAY'S PHARMACIST®

Pharmacy Times®

JUNE 2022 | VOLUME 88 NUMBER 6 | SINCE 1897

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PAIN MANAGEMENT

Treating Migraines With Few Adverse Effects

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Related Anxiety, Depression Risk

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COVID-19 and Medical Devices

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Publisher's Note

Leading the Way in Addressing Health Care Disparities

MIKE HENNESSY JR
President & CEO
MJH Life Sciences®

THE AMERICAN PHARMACISTS ASSOCIATION (APHA)'S House of Delegates recently passed a policy aimed at breaking down the barriers that stand in the way of patients receiving optimal care from pharmacists.

Saying that the COVID-19 pandemic has highlighted tremendous disparities in the United States, the association noted in a statement that pharmacists can directly address these disparities among socially disadvantaged and underserved communities.

The APhA also called upon the American Medical Association (AMA) to "join dozens of other health care organizations [that] recognize and support pharmacists providing essential patient care, such as testing and immunization, which has been and will be so important throughout this pandemic and beyond."

Not mincing words, the APhA called out the AMA for standing in the way of expanded scopes of practice for pharmacists, saying that the medical association's position impedes the ability of health care professionals to work together to provide care to vulnerable populations.

This issue is not going away, and the rallying cry is likely to only get louder in the months ahead. *Pharmacy Times*® will follow this issue closely and continue to provide pharmacy professionals with updates on this important front online and in print.

Also in print this month is our Cover Feature on the various treatment options for migraine headaches, including calcitonin gene-related peptide antagonists, ergotamine, hormone therapy, lasmiditan, and triptans. The June issue also contains articles on diabetes and mental health, and sinusitis, and post-vaccine care.

Meanwhile, we hope you find the *Pharmacy Times*® *OTC Guide*® survey helpful. This special report has grown each year since its launch in 1997, when 85 therapeutic categories were included. This year, we covered 149 therapeutic categories. For the 11th year, the *Pharmacy Times*® *OTC Guide*® survey will be available to consumers through a special collaboration with *U.S. News & World Report*. In addition to the valuable charts that summarize the OTC products most often recommended by pharmacists in 15 distinct health areas, this edition of the *OTC Guide*® includes a number of articles related to the use and management of OTC products.

We wish you a great start to summer!

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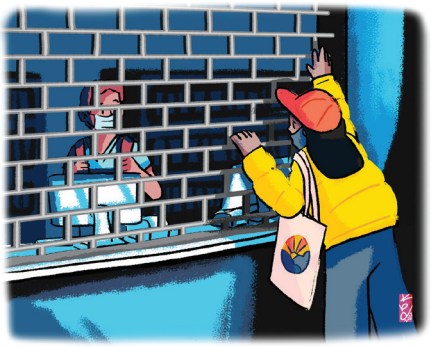

Interactives®

Market Place Resources

Favorites on PharmacyTimes.com

- Pharmacist Medication Insights: Signs of Taking Too Much Vitamin D
- Help Manage Toxicities With BRAF and MEK Inhibitors
- Study: Half of Patients Hospitalized With COVID-19 Have at Least 1 Symptom 2 Years Later
- PQA's Resource Guide Lays Framework As Opportunity for Different Health Care Settings
- Study: Restricted Sleep Increases Some Symptoms of Migraine
- Updates on 2022 Changes to the American Diabetes Association Standards of Care
- PQA Sees the Social Determinants of Health Guide Expanding, Evolving

Continuing Education

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

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

- Analyze the regulations and approval pathways for biologics and biosimilars
- Explain requirements for an interchangeable biosimilar
- Explore advancements of biosimilar insulin in reducing barriers affecting insulin use, access, and adherence for patients with diabetes
- Identify the role of the pharmacist in addressing patient barriers with insulin treatment and counseling on newest available treatment options

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

- Review the regulations and approval pathways for biologics and biosimilars
- Outline requirements for an interchangeable biosimilar
- Discuss advancements of biosimilar insulin in reducing barriers affecting insulin use, access, and adherence for patients with diabetes
- Express the role of the pharmacy technician in addressing patient barriers with insulin treatment and referring patients to the pharmacist as appropriate

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Social Comments

ON TWITTER

Marsha Millonig @CatalystEnterpr · Apr 14

Billing for care provided in the pharmacy is the profession's greatest challenge and opportunity of this decade, and will not succeed without strong pharmacy technician support. Yet, leaders are worried about burnout. Learn more. ow.ly/4gWz50IJjs5 #rxspeaks @Pharmacy_Times

pharmacytimes.com

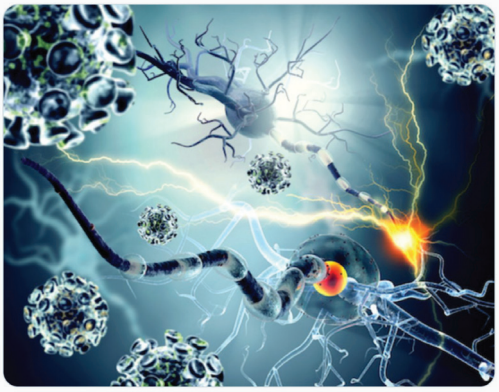
Billing for Care Presents Challenges and Opportuni...

Strong support from pharmacy professionals and a shift in systems and workflows help pave the way ...

WORTH MENTIONING

We Are GNP @WeAreGNP · Apr 13

.@Pharmacy_Times looks at the benefits of advanced pharmacist certification with a focus on multiple sclerosis. Pharmacists can help educate their patients and empower them to take a more active role in managing their health. pharmacytimes.com/view/focus-on-...



PQA @PQAAlliance · Apr 13

See PQA CEO @CostMJ's column in the April issue of @Pharmacy_Times: "Implement Pharmacy Performance Measures for #ValueBasedCare" #TwitteRx

> **Micah Cost** @CostMJ · Apr 12
>
> Ensuring patient access to high-quality pharmacist-provided care is essential. @PQAalliance continues to forge ahead with the development of a set of pharmacy performance measures suitable for use in value-based arrangements between payers and pharmacies. pharmacytimes.com/view/implement...

Parata Systems @ParataSystems · Apr 13

With record staffing shortages, it's critical to reimagine the role of an #RxTechnician - one that is more aligned with their talents. In her new piece for @Pharmacy_Times, @EllenyJohnson shares why the solution should be automation. Read more: pharmacytimes.com/view/automatio...

2 1

BE SOCIAL!

Tell us why you're proud to be a pharmacist and why the profession is so important.

Use #APharmacistIs on social media or email submissions to Aislinn Antrim at aantrim@pharmacytimes.com.

FDA Approvals

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

Drug name	Indication	Manufacturer	Date approved
Vonoprazan, amoxicillin, clarithromycin (Voquezna Triple Pak)	Indicated for the treatment of *Helicobacter pylori* infection	Phathom Pharmaceuticals, Inc	5/3/22
Vonoprazan and amoxicillin (Voquezna Dual Pak)	Indicated for the treatment of *H pylori* infection	Phathom Pharmaceuticals	5/3/22
Fam-trastuzumab deruxtecan-nxki (Enhertu)	Indicated for adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)–positive breast cancer who were previously administered an anti–HER2-based regimen in the metastatic, neoadjuvant, or adjuvant setting, and who developed disease recurrence during or within 6 months of completing therapy	AstraZeneca and Daiichi Sankyo	5/4/22
Baricitinib (Olumiant)	Indicated for the treatment of adult patients hospitalized with COVID-19 who require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation	Eli Lilly and Company and Incyte	5/10/22
Mesalamine extended-release capsules	Indicated as a generic for Pentasa extended-release capsules, 500 mg, for the treatment and prevention of flare-ups of mild to moderately active ulcerative colitis	Sun Pharmaceutical Industries Limited	5/12/22
Tirzepatide (Mounjaro)	Indicated to improve glycemic control in adults with type 2 diabetes	Eli Lilly and Company	5/13/22
Segesterone acetate and ethinyl estradiol vaginal system (Annovera)	Indicated as a procedure-free, long-lasting, reversible birth control. The new approval includes minor revisions to the in vitro release testing specification that enabled normal manufacturing variability.	TherapeuticsMD, Inc	5/20/22
Ivosidenib (Tibsovo)	Indicated in combination with azacytidine for the treatment of individuals with newly diagnosed *IDH1*-mutated acute myeloid leukemia who are 75 years or older or who have comorbidities that preclude the use of intensive induction of chemotherapy	Servier	5/25/22
Nivolumab (Opdivo) with fluoropyrimidine and platinum-containing chemotherapy	Indicated as a first-line treatment for adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma, irrespective of PD-L1 status	Bristol Myers Squibb	5/27/22
Nivolumab (Opdivo) plus ipilimumab (Yervoy)	Indicated as a first-line treatment for adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma, irrespective of PD-L1 status	Bristol Myers Squibb	5/27/22
Tisagenlecleucel (Kymriah)	Indicated for the treatment of adults with relapsed or refractory follicular lymphoma after 2 or more lines of systemic therapy	Novartis	5/27/22
FreeStyle Libre 3 system	Indicated for use by individuals 4 years or older living with diabetes	Abbott	5/31/22

FOR THE FULL FDA APPROVALS LIST, GO TO PHARMACYTIMES.COM

Do New DIR Rules Increase Transparency or Accelerate Patient-Member Channeling?

Fees Are Now So Large That "Hiding the Cheese" Will Be Harder to Accomplish in a Year and a Half

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

AUTHOR BIO

TROY TRYGSTAD, PHARMD, PHD, MBA, is the executive director of Community Pharmacy Enhanced Services Network (CPESN) USA, a clinically integrated network of more than 3500 participating pharmacies.

"CMS IS FINALIZING A POLICY that requires Part D plans to apply all price concessions they receive from network pharmacies to the negotiated price at the point of sale, so that the beneficiary can also share in the savings. Specifically, CMS is redefining the negotiated price as the baseline, or lowest payment, to a pharmacy, effective January 1, 2024."[1]

That is an excerpt from the Centers for Medicare & Medicaid Services (CMS) website that describes via a fact sheet the new rule(s) recently released regarding direct and indirect remuneration (DIR) fees.

Only in America could we conceive of a system so byzantine and so creatively dysfunctional that a term of financing art must be created called "direct and indirect remuneration."

And we are supposed to be the standard bearer of consumer-driven capitalism and free markets? Yeah, no.

Get the popcorn out because this will have potential implications across more payers than just Medicare and it may lead to entirely new ways to obfuscate pricing and reimbursement. The stakes are very high for a singularly important reason. If the federal government goes through with it, consumer-enrollee patients, government employees, judges, legislators, pharmacies, and even other countries will find out what only the pharmacy benefit managers (PBMs) now know: what the PBM paid the pharmacy for the product for a given prescription fill.

Back to the Beginning

About 2 decades ago, the federal government wanted to ensure that it was getting a good deal from newly legislated Medicare coverage with Part D plans, so it required plans to account for all money in and out of the plan, so that the CMS could know what was actually paid after transactions traveled through the various spreadsheet washing machines. The result was 11 categories of DIR. The hoped-for result was to avoid CMS and member overpayment related to an arbitrage of sorts where the PBM or the plan could take parts and pieces of each transaction with various actors for themselves. #epicfail

In 2006, when Part D plans adjudicated their first pharmacy claims, the generic dispensing rate hovered around 53%.[2] Manufacturers were enduring the era of the "patent cliff" and grasping attempts to circumvent it by sending hundreds of "me too" drugs to the marketplace.

PBMs and health care purchasers were aligned with what they wanted to do by managing the drug benefit(s), namely, to prior authorize branded drugs without due value as determined by the pharmacy and therapeutics committee, or automatically prior authorize or otherwise disincentivize the purchase of brands when a generic is available

But then generic dispensing rates (GDRs) skyrocketed between 2006 and 2016, with GDR reaching nearly 90% and a subsequent rise in new-generation specialty products and innovative non–specialty brand products coming to market in substantial numbers.

The business model for PBMs flipped during this period, from value produced by keeping drug costs down to a "pay-to-play" system.

How can a noncommoditized, nontransactional (tollbooth) profit be made when alignment, or drug cost savings, with customers is taken away by generics flooding the marketplace? When 90% of transactions

have no or very little benefit to the purchaser, it is time to figure out another way to make money.

Simultaneously, manufacturers were reeling from the era of brand to generic shifts and the petering out of the product's ability to maintain, in effect, blockbuster patent extensions.

Thus, a marriage was made. Manufacturers needed formulary coverage of newer and more expensive products that applied to fewer and fewer patients and PBMs needed to figure out a way to generate nontransactional margins, because the buy-sell savings from brand-to-generic switches had largely gone away and along with it, alignment with employer, government, and health plan purchasers. The solution was to raise list prices and provide substantial rebates to the PBM in return for formulary coverage, no matter how nonsensical that coverage might be to the purchaser. Keep part of the rebate and pass on most of the remainder to carriers under the medical-loss ratio. Everyone now benefits from the drug-cost pie getting bigger, not smaller. Except, of course, the pharmacies' and purchasers' reimbursement as a percentage of list price has been reduced, not increased, over the same period. Rebate strategies along with self-channeling specialty dispensing became the new PBM business model.

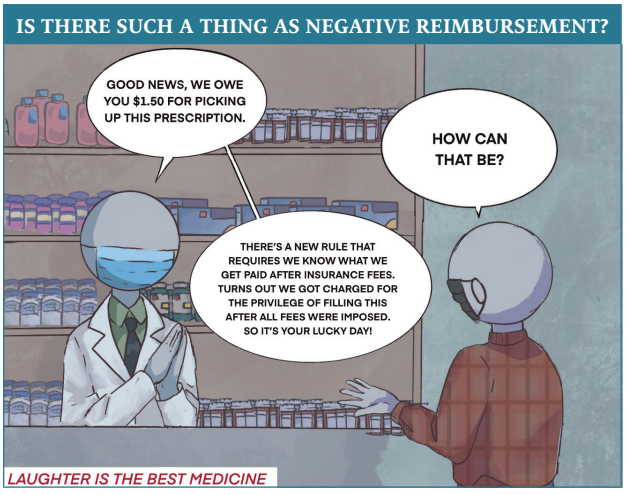
Do not hate the player; hate the game. The federal government spawned the rebate game in a concession with manufacturers to avoid direct price negotiations when it passed the Omnibus Budget Reconciliation Act of 1990 to ensure that Medicaid programs received the best price through the Medicaid Drug Rebate Program,[3] thus "hiding the cheese" on a massive scale was born.

The size of the 11-category DIR effect for PBMs was relatively small in 2006, with 53% GDR in Part D, but as GDR grew, so did the dependency on indirect remuneration through all sorts of hidden clawbacks and share-backs and, of course, pocketing of a portion of manufacturer rebates to make quarterly earnings numbers on Wall Street for manufacturers, PBMs, and plans alike.

This dependency on rebate schemas metastasized across all payer types and entering the second decade of the century, it became the primary driver for procurement, coverage, reimbursement, provider of "choice" and even quality "performance" across the entire drug supply and provider chain.

Squeezing the Proverbial Balloon

In this new rebate era, DIRs increased by some accounts 107,400% from 2010 to 2020.[4] As list-to-net spread grew, so did the pesky problem of passing all those rebates and other indirect remunerations to the PBM and the plan on to CMS or patients, and to maintain margins in Medicare that matched those experienced in commercial and other coverage populations, DIR fees to the pharmacy after the fact, or post–point of sale, grew commensurately.



The net effect became CMS getting its DIR savings from the pharmacies instead of the Medicare Advantage plan and PBM, a classic "squeezing of the balloon" in the direction of the downstream actors.

Potential Consequences of the New Rule

As with the conception of DIR and now the new rules of "lowest price to the pharmacy," there are usually expected and unexpected, or unintended, effects. Plans have 18 months to prepare for their 2024 benefit year and infrastructure, payment schema(s), regulatory submissions, and bids. The net effect could be:

- doubling down on "performance" and a high-stakes game of outcomes measurement politics, calculation, and implementation resulting in spirited debate about what metrics are most favorable to the government, patient-members, pharmacies, and plans;
- doubling down on "preferred" networks and new types of network concepts;
- new schemes to "hide the cheese" and avoid point-of-sale transparency;
- new types of fees not associated with a given prescription fill, such as "network access fees;"
- pharmacy awareness of net reimbursement for a given fill at the point of sale (lowest possible reimbursement); and
- reduction in out-of-pocket costs to patient members.

Thanks to Ben Jolley, pharmacist at Jolley's Compounding Pharmacy in Salt Lake City, Utah, for reviewing this article for accuracy and presentation. ■

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

Lyme Disease Vaccine Candidate Produces Positive Pediatric Data

PFIZER AND VALNEVA HAVE ANNOUNCED positive phase 2 pediatric data for their vaccine candidate for Lyme disease, VLA15.

Based on the phase 2 results, the companies will include children in an upcoming phase 3 trial. The trial will evaluate VLA15 in individuals 5 years and older and is expected to begin in the third quarter of 2022.

"Lyme disease affects all age groups, but with their affinity for being active outdoors, the pediatric population is at the greatest risk of Lyme disease. These first pediatric results are therefore extremely important and support the inclusion of pediatric participants in our planned phase 3 trial," Juan Carlos Jaramillo, MD, chief medical officer of Valneva, said in a news release.

The phase 2 VLA15-221 trial (NCT04801420) is the first clinical study of VLA15 that included a pediatric population. Investigators compared VLA15's immunogenicity and safety results after administration of 2 or 3 primary series doses. Participants were divided into groups by age: 5 to 7 years, 12 to 17 years, and 18 to 65 years.

The 2-dose series was administered at the start of the trial and then at 6 months. The 3-dose series was administered at the start of the trial, then at 2 and 6 months.

In children who received either dosing series, investigators found that the vaccine candidate was more immunogenic than in adults receiving either series.

The data build on the immunogenicity profile that previously was reported for adult individuals aged 18 to 65 years. As with results from the adults, the immunogenicity and safety data support a 3-dose primary vaccination series in children during the phase 3 study.—*Ashley Gallagher*

Cognitive Behavioral Therapy May Ease Depression in Individuals With Dementia

PSYCHOLOGICAL INTERVENTIONS such as cognitive behavioral therapy may be effective and worthwhile for individuals with dementia who have depression, according to results of a new study.

Feelings of anxiety and depression are common in individuals with dementia and mild cognitive impairment. But medications used to manage these symptoms may not be effective in individuals with dementia and could cause adverse effects, the study results show.

"We currently have no standard treatments for depression for people with dementia, as antidepressants do not work for them," lead author Vasiliki Orgeta, PhD, said in a statement. "Yet, despite the lack of supporting evidence, they are still prescribed for many people living with dementia, which is an important problem given that more and more evidence is accumulating, suggesting that not only do they do not improve symptoms, but they may increase risk of mortality."

The findings, which were published by the Cochrane Database of Systematic Reviews, are the first to show that psychological interventions are effective in the context of ineffective drugs for depression in dementia. The results also showed that these interventions may provide additional benefits in terms of improving everyday function and patient quality of life. Based on these findings, the investigators are calling for clinical guidelines for dementia to be revised to recommend psychological therapies, specifically cognitive behavioral therapy.

Individuals with dementia are twice as likely as others their age to receive a diagnosis of a major depressive disorder, according to the study results.—*Aislinn Antrim*

Genetic Tests, Health Screenings May Identify Those at Risk of Premature Heart Disease

GENETIC TESTS AND HEALTH SCREENINGS may help identify more than 1 million adults in the United States who carry a gene for familial hypercholesterolemia, which is a common genetic disorder that causes elevated low-density lipoprotein (LDL) cholesterol, according to results of a study published in the *Journal of the American Heart Association*.

"Currently, most individuals aren't diagnosed with familial hypercholesterolemia until they are in their 50s. If a young adult is identified to have familial hypercholesterolemia, they would likely benefit from earlier and more aggressive treatment to prevent heart attack and stroke," Brandon Bellows, PharmD, MS, an assistant professor of medical sciences at Columbia University in New York, New York, said in a statement.

The American Heart Association recommends that all individuals 20 years or older have their cholesterol and other heart risk factors checked every 4 to 6 years if their risk remains low.

Familial hypercholesterolemia screening is not standard and requires additional clinical information or diagnostic genetic testing, but genetic testing may not be affordable for individuals if it is not covered by insurance.

In the study, investigators aimed to determine how many individuals with familial hypercholesterolemia could be identified if they were screened using clinical factors, including cholesterol levels and the presence of early heart disease for them or close family members, with and without genetic testing.

The investigators gathered clinical information and genetic test results for approximately 50,000 individuals aged 40 to 69 years old from the United Kingdom Biobank between 2006 and 2010. They estimated the probability each individual had of carrying the generic variant based on their clinical information. Additionally, they applied the relationships observed in the database to a data set of almost 40,000 individuals, 20 years or older, from the National Health and Nutrition Examination Survey to estimate familial hypercholesterolemia genetic variants in the US population who did not have genetic test results.—*Ashley Gallagher*

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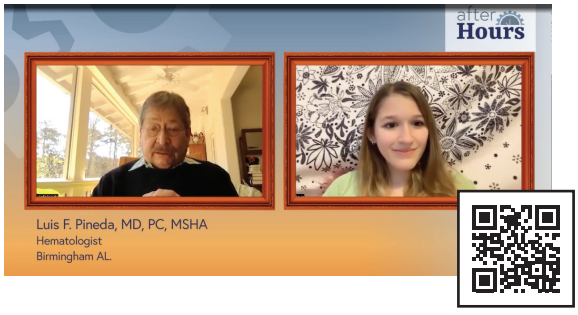


AFTER HOURS

Cooking With Cancer

Luis F. Pineda, MD, PC, MSHA, discusses how he combines his work as an oncologist with his passion for cooking. He explains how he created his own program, Cooking With Cancer, designed specifically for patients with cancer, caregivers, and those who work in the health care industry.

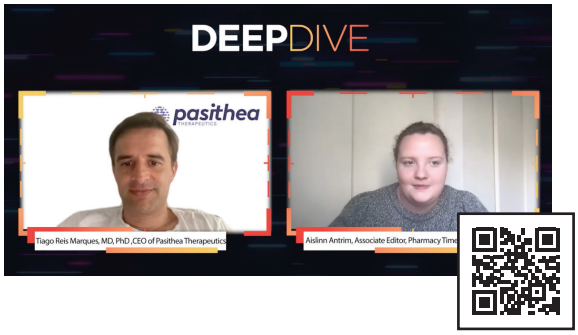
TO WATCH: https://bit.ly/39P1pqT

WELLBEING CHECKUP

Prioritizing Mental Health

Infectious diseases and vaccine safety expert Jan Bonhoeffer, MD, PhD, discusses strategies health care professionals can use to ensure they are tending to their own mental health.

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



DEEP DIVE

Deep Dive Into Psychedelic Medicine's Potential

Tiago Reis Marques, MD, PhD, discusses the potential role for ketamine and other psychedelic medicines in the opioid epidemic, both to manage chronic pain and to treat addiction. He also discusses the benefits of in-home infusions for ketamine, which he says are just as safe as in-clinic infusions when administered and overseen by a medical professional.

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

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AUTHOR BIO

KATHLEEN KENNY, PHARMD, RPH,

has more than 25 years of experience as a community pharmacist. She is a freelance clinical medical writer based in Homosassa, Florida.

Pharmacists Can Treat Migraines With Few Adverse Effects

Options Include Calcitonin Gene-Related Peptide Antagonists, Ergotamine, Hormone Therapy, Lasmiditan, and Triptans

By KATHLEEN KENNY, PHARMD, RPH

Migraine headaches are characterized by recurring episodes of pulsing or throbbing pain on 1 side of the head, often accompanied by nausea, vomiting, and/or sensitivity to light and sound.

»

The pain comes from the activation of nerve fibers inside the walls of the blood vessels of the meninges.[1] Left untreated, or unsuccessfully treated, the pain can last from hours to days and can be moderate to severe, often becoming debilitating.[1]

Adults and children can suffer from migraines. Women are 3 times more likely to experience migraines than men.

Migraines typically occur in the morning upon waking. Some patients experience migraines at predictable times, such as before a menstrual cycle or at the end of a particularly stressful week. In some patients, migraines occur in stages.

MIGRAINE STAGES

Prodrome. Hours or days before a migraine, many individuals experience symptoms such as bloating, changes in appetite, constipation, diarrhea, fatigue, mood changes, and severe thirst, in addition to sensitivity to light, odors, and sound.[2]

Aura. Aura usually begins gradually over 5 to 25 minutes. Aura usually lasts less than an hour. These symptoms stem from the nervous system and can involve changes in smell, taste, and touch; difficulty speaking; a heavy feeling in the arms and legs; numbness on 1 side of the body; ringing in the ears; and vision changes.[2]

Attack. The actual migraine attack tends to get worse with physical activity and can last a few hours or several days.[2]

Postdrome. After a migraine attack, patients are often left feeling confused, exhausted, and weak. This can last a day or more.[2,3]

CAUSES

Migraines have a genetic component to them. Four of 5 patients with migraines have a family member who suffers the same affliction. If 1 parent has migraines, a child has a 50% chance of having them as well. That number jumps to 75% if both parents suffer from migraines.[2]

Having other medical conditions increases the risk of developing migraines. These include anxiety, bipolar disorder, depression, epilepsy, and sleep disorders.[2]

TRIGGERS

Everyone has different triggers that may bring on a migraine. These include alcohol; chocolate; food additives, such as monosodium gluconate or nitrates; hormonal changes; medications, such as vasodilators; stress; tobacco; too little or too much caffeine; too little or too much sleep; and weather changes.[2]

TREATMENT

Although there is no cure for migraines, treatment focuses on symptoms relief and prevention of additional attacks. Some tips for nonmedical relief of symptoms may include drinking fluids; placing a cool compress or ice pack on the back of the neck, forehead, or top of head; and resting with the eyes closed in a cool, dark, quiet area.[3]

Lifestyle changes may help prevent migraine headaches. Some of these include logging triggers to avoid them in the future, stress management techniques, and weight loss.

However, medical intervention is often required. Usually, the sooner treatment begins after migraine onset, the better it will work.

OTC pain relievers containing acetaminophen, aspirin, caffeine, and/or ibuprofen often work well. Of course, products containing aspirin should not be given to patients younger than 19 years because of the risk of Reye syndrome.

If patients are taking these OTC pain relievers more than 2 days a week, they should be directed to see a physician, who may prescribe a product to better manage the migraines.[2]

Many patients experience nausea and sometimes vomiting with migraines. Physicians will often prescribe medication to control nausea, such as metoclopramide, ondansetron, or promethazine, to help resolve this symptom.[2]

Triptans are FDA-approved, first-line agents used to treat migraines.

Triptans reverse the vasodilation that causes migraines by selectively binding to the vascular serotonin receptor 5-HT1B. They also selectively bind to the neurogenic and central serotonin 5-HT1D receptors, thus inhibiting activation of the trigeminal nerves. This also results in blockage of the transmission of pain signals to the brain.[4]

Triptans are available in multiple dosage forms, including nasal sprays, oral tablets, orally disintegrating tablets, and subcutaneously injectable products.[4]

Triptans may cause coronary vasoconstriction, dizziness, and nausea as well as a group of adverse effects (AEs) called "triptan sensations" that include chest tightness, flushing, neck pain, paresthesia, and tingling.[4]

Ergotamine is also used to treat migraines by selectively binding to and activating serotonin receptor 5-HT1D, and they act similarly to triptans. Ergotamine also binds to alpha-adrenergic receptors, stimulating vascular smooth muscle, resulting in vasoconstriction.[5]

Adverse reactions to ergotamine are numerous and range from relatively benign symptoms such as dizziness, drowsiness, and xerostomia to severe symptoms including arrhythmias and decreased blood flow.[5] Therefore, ergotamine derivatives have fallen out of favor as first-line migraine treatments.

Lasmiditan is the first FDA-approved "ditan" used to treat migraines. Lasmiditan has a strong affinity to bind to serotonin receptors 5-HT1F, which are involved in pain signaling. These receptors are located both centrally and peripherally. Unfortunately, the mechanism of action of ditans are not clearly understood.[6]

Adverse reactions to lasmiditan include central nervous system depression, driving impairment, headaches related to overuse, and serotonin syndrome.[6]

Calcitonin gene-related peptide (CGRP) antagonists block the effects of CGRP, a small protein located in the trigeminal nerve.

This blockage results in inhibition of neurogenic inflammation, inhibition of pain signals, and inhibition of vasodilation without causing vasoconstriction.[7,8]

The most common AEs of CGRP antagonists include constipation and injection site reactions. Less commonly, these medications may cause new or worsening constipation and hypertension with serious complications.[7]

Hormone therapy can be used for patients who suffer from migraines around their menstrual cycle.

Additional forms of treatment for consideration include acupressure, acupuncture, biofeedback, chiropractic care, cognitive behavioral therapy, craniosacral therapy, and massage.[2]

Because each individual's migraines are different, it stands to reason that not every available medication works in every case. Pharmacists can help patients determine which medications might work for them and educate them about how the medications work and their possible AEs. ■

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CONTEMPORARY Clinic®

Understand the Significance of Identifying and Treating Dry Mouth

Pharmacists Can Help Select Nonprescription Products to Treat Xerostomia and Recommend Further Medical Care When Warranted

By YVETTE C. TERRIE, BSPHARM, RPH

XEROSTOMIA, COMMONLY KNOWN AS DRY MOUTH, is defined as a syndrome in which the flow of saliva is completely halted or limited. It is often overlooked, unrecognized, and undertreated, according to the American Dental Association.[1,2]

If left untreated, xerostomia can cause discomfort and difficulty chewing, speaking, swallowing, and tasting. It can also contribute to dental caries, halitosis, periodontal disease, and other oral health issues, including candidiasis infection because of the disturbance of the balance of oral microflora resulting from diminished salivary flow.[1,3] The effects of xerostomia can range from mild to severe, and patients with severe cases often experience a reduced quality of life.[1-5]

The etiology of xerostomia is multifactorial, and contributing factors include certain disease states, medical procedures, and use of some medications.[1,2] The exact incidence of xerostomia is unknown, but statistics indicate that xerostomia in the US population ranges widely from 0.9% to 64.8% in the general population, is in an estimated 30% of adults older than 65 years, and in 40% of those older than 80 years.[2,4] Study results show that the incidence of xerostomia increases with age because many older individuals are likely to take multiple drugs associated with diminished salivary flow rate for the treatment of various chronic illnesses.[4] Moreover, Sjögren syndrome, a chronic inflammatory autoimmune disorder in which immune cells attack and destroy the glands that produce tears and saliva, is a common cause of xerostomia.[1,2] A host of other conditions also may contribute to the development of xerostomia, including chronic active hepatitis, Crohn disease, depression, hormonal changes related to menopause, hypertension, hypothyroidism, HIV, Parkinson disease, sarcoidosis, scleroderma, and uncontrolled diabetes.[1,2] Individuals receiving radiation therapy to the head and neck may also develop xerostomia.[1,2] Other possible causes may include alcohol, breathing through the mouth, caffeine, and smoking.[1]

The American Academy of Oral Medicine indicates that more than 1100 medications have the potential to negatively alter or diminish salivary production, thus contributing to xerostomia.[6] Examples of medications commonly associated with salivary dysfunction and xerostomia include those with anticholinergic effects or that cause depletion of salivary flow, such as antidepressants, antihistamines, antihypertensive medications, antipsychotics, antiseizure/antispasmodic drugs, decongestants, diuretics, and sedatives.[1,7] Study results also show that patients who are taking multiple medications may also be at greater risk of developing xerostomia as an adverse effect of therapy.[1,8]

CLINICAL STUDIES AND RECENT NEWS

Although many patients with COVID-19 experienced loss of smell and taste, various study results indicate that xerostomia was commonly reported among those with COVID-19 and frequently occurred before

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TABLE. Patient Education Resources About Xerostomia

American Academy of Oral Medicine website: http://www.aaom.com/index.php?option=com_content&view=article&id=107:xerostomia&catid=22:patient-condition-information&Itemid=120
American Dental Association website: http://www.mouthhealthy.org/en/az-topics/d/dry-mouth
National Institute of Dental and Craniofacial Research website: http://www.nidcr.nih.gov/oralhealth/topics/drymouth/drymouth.htm

other common symptoms.[9-11] Findings from a recent review of more than 180 published studies showed that approximately 4 in 10 patients experience impaired taste or a total loss of taste, but xerostomia affected more than 43% of those with COVID-19.[12,13]

In a recent publication, authors indicated that because older adults take more medications than any other age group, this patient population is more likely to experience xerostomia. They also noted that clinicians should understand the significance of xerostomia on oral health and its negative impact on patient quality of life and that there is a need for collaborative efforts among oral health personnel and pharmacists in conjunction with general practitioners, geriatricians, and nurses to augment cognizance about xerostomia and ensure affected patients are properly advised and managed.[14]

Findings from a recently published observational study showed that oral sensory complaints often reported during perimenopause include burning sensations in the mouth, taste disturbance, and xerostomia. The authors concluded that there are correlations among burning mouth, menopausal symptoms, taste disturbance, and xerostomia.[15]

CONCLUSION

Pharmacists are key in identifying those individuals most susceptible to xerostomia because of chronic illnesses and/or the use of certain medications, and they can provide clinical recommendations to assist patients in the management of xerostomia and minimize its severity. Pharmacists can also educate patients about the various OTC artificial saliva substitutes and dry mouth relief products available in the form of chewing gums, gels, liquids, lozenges, mouthwashes, sprays, and toothpastes. For most patients with xerostomia, alcohol-free mouth rinses are preferred because alcohol may exacerbate xerostomia. During counseling, pharmacists can advise patients to maintain daily dental hygiene, including brushing and flossing twice a day, routine professional dental care, and the need to discuss xerostomia with their primary health care providers if symptoms do not resolve or worsen after self-treatment. ■

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CBD Tinctures

Manufactured by CBD Living

HOT PRODUCT

CBD Living has introduced 3 new tincture flavors: chocolate mint, green apple, and salted caramel. Each bottle contains 750 mg of broad-spectrum cannabidiol (CBD) that is free of genetically modified organisms, gluten, and tetrahydrocannabinol, and is vegan. CBD Living products are manufactured with organic hemp grown on state-licensed hemp farms in Colorado and Oregon, according to a statement from the company. The CBD tinctures allow oil-soluble nutrients to be delivered in an oil formulation, providing fast, sustained relief. All CBD Living products are made in the United States.

FOR MORE INFORMATION:
cbdliving.com

Wellblends

Manufactured by Nature Made

In its new Wellblends line, Nature Made has developed products to address immunity, sleep, and stress. The line features 13 products, including 4 for immune health, 2 for energy and mood, 1 for relaxation, 5 for sleep, and 1 for stress relief. The line is scientifically designed to target specific areas that can affect other areas of wellness, according to the company. For example, disrupted sleep can cause fatigue and increase stress, and stress can affect how the immune system functions.

FOR MORE INFORMATION:
naturemade.com

ProBioraKids for Oral Health

Manufactured by ProBiora Health

ProBiora Health has launched a pediatric version of its oral-care probiotic. The probiotic contains good bacteria that eliminate the bad bacteria that can cause cavities and gum disease, including *Streptococcus oralis KJ3*, *Streptococcus rattus JH145*, and *Streptococcus uberis KJ2*. The probiotic also provides fresh breath and whiter teeth. ProBioraKids is gluten-free and vegan and has no artificial flavors, colors, or sweeteners. It is designed to be taken at bedtime, after brushing and flossing, and is dissolvable.

FOR MORE INFORMATION:
probiorahealth.com

Dailies Total1 for Astigmatism

Manufactured by Alcon

Alcon has launched new contact lenses for individuals with astigmatism. Dailies Total1 for Astigmatism is the first water-gradient contact lens. Many individuals who have astigmatism often experience discomfort or dryness when wearing contact lenses. Alcon's water-gradient lenses are designed to settle more easily and stabilize the lipid layer of the tear film. The lens material has a gradual increase in water content that helps provide moisture to the eyes, and the lenses are positioned to fit and allow those with astigmatism to wear contact lenses more comfortably.

FOR MORE INFORMATION:
alcon.com

INFECTIOUS DISEASE | RESPIRATORY | VACCINES

Postvaccine Care

By AMMIE PATEL, PHARMD, BCACP; AND RUPAL PATEL MANSUKHANI, PHARMD, FAPHA, CTTS

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CASE 1: Egg Allergy

Q **AG is a 29-year-old woman who is hesitant about the influenza vaccine and is getting it only because her employer requires it. While reading the screening and consent form, she mentions she has an egg allergy, and the influenza vaccine contains egg. She can tolerate foods containing eggs, such as bread and cake, but she has experienced hives and itching after eating scrambled eggs. What should the pharmacist advise?**

A Most flu vaccines are grown in eggs and include small amounts of egg protein called ovalbumin.[1] Cell culture-based (Flucelvax Quadrivalent) and recombinant (Flublok Quadrivalent) influenza vaccines are completely egg free. Approximately 0.2% of adults and 1.3% of children have an egg allergy. It should be noted that in describing her reaction, AG said she experienced hives and itching after consuming lightly cooked eggs. Studies have been conducted to assess the safety of influenza vaccines in individuals who have egg allergies. All individuals with egg allergies in the study, even those with a history of anaphylaxis, received the trivalent inactivated influenza vaccine without serious reactions. Given that AG does not have a history of angioedema or other serious reactions to egg, the CDC recommends such patients receive any licensed form of the influenza vaccine at a pharmacy. Had AG reported a history of serious reactions to eggs, she should have been instructed to receive the influenza vaccine in an inpatient or outpatient medical center under provider supervision, not in a pharmacy. If AG has an allergic reaction to the influenza vaccine with angioedema and/or respiratory distress, the emergency medical system should be activated and a 0.3-mg dose of epinephrine administered intramuscularly, using a premeasured or prefilled syringe or an autoinjector, should be delivered in the mid-outer thigh while awaiting emergency medical response.[2,3]

CASE 2: Syncope

Q **JG is a 17-year-old girl who came to the pharmacy with her mother to get a HPV vaccine. JG is afraid of needles and vaccines and says she had heard about teenagers who have fainted after receiving the human papillomavirus (HPV) vaccine. She asks about syncope after vaccination and how it could be prevented and treated. What should the pharmacist tell her?**

A Syncope, or fainting, is caused by decreased blood flow to the brain that leads to temporary loss of consciousness. Although syncope can occur with any vaccine, it is most common after HPV, meningococcal, and tetanus, diphtheria and pertussis vaccines. In addition, syncope is reported more frequently (62%) in adolescents aged 11 to 18 years. Although patients recover from syncope almost immediately, the potential injuries associated with fainting and falling are of greater concern. Per the CDC, 12% of serious syncope episodes reported to the Vaccine Adverse Event Reporting System resulted in head injuries.[4,5]

Typically, when patients present with a fear of needles or vaccination, the pharmacist should either reassure about the procedure or simply comfort them and consider providing them with a beverage or snack. Most importantly, preventing complications and head injuries from syncope require preparation prior to vaccination and quick action if syncope occurs. Make sure the patient is lying down or seated during vaccination. Monitor patients closely for 15 minutes after they are vaccinated. If syncope occurs, have the patient lie flat and maintain an open airway. Apply a cool, damp cloth to the face and neck and elevate the feet. Monitor the patient closely until full recovery and activate the emergency medical if the patient does not recover immediately or has been injured.[4,5]

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

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CASE 3: Subdeltoid Bursitis

Q **ST is a 70-year-old woman who is getting her influenza and pneumococcal vaccines. She asks to speak with the pharmacist, as she had read about adverse effects of intramuscular vaccines, including shoulder bursitis or subdeltoid bursitis. What information should the pharmacist provide?**

A Subdeltoid bursitis following intramuscular (IM) vaccination, also called shoulder injury related to vaccine administration (SIRVA), presents as shoulder pain and limited range of motion following IM injection, owing to an anti-inflammatory reaction. Patients who suffer from SIRVA experience pain at rest that worsens with movement. A retrospective study of 3 million individuals who received the influenza vaccine showed 16 cases of subdeltoid bursitis within 2 days of vaccine administration. SIRVA may be treated with anti-inflammatory medications, ice, OTC or prescription analgesics, physical therapy, and rest.[6]

The correct anatomical location of an IM injection is in the lower two-thirds of the deltoid, and the appropriate length needle must be selected based on patient muscle mass to reduce the risk of injecting too deeply, past the muscle and into the bursa. Patients who experienced SIRVA were noted to have received the injection higher than recommended. The CDC has developed and disseminated guidelines for appropriate IM vaccine administration technique and needle selection.[6,7]

CASE 4: COVID-19 Vaccine

Q **JS is a 42-year-old woman who is getting her second dose of the Moderna COVID-19 vaccine. She was initially hesitant to get the vaccine, but her employer mandates it. JS said she felt fine after the first dose, aside from fatigue on the evening of the vaccination. She is nervous about the second dose because she has heard and read mixed reports about patient reactions. JS inquires about self-care following this dose. What information can the pharmacist provide?**

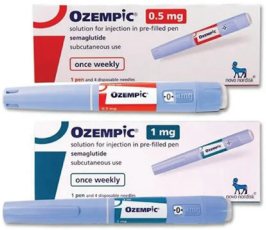
A Some individuals do have adverse effects (AEs) from the COVID-19 vaccines, and JS is right to prepare for self-care to prevent and manage AEs. On a positive note, the reported AEs are the symptoms of building immunity and protection. Reported local AEs at the injection site include pain, redness, and swelling. Systemic reactions include chills, fatigue, fever, headaches, or nausea. OTC acetaminophen and ibuprofen are recommended to treat the AEs, unless a physician indicates otherwise. It is not recommended that patients take either of these agents prior to the vaccination. Nonpharmacologic recommendations for local reactions include the application of a cold, wet washcloth over the injection site and lightly moving the arm that has received the injection after vaccination. Nonpharmacologic recommendations for systemic reactions include drinking plenty of water and wearing loose-fitting clothing to reduce discomfort from fever.[8]

HOT PRODUCT

Semaglutide (Ozempic)

Manufactured by Novo Nordisk

The FDA has approved a 2-mg dose of semaglutide (Ozempic) as a once-weekly subcutaneous injection indicated for the treatment of adults with type 2 diabetes (T2D) along with diet and exercise to improve blood sugar and reduce the risk of major cardiovascular events. This approval expands the indication for the drug to include the 0.5-, 1-, and 2-mg doses for the treatment of T2D. Semaglutide is a glucagon-like peptide-1 receptor agonist, and the approval is based on results from the SUSTAIN FORTE trial (NCT03989232).



FOR MORE INFORMATION:
ozempic.com

Dexmedetomidine (Igalmi)

Manufactured by BioXcel Therapeutics, Inc

The FDA has approved dexmedetomidine (Igalmi) sublingual film for the treatment of adults with agitation associated with bipolar disorder I or II and schizophrenia. The approval is based on 2 double-blind phase 3 trials that evaluated the agent for the acute treatment of agitation associated with schizophrenia (SERENITY I; NCT04268303) or bipolar I or II disorder (SERENITY II; NCT04276883). Common adverse events included bradycardia, dizziness, dry mouth, hypotension, oral hypoesthesia, orthostatic hypotension, paresthesia, QT interval prolongation, and somnolence; none were serious. Dexmedetomidine can be self-administered under the supervision of a health care provider. BioXcel plans to launch the drug in the United States in the second quarter of 2022.

FOR MORE INFORMATION:
bioxceltherapeutics.com

Sirolimus Topical Gel (Hyftor) 0.2%

Manufactured by Nobelpharma America, LLC

The FDA has approved sirolimus topical gel (Hyftor) 0.2% for the treatment of facial angiofibroma in patients 6 years and older with tuberous sclerosis complex (TSC). Sirolimus is the first topical treatment to gain FDA approval for facial angiofibroma associated with TSC. It was also previously granted orphan drug designation. Clinical trial results showed the gel improved redness and the size of facial angiofibromas over a 12-week period. It was contradicted for individuals with a history of hypersensitivity to other topical medications or other gel components. TSC is a rare autosomal dominant genetic disease that causes benign tumor growth throughout the body, which may result in behavioral or neurological manifestations such as autism, intellectual disability, and epilepsy.

FOR MORE INFORMATION:
nobelpharma-us.com

Abacavir, Dolutegravir, and Lamivudine Combination (Triumeq PD)

Manufactured by ViiV Healthcare

The FDA has approved a new drug application for a dispersible tablet formulation of the fixed-dose combination of abacavir, dolutegravir, and lamivudine treatment (Triumeq PD) for the treatment of children with HIV. The indication is for a single-tablet regimen in pediatric patients with HIV-1 who weigh between 10 kg and 25 kg. The drug is a fixed dose and forms a complete regimen for the management of HIV-1 infection. The tablets contain 600 mg of abacavir, 50 mg of dolutegravir, and 300 mg of lamivudine. They can be taken with or without food and without a boosting agent. The indication expands on the previous indication for the treatment of HIV-1 in virologically suppressed adolescents 12 years or older who weigh at least 35 kg and are on a stable antiretroviral regimen.

FOR MORE INFORMATION:
viivhealthcare.com

INFECTIOUS DISEASE | PRESCRIPTION | RESPIRATORY

Chronic Sinus Infections Are Costly and Painful

Early Intervention, Prudent Use of Antibiotics Can Help Patients Treat Condition, Speed Recovery

By JEANNETTE Y. WICK, RPH, MBA, FASCP

WHEN THE PARANASAL SINUSES AND nasal cavity mucosa become inflamed, individuals often develop intrusive and long-lasting symptoms.

With approximately 30 million Americans experiencing sinusitis annually, pharmacists see their fair share of patients with this condition.[1] Chronic sinusitis consumes almost 3 times as much of our health care dollars ($8.3 billion) than acute sinusitis, making it a significant concern.[1]

When diagnosing sinus infections or rhinosinusitis, clinicians should look at major and minor symptomatology (**Table 1**[2,3]); diagnosis requires 2 major factors or 1 major and 2 minor factors. Symptom duration also contributes to the diagnosis. Acute sinusitis lasts fewer than 4 weeks and subacute lasts 4 to 12 weeks sinusitis. Once symptoms persist for 12 weeks or longer, the sinusitis becomes chronic by definition. This review focuses on chronic sinusitis.

MECHANICS

Sinusitis results from sinus dysfunction when an allergen, bacterial, fungal, or viral assault causes mucosal edema that narrows the sinus ostia, creating mechanical obstruction.[4] Obstruction increases pressure in the sinus cavity transiently. As air exchange is impaired and the sinuses lose air, the pressure inside the sinus is lower than atmospheric air pressure. When patients perform normal activities, such as blowing their noses or sniffing, the negative pressure lets nasal bacteria into the sinuses, and they secrete mucous in response. With nowhere to go, fluid accumulates in the sinus, impairing the mucociliary apparatus. The result is painful infection.[4]

MEDICAL TREATMENT

Medical therapy with antibiotics, nasal saline irrigation, or oral or topical glucocorticoids attempts to control predisposing factors, help sinus secretions drain, reduce sinus tissue swelling, and treat infections.[5] The American Academy of Otolaryngology-Head and Neck Surgery Foundation clinical practice guidelines recommend a measured approach to chronic sinusitis.[2] If possible, clinicians should determine whether the condition is bacterial, viral, or noninfectious by culturing sinus aspirates or by endoscopy. They also recommend confirming the diagnosis using anterior rhinoscopy, nasal endoscopy, or CT scan in complicated cases.[2]

In adults with uncomplicated acute bacterial rhinosinusitis, clinicians can offer watchful waiting, without antibiotics, as most sinusitis is viral, or antibiotic therapy.[2,6] *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus,* or *Streptococcus pneumoniae* and other *Streptococcus*

TABLE 1. Major and Minor Symptomatology Associated With Chronic Sinusitis[2,3]

Major	Minor
• Anosmia/hyposmia • Discolored posterior drainage, nasal discharge, or purulence • Facial congestion or fullness • Facial pain or pressure • Fever • Nasal blockage or obstruction • Purulence on nasal examination	• Cough • Dental pain • Ear fullness, pain, or pressure • Fatigue • Halitosis • Headache

AUTHOR BIO

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TABLE 2. Controlling Factors That Predispose to Chronic Sinusitis[2,8]

Factor	Intervention
Allergic or environmental	• Reduce exposure to cigarette smoke, dust, mold, and other environmental chemical irritants. • Recommend oral or topical antihistamines, cromolyn, immunotherapy, and topical steroids. • Recommend smoking cessation.
Patch	• Application site reactions are possible. • Does not address sudden cravings • Nonprescription • One patch lasts 24 hours. • Smokers use a step-down program based on their pack-per-day habit and gradually reduce their nicotine dependency.
Asthma	• Consider a trial of a leukotriene inhibitor.
Gastroesophageal reflux disease	• May cause changes in behavior or mood, dry mouth, headache, or insomnia • May reduce weight gain associated with cessation • Prescription • Started 1 week before the quit date; taken twice daily • Use with extreme caution in patients with hepatic or renal failure or seizure disorders
Clonidine	• Prescription • Recommend better control of reflux for older patients because of its anticholinergic properties. • Second-line treatment when first-line treatments are contraindicated or not successful, or as preferred by the patient.
Varenicline	• Receive vaccinations routinely. • Reduce viral exposures by improved personal hygiene, such as frequent handwashing, keeping hands away from face, and wearing a mask when around others who have symptoms.

species are most often identified as infectious agents. Initially, prescribers would employ empiric amoxicillin with or without clavulanate for 5 to 10 days.[2] If the patient's sinusitis fails to improve or worsens within 7 days, clinicians should reassess, ruling out other conditions and looking for comorbid conditions, such as asthma, ciliary dyskinesia, cystic fibrosis, and immunodeficiency, which could cause or exacerbate the sinusitis. In addition, clinicians should recommend saline nasal irrigation and/or steam inhalation, topical intranasal corticosteroids, or both for symptomatic relief.[2] Further antibiotic treatment should be culture directed. Clinicians should not prescribe antibiotics for viral infection or systemic or topical antifungal therapy in patients with chronic sinusitis.[2,7] Concurrently, clinicians should educate patients about controlling predisposing factors (**Table 2**[2,8]).

COUNSELING IN THE PHARMACY

A few points about sinusitis can help pharmacists counsel patients appropriately. In the first 2 weeks of a sinus infection, OTC decongestants, steroid nasal sprays, and saline sprays can often resolve the infection.[2,3] After 10 days, if the drainage is colored, an antibiotic, while continuing decongestants, saline spray, and topical steroid sprays, is probably necessary.[2]

Patients often perceive sinus infection as dental pain because the roots of the upper back teeth are near the sinus cavity and may become painful pursuant to sinus infection.[9,10] Sinus pain is positional, changing with movement, so asking whether the pain changes when the patient bends from the waist will pinpoint a sinus infection, whereas dental pain will not change with position. When patients have sinus-related dental pain, large-volume saline irrigation is often helpful.[5,10]

Some individuals experience lingering symptoms despite the initial course of antibiotics. Sinuses are a closed cavity and eradicating infection may require 3 to 4 weeks of antibiotics, plus additional methods to encourage drainage of the sinuses.[2]

Longer treatment durations are not associated with improved outcomes.[11] Untreated sinus infections can result in intracranial, orbital, and other neurological complications.[12]

CONCLUSION

Early intervention is important for sinus infections. In resistant chronic sinusitis, a patient will need a referral to an otolaryngologist for surgical evaluation. Surgery reestablishes sinus ventilation and corrects mucosal opposition to restore the mucociliary clearance system. ■

AUTHOR BIO
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PRESCRIPTION

Opdualag From Bristol Myers Squibb

By MONICA HOLMBERG, PHARMD, BCPS

THE FDA HAS APPROVED NIVOLUMAB AND RELATLIMAB-RMBW INTRAVENOUS (IV) INJECTION (Opdualag; Bristol Myers Squibb) to treat metastatic or unresectable melanoma in patients 12 years or older.[1]

The incidence of melanoma has been increasing over the past 3 decades, with an estimated 99,780 new melanoma diagnoses and 7650 melanoma-related deaths expected to occur in the United States in 2022.[2]

PHARMACOLOGY AND PHARMACOKINETICS

Nivolumab is a human IgG4 monoclonal programmed death receptor-1 (PD-1) blocking antibody. It binds to the PD-1 receptor, blocks the interaction with its ligands PD-L1 and PD-L2, and reduces PD-1 pathway-mediated inhibition of the immune response. Relatlimab is a human IgG4 monoclonal lymphocyte activation gene-3 (LAG-3) blocking antibody. By binding to the LAG-3 receptor, blocking the interaction with its ligands, and reducing LAG-3 pathway-mediated inhibition of the immune response, promotion of both cytokine secretion and T-cell proliferation occurs. Combination therapy with both nivolumab and relatlimab leads to increased T-cell activation compared with monotherapy with either agent alone. The half-life of nivolumab is 26.5 days, whereas relatlimab is 26.2 days.[1]

DOSAGE AND ADMINISTRATION

The recommended dose of Opdualag for patients 12 years or older who weigh at least 40 kg is 480 mg of nivolumab and 160 mg of relatlimab IV every 4 weeks until the disease progresses or unacceptable toxicity occurs. It should be given as a 30-minute infusion through an IV line containing a nonpyrogenic, sterile, low-protein–binding in-line nylon, polyethersulfone, or polyvinylidene fluoride filter with a pore size of 0.2 µm to 1.2 µm. Other medications should not be coadministered through the same IV line.[1]

CLINICAL TRIALS

The efficacy of Opdualag was evaluated in RELATIVITY-047 (NCT03470922), a double-blind, randomized trial of 714 participants with previously untreated metastatic or unresectable stage 3 or 4 melanoma. Patients with active autoimmune disease, active or untreated brain or leptomeningeal metastases, medical conditions requiring systemic treatment with moderate- or high-dose corticosteroids or immunosuppressive medications, and uveal melanoma were excluded from the trial. Participants were randomized 1:1 to receive either nivolumab 480 mg IV every 4 weeks or Opdualag (nivolumab 480 mg and relatlimab 160 mg) IV every 4 weeks until their disease progressed or unacceptable toxicity occurred. Tumors were evaluated 12 weeks after randomization and every 8 weeks thereafter up to week 52, then every 12 weeks. The trial met its primary end point, which was progression-free survival. The median progression-free survival was 4.6 months for the nivolumab group and 10.1 months for the Opdualag group. Secondary end points were overall survival, which did not demonstrate a statically significant difference, and overall response rate.[1,2]

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

There are no contraindications to treatment with Opdualag. Immune-mediated adverse reactions (IMARs), which may be severe or fatal, can occur in any organ system or tissue and at any time after starting or discontinuing treatment with LAG-3 and PD-1/PD-L1 blocking antibodies. Patients should be monitored for early identification and management of IMARs. Occurrence of an IMAR may warrant either discontinuing or holding of Opdualag. Creatinine, liver enzymes, and thyroid function should be assessed at baseline and throughout treatment. Opdualag can cause severe infusion-related reactions. Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation before or after being treated with a PD-1/PD-L1 blocking antibody. Because Opdualag can cause fetal harm, women of childbearing potential should use effective contraception during treatment. Opdualag should not be used during breastfeeding.

The most common adverse reactions are diarrhea, fatigue, musculoskeletal pain, pruritus, and rash. The most common laboratory abnormalities are decreased hemoglobin, lymphocytes, and sodium, increased alanine transaminase and aspartate transaminase.[1,2] ■

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

PRESCRIPTION

Infant's Mom Discovers Wrong Directions on Pediatric Propranolol Oral Liquid Label

Case Highlights the Need to Stop, Listen, and Investigate When Patients or Parents Express a Safety Concern

By MICHAEL J. GAUNT, PHARMD

AUTHOR BIO

MICHAEL J. GAUNT, PHARMD, is a senior director of error reporting programs at the Institute for Safe Medication Practices in Horsham, Pennsylvania.

ORAL PROPRANOLOL LIQUID WAS PRESCRIBED for a 7.2-kg, 3-month-old baby with infantile hemangioma, which is a rapidly growing benign vascular tumor.

The pharmacy contacted the physician's office to clarify the order.

When the patient's mother picked up the prescription, propranolol 20 mg/5 mL (4 mg/mL) was dispensed with the following instructions: "Administer 3.5 mL once on day 1, administer 3.5 mL twice daily for the next 6 days, then administer 7.5 mL twice daily for a maintenance dose."

Based on the concentration dispensed, this would equate to 14 mg once on day 1 (1.9 mg/kg/day), 14 mg twice daily for the next 6 days (3.9 mg/kg/day), followed by 30 mg twice daily (8.3 mg/kg/day) for the maintenance dose. This maintenance dose is much higher than the typical daily oral maintenance dose (1 to 3 mg/kg/day) for children and infants for this indication.

At the pharmacy, the mother was neither counseled nor provided with an oral syringe to administer the medication to her infant. After the mother returned home, she called the pharmacist to question the dose. The pharmacist confirmed that the dose was higher than recommended for a 7.2-kg infant with infantile hemangioma.

However, the pharmacist stated, "It should be fine if this is how the doctor wanted it."

If the mother was still concerned about the dose, the pharmacist suggested calling the physician's office herself. The mother called the prescriber to express her concerns. The prescriber confirmed the dosing directions provided on the pharmacy label by the pharmacy were incorrect. The prescriber told the mother that, when the pharmacist called for clarification, the dosing directions were mistakenly communicated to the pharmacist in mL, not mg.

The intended instructions were "3.5 mg (0.88 mL) for the first day (0.49 mg/kg/day), 3.5 mg (0.88 mL) twice daily for

> At the pharmacy, the mother was neither counseled nor provided with an oral syringe to administer the medication to her infant.

the following 6 days (0.97 mg/kg/day), followed by 7.5 mg (1.88 mL) twice daily (2.1 mg/kg/day) for the maintenance dose."

Fortunately, the infant's mother kept questioning the directions, and the error was caught before the infant was given the medication.

There are 3 propranolol oral liquid concentrations available, including 2 concentrations of generic products, 20 mg/5 mL (4 mg/mL) and 40 mg/5 mL (8 mg/mL), and a different concentration for a brand product, Hemangeol 4.28 mg/mL. Hemangeol is the only liquid propranolol approved by the FDA for the treatment of proliferating infantile hemangioma requiring systemic therapy. The generic products are used off label for this indication. In the United States, the existing generic propranolol solutions are expressed in terms of propranolol hydrochloride, and the FDA had previously requested that Hemangeol concentration and dosages be communicated similarly. Outside the United States, the Hemangeol concentration is expressed as 3.75 mg/mL of propranolol base, which is equivalent to 4.28 mg/mL. Unfortunately, the Hemangeol 4.28 mg/mL concentration can add to the risk of dosage calculation errors compared with the available generic 4- or 8-mg/mL concentrations.

SAFE PRACTICE RECOMMENDATIONS

To avoid confusion among the multiple concentrations and between mg and mL doses, propranolol oral liquid doses should always be prescribed in mg. Prescribers should include the patient's weight in metric units on the prescription. Otherwise, pharmacists will need to confirm the weight so they can calculate and verify the mg/kg dose. If the dose is outside the normal range, pharmacists should clarify the order directly with the prescriber, referring to the mg dose. Once the drug has been prescribed in mg, pharmacists may need to calculate and transcribe the mL dose based on the drug's concentration for the patient's instructions if the electronic prescribing system does not calculate the volume automatically. Then, if the volume amount must be entered manually, an independent double check of the calculation should be required.

Labels on prescription oral liquids should specify the dose in mL in the instructions for use for the patient/parent to measure each dose, and then the product's concentration should be listed elsewhere on the label. Weight-based medication doses should be rounded or standardized automatically at the time of prescribing to a dose that is not greater than or less than 10% of the originally prescribed dose. For example, 3.5 mg (0.88 mL) of propranolol 4 mg/mL should be rounded to 3.6 mg (0.9 mL) to facilitate the ease of measuring doses. Pharmacies should provide patients with an appropriately sized, metric-only oral syringe or dosing cup for safe dose measurement and administration of oral liquids. Pharmacists should employ the "teach-back" method, which incorporates a return demonstration by the patient or parent to confirm their ability to measure each dose. Importantly, when patients or parents express a safety concern, stop, listen, and investigate to confirm that there are no errors. ■

Brimonidine Tartrate/Timolol Maleate Ophthalmic Solution 0.2%/0.5%

Marketed by Sandoz

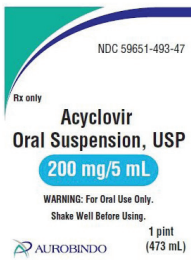
HOT PRODUCT

Compare To: Combigan

Sandoz has announced the generic version of AbbVie's Combigan, a brimonidine tartrate/timolol maleate ophthalmic solution in the 0.2%/0.5% strength. The eye drop combination is used to reduce eye pressure for individuals with ocular hypertension. It is an α-adrenergic receptor agonist with a β-adrenergic receptor inhibitor indicated to lower elevated intraocular pressure for individuals who need adjunctive or replacement therapies. The most common adverse events include allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging.

FOR MORE INFORMATION:

sandoz.com



Acyclovir Oral Suspension USP, 200 mg/5 mL

Marketed by Aurobindo Pharma Limited

Compare To: Zovirax

The FDA has granted its final approval to Aurobindo Pharma Limited's acyclovir oral suspension USP in the 200-mg/5-mL strength. The abbreviated drug application listed the suspension as the generic equivalent to Zovirax from Mylan Pharmaceuticals Inc. It has 3 different indications, including the acute treatment of herpes zoster, known as shingles; the treatment of initial episodes and management of recurrent episodes of genital herpes; and the treatment of varicella zoster virus, known as chickenpox. It is considered an AB-rated generic equivalent by the FDA.

FOR MORE INFORMATION:

xiromed.com

Vigabatrin Oral Solution
Marketed by Lupin Limited

Compare To: Sabril
The FDA has approved the abbreviated new drug application for Lupin Limited's vigabatrin. The oral solution is in the 500-mg strength and is the generic equivalent to Sabril from Lundbeck Pharmaceuticals LLC. The product will be manufactured at Lupin's facility in Goa, India, and has estimated annual sales of $275 million in the United States. Sabril is indicated as an adjunctive therapy for individuals 2 years or older who have refractory complex partial seizures and have not responded to alternative treatment.

FOR MORE INFORMATION:
lupin.com

Budesonide and Formoterol Fumarate Dihydrate Inhalation Aerosol
Marketed by Viatris Inc

Compare To: Symbicort
The FDA has approved budesonide and formoterol fumarate dihydrate inhalation aerosol, which is the first generic version of Symbicort from AstraZeneca. It is indicated for the treatment of individuals 6 years or older with asthma, as well as for the maintenance treatment of airflow instruction and reducing exacerbation for those with chronic obstructive pulmonary disease, including chronic bronchitis and/or emphysema. The drug device combination includes a metered-dose inhaler that contains both drugs, reduces inflammation, and relaxes the muscles in the airways to improve breathing. The generic version of the drug should not be used to treat acute asthma attacks.

FOR MORE INFORMATION:
viatris.com

Pharmacist Alleges Disability Discrimination Was Basis for Termination

Trial Court Denial of Claim Is Pursued on Appeal Based on Alleged Error by Judge When Granting Summary Judgment

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

ISSUE OF THE CASE

Can a pharmacist maintain a federal lawsuit alleging disability discrimination based on both the existence of a disability and retaliation for his disability claims?

FACTS OF THE CASE

A pharmacist practicing in a hospital setting in a north central state was terminated from his position. He filed a lawsuit against his former employer and several of its employees, alleging refusal to grant him a reasonable accommodation. The original federal case filing by his attorney included several alleged violations of the pharmacist's legal rights, including allegations of general harassment and violation of his privacy rights related to the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

An initial assessment of the case was made by a federal magistrate judge, a judicial officer affiliated with a US District Court who deals with the preliminary assessment of the case. The magistrate judge forwarded several recommendations to the federal trial court judge overseeing the case, including dismissal of all the individual employee defendants. He also recommended dismissal of the allegations of general harassment and the HIPAA claim. The presiding US District Court judge adopted those recommendations.

The hospital's attorney then made a motion seeking summary judgment on several other claims of the pharmacist in the initial court filing, including those under the Americans with Disabilities Act (ADA); those related to nationality, religious, and sexual orientation discrimination; and claims rooted in the state civil rights laws and human rights act. The magistrate judge had recommended that the hospital's motion be granted, and the district court judge agreed. Granting a summary judgment motion is appropriate when a judge concludes there is no genuine dispute regarding a remaining material fact, and the party making the motion is entitled to judgment as a matter of law.

The pharmacist filed an appeal with the US Court of Appeals, arguing that the trial court judge had erred when granting summary judgment on his claims alleging ADA failure to accommodate, discriminatory termination, and retaliatory termination. He sought to have the lower court's ruling dismissing his case overturned and the matter returned to the trial court for trial proceedings.

AUTHOR BIO

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THE RULING

The federal appellate court denied the appeal and affirmed the trial court's granting of summary judgment for the health system that had employed the pharmacist.

THE COURT'S REASONING

The appeals court began by noting that the pharmacist had received a diagnosis of attention deficit/hyperactivity disorder and posttraumatic stress disorder. The pharmacist claimed the health system knew of these diagnoses when he started working there 15 years earlier. Further, he claimed that irritability and tardiness are symptoms of his diagnoses and that he had been fired because he pursued disability claims. The health system's response was that the pharmacist was fired after refusing to attend a meeting with his supervisor, a human resources manager, and a union representative.

The court pointed out that to prevail, the pharmacist must demonstrate that a reasonable accommodation is possible because the system knew he was disabled, he had requested an accommodation, the system failed to engage in a flexible and informal interactive process with him about possible accommodations, and his disability could have been reasonably accommodated had that interaction occurred. If the pharmacist could show all 4 things, the burden of proof would shift to the health system "to show that it is unable to accommodate" the request, according to the court.

The pharmacist presented no evidence that the health system did not engage in a flexible and informal interaction about his request to randomly arrive late for work. Next, despite providing a letter about his diagnoses, he did not comply with the request to provide a written accommodation form or other paperwork from his physician. The court pointed out that the pharmacist was aware of those documentation requirements to support an accommodation because he had previously gone through the process to adjust his workstation and work schedule.

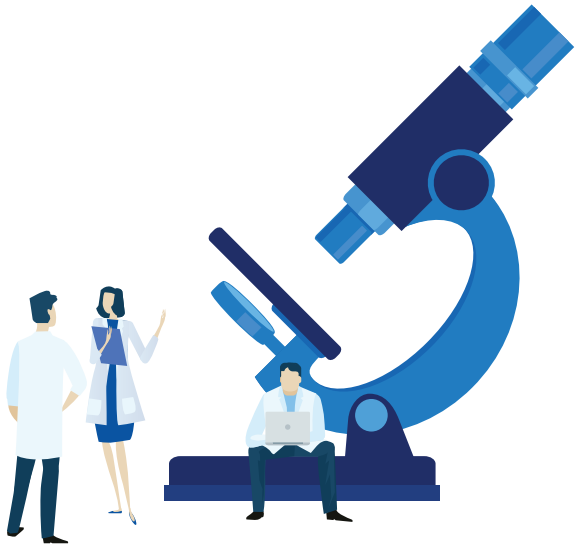
> The magistrate judge had recommended that the hospital's motion be granted, and the district court judge agreed.

The record led the court of appeals to conclude that the breakdown in communication regarding the accommodation was attributable to the pharmacist. He had been on a performance improvement plan because of being absent from work 4 times in a 6-month period and late to work 89 times during the same period. He had also failed to establish a causal connection between his asserting his rights under the ADA and his termination. Finally, the system had documented numerous instances of the pharmacist refusing to process prescription changes and making several offensive comments to other employees of the system.

The appeals court stated clearly that the pharmacist was "fired for misconduct, and no reasonable jury could find that the evidence in this case shows a causal connection between his termination for insubordination and his disability or ADA claims."

The court cited a prior decision, stating that the "ADA confers no right to be rude."

The decision of the trial court was affirmed. ■



INFECTIOUS DISEASE | RESPIRATORY | VACCINES

COVID-19 Affects Development of Medical Devices

Companies, FDA Caught Unaware by Surge in Virus Cases, Leading to Shortage of Critical Items

By MELISSA A. KLONOWSKI AND JOSEPH L. FINK III, JD, DSC (HON), BSPHARM, FAPHA

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FROM ADHESIVE BANDAGES TO HEART MONITORS, medical devices are all around us. Some of these are easily accessible in stores, whereas others are exclusive to clinics and hospitals. How is it possible to determine which medical devices are effective and safe for use with patients?

The current process for approving medical devices is administered by the FDA. The FDA oversees the premarket audit, clearance, and approval process by sorting the medical devices into 3 classes based on risk level. Traditionally, this process has been effective and efficient enough. However, with the COVID-19 outbreak, there have been issues with delays and shortages of vital medical devices, such as testing kits and ventilators.

In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act to allow the FDA to gain more authority in regulating drugs and food. In 1976, the Medical Device Amendments gave the FDA the ability to oversee premarket and postmarket approval processes for medical devices.[1] This process involves sorting medical devices into 3 different classes. Class I is general controls and can be with or without exemptions. This class contains medical devices that pose the lowest risk. Class II is general controls and special controls and can also be with or without exemptions. Finally, class III is general controls and premarket approval. Depending on the class categorization, the manufacturer of the medical device may be required to submit certain paperwork, such as a 510(k) or a postmarket approval application.

"A 510(k) is a premarket submission made to [the] FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device. Firms making submissions must compare their device [with] 1 or more similar legally marketed devices and make and support their substantial equivalence claims," according to the FDA.[2,3]

Completing this process is expensive and time-consuming. It is estimated that for manufacturers who had to fill out the

premarket approval (PMA) applicaton, usually for class III devices, they were required to "submit all available scientific knowledge concerning investigations; clinical and nonclinical data of the device's safety and effectiveness; detailed information regarding its design, components, ingredients, properties, and principles of operation; any applicable performance standards; and other information deemed relevant by the FDA," according to an article in the *University of Michigan Journal of Law Reform*.[1]

On top of that, the FDA is allowed to request more information from the manufacturer. Megan Andersen, writing in the *University of Michigan Journal of Law Reform*, goes further to draw evidence from a 2010 study regarding the costs incurred to go through the medical device approval process, specifically with a PMA.

"According to a 2010 independent analysis, 'the average total cost from concept to approval was approximately $94 million' for PMAs, with $75 million spent on clinical stages required by the FDA application process. The same study showed that from first communication with the FDA, it took an average of 54 months for FDA reviewers to make a determination on the device," she wrote.[1]

With the FDA taking many years to review medical devices, the process can get backed up, making it less efficient to get more medical devices out there. This ties in with the recent COVID-19 pandemic. Medical device companies and the FDA were unprepared for the sudden surge in virus cases, leading to a shortage in medical devices, such as ventilators. "There's currently thought to be a global shortage of thousands of ventilators as the world attempts to tackle the deadly pandemic," according to Shrinidh Joshi, PhD, a freelance writer with over 10 years of experience in pharmaceutical and other medical writing.[4]

In addition, there have been delays in being able to obtain data on the effectiveness of a product. "Medical device manufacturers rely heavily on health care facilities for their clinical trial data collection…As the COVID-19 pandemic continues to unfold, medical device companies are finding

How is it possible to determine which medical devices are effective and safe for use with patients?

it difficult to make informed decisions about their products, supply chains, and regulatory obligations in the midst of uncertainty," Joshi wrote.[4]

The medical device approval process is a huge job left in the hands of 1 organization. Streamlining the process makes things simpler. There are plans within the Senate to fund the FDA with an additional $200 million. "The bill focuses on increases for food safety and medical product safety activities of the agency," according to the United States Senate Committee on Appropriations.[5]

It is yet to be determined how much will go toward medical devices and whether it will even be effective. However, if there is going to be anything done about the huge backup in medical device approval, then Congress must enact this bill. The pandemic has resulted in mass struggle for the world and has especially affected the medical field. Hospitals are crammed, and there are shortages of important devices, not to mention delays in approving medical devices, which was a problem even before the pandemic. It is time for Congress to act. ■

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Left photo: Malley's Compounding Pharmacy Sign; ***Right photo:*** Anne Henriksen, PharmD

Malley's Is "a Place Where People Connect, Share, and Know Each Other"

The Washington State Pharmacy Employs Technology for Traditional Dispensing and in Its Compounding Lab

By KAREN BERGER, PHARMD

MALLEY'S COMPOUNDING PHARMACY IN RICHLAND, WASHINGTON, aims to create an environment that is welcoming while also employing the latest technology, according to Anne Henriksen, PharmD, the owner and pharmacist-in-charge, and a graduate of Washington State University College of Pharmacy and Pharmaceutical Sciences.

The pharmacy opened in the 1940s and has had several name changes under several owners, "from Johnson's to Miller's to Malley's, which stuck through several owners," Henriksen said.

"Customers come in and tell us stories of growing up and coming into Malley's and buying candy. Some even had their first job at Malley's," Henriksen said.

After graduating from pharmacy school, she completed a residency and fellowship in geriatrics and geropsychiatry and thought she was set for a career in academia.

"I love academia and teaching, but honestly, my motivation for completing my training was not career driven, but personal growth. I had the opportunity to work with some of my mentors for 2 years and learn a subject I love," Henriksen said.

She soon met her husband and moved back home.

"It seemed a natural fit, although I had some who told me I was throwing away my career," Henriksen said.

For 2 years, Henriksen was the director of pharmacy at a Federally Qualified Health Center.

"This opportunity mixed my previously completed clinical training with some hands-on, real-life business management and team leadership. It was the perfect segue into pharmacy ownership, and it was during this time that I learned of a small independent for sale," Henriksen said.

Fast-forward to the present, and Malley's is a busy pharmacy with 2 primary departments: traditional dispensing and compounding.

In the traditional dispensing department, the staff members use technology to ensure safety, including an Eyecon and the RxSafe.

"The RxSafe stores original prescription bottles by serial number. When we are ready to fill a prescription, we scan a label and the RxSafe pulls the stock bottle for that prescription," Henriksen said.

AUTHOR BIO

KAREN BERGER, PHARMD, is a pharmacist at an independent pharmacy in northern New Jersey.

PHOTOS COURTESY OF THE AUTHOR.

From left to right: Evie Mensonides, PTCB; Tiffani Harker; Samantha Martinez; Anne Henriksen, PharmD; Jessica Tyrrell, PTCB; and Patty German, PharmD

"We then double verify the stock bottle is correct when we scan the national drug code on the Eyecon. The Eyecon is an infrared counting technology; it knows how many pills are necessary to fill the prescription and alerts us if we are over or under that number. It also stores an image of our completed count," Henriksen said.

"I would not own a pharmacy without an Eyecon," she said.

In the compounding laboratory, the staff members also use technology, including a MAZ and RAM mixers.

Henriksen and her employees are also known as experts on methylenetetrahydrofolate reductase (*MTHFR*) gene mutation.

"We provide a wide variety of supplements from many professional-grade lines," she said. "We have extensive knowledge on not only the *MTHFR* genes, but also other genes along the MTHFR pathway that can affect methylation."

Meanwhile, Malley's tries to make patients feel welcome by carrying candy from a local candy company.

"We have this candy for sale but frequently throw a few pieces of candy in the bags of our customers or hand a piece or 2 to the child of a customer. Candy isn't appropriate for every customer, but when we are able to, it sure makes their faces light up," Henriksen said.

Henriksen appreciates the past but knows it is important to look to the future.

"Our long-standing history makes us unique, but we aren't a store that's stuck in the past. We are always looking for ways to practice pharmacy in 2022 and beyond on our terms and in ways we love," Henriksen said.

"Just last week we had 2 customers at the registers. At one register, a customer was showing my staff pictures of a recent concert he had attended, a big concert of a big name in Vegas. The customer I was helping smiled and said to me, 'I love that you have created a place where people connect, share, and know each other.'" Henriksen said.

Although it is cliché, she said Malley's is really like a family.

"Especially in the past 18 months, we have grown closer as some have gone through personal struggles. We have faced countless changes," Henriksen said.

"We laugh about how to succeed in pharmacy: You need a blend of a personality type that is rigid enough to strive for perfection and flexible enough to adapt to the never-ending changes [in] health care. When things get tough, you might see us doing a wiggle dance, saying 'flexible people are happy people' to get through our day," Henriksen said. ■

VISIT MALLEY'S WEBSITE!

Implementing Services into Community Pharmacy Workflow Presents Challenges

Areas for Improvement Include the Business Model, Health Care Team Buy-in, Patient Engagement, and Technology

By JENNIFER GERSHMAN, PHARMD, CPH, PACS

THE MEDICARE PRESCRIPTION, DRUG, IMPROVEMENT, AND MODERNIZATION ACT OF 2003 established requirements under Part D to provide medication therapy management (MTM) services to eligible Medicare beneficiaries.[1]

This set the stage for an expansion of pharmacists' roles in patient care. In 2018, approximately 65% of plans reported using community pharmacists through vendor contracts.[2,3] However, challenges exist with implementing MTM services into the community pharmacy workflow.

OVERCOMING OBSTACLES

The results of one cross-sectional study from a random sample of Medicare beneficiary enrollment data evaluating 2014 Part D MTM files showed that community pharmacists provided more medication therapy problem (MTP) recommendations ($P < .001$) but resolved fewer MTPs than those provided by non-community pharmacists (eg, MTM vendor in-house pharmacists, Medicare Part D plan pharmacists).[2] Evidence shows that the following are challenges to implementing MTM services in the community practice setting: business model obstacles, incorporating programs within the health care team, integration into the pharmacy workflow, lack of patient engagement, and technology adaptation struggles (**Figure**[2-5]). Challenges to incorporating MTM services into the pharmacy workflow include difficulty training personnel, inadequate dedicated physical space to perform consults, and lack of time.[2,3] Busy chain pharmacies can have difficulty incorporating MTM services because of the many pharmacist responsibilities that include administering immunizations and dispensing medications. Evidence shows that access to technology is critical for MTM services, especially to review electronic medical records.[3,4] Typically, MTM vendors use web-based software for documentation and billing, so incorporating trained pharmacy technicians into this task is critical. The results of another study identified barriers and implementation strategies for integrating a web-based medication management application in community pharmacies.[4] Additionally, the study results showed that clinical training, computer literacy, and leadership training facilitated implementation of a web-based program into the practice setting.[4] However, staff opposition to change and provider reluctance to share data were considered barriers to implementing the technology.[4]

Lack of patient interest in MTM services is also an obstacle.[3] Additionally, many patients are unaware that pharmacists' clinical training goes beyond dispensing medications.[3] Pharmacists can develop a standardized approach to delivering MTM services and explain their roles to patients. Pharmacists and physicians can also successfully work together through collaborative drug therapy management to improve communication and patient care services.[3] The results of a third study showed there was an increase in MTM

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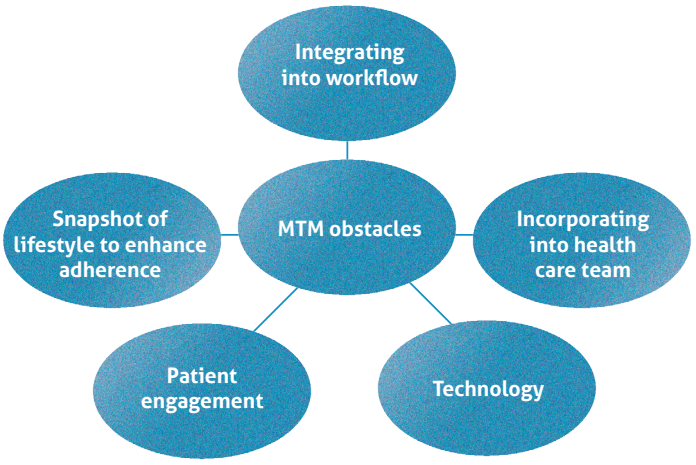
FIGURE. MTM Obstacles[2-5]



MTM, medication therapy management.

completion rates after an educational intervention was implemented at community pharmacies ($P < .001$).[5]

More than 600 pharmacist practitioners and program directors who provided survey responses thought that comprehensive medication management (CMM) services allow health care organizations to achieve clinician satisfaction, cost savings, improved outcomes, and patient satisfaction, according to the results of a report from Health2 Resources.[6]

The CMM approach focuses on clinical, patient, and personal goals to improve health outcomes.[6] Goodrich Pharmacy, an independent pharmacy in Anoka, Minnesota, and HealthPartners have successfully performed CMM.[6] HealthPartners started paying for CMM services in 2006.[6] At press time, Goodrich Pharmacy employed 18 pharmacists at 7 sites and they used CMM with approximately 900 patients.[6] ■

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PHARMACIST SPOTLIGHT

In an interview, Mallory K. Tucker, PharmD, BCMTMS, clinical lead pharmacist, discussed strategies to incorporate medication therapy management (MTM) services at independent pharmacy Atchley Drug Center in Greeneville, Tennessee.

She has received training through the American Pharmacists Association certificate program on delivering MTM services and recently became board certified through the National Board of Medication Therapy Management. This training allowed Tucker to implement a variety of strategies to improve MTM completion rates at her pharmacy.

"I do all our work with OutcomesMTM, and I took us from a 1- to a 5-star rating in 2 months," she said.

Over a 2-month period, Tucker submitted 200 claims in the form of comprehensive medication reviews (CMRs) and targeted intervention programs (TIPs). The MTM services were performed through a combination of face-to-face and telephone consults, with most patients filling prescriptions at Atchley Drug Center. For MTM patients who have not filled with their pharmacy before, Tucker determines their primary provider and current pharmacy. Additionally, she answers many questions about CMRs and other MTM services to build patient relationships.

Tucker incorporated the CMRs and TIPs throughout the workday by placing notes on the medication bags for consultations when patients came to pick up medications. Notes were made during consultations, and she documented all the information into OutcomesMTM in the afternoon. Common disease states for MTM services included diabetes, hyperlipidemia, and hypertension.

DIABETES | MENTAL HEALTH

Shine a Light on Diabetes and Mental Health

Appropriate Screening Tools Can Help Identify Individuals at Increased Risk for or With Anxiety, Depression, and Eating Disorders

By MARIA S. CHARBONNEAU, PHARMD; AND CAMILLE C. CHARBONNEAU, PHARMD, BCPS, CDOE, CVDOE

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INDIVIDUALS WITH DIABETES are at increased risk for anxiety, depression, and eating disorders.[1]

Additionally, diabetes can lead to mental health issues related to diabetes distress.[2] Mental health issues may be barriers to diabetes self-management and may increase the risk for long- and short-term diabetes complications.[1]

Despite the profound impact mental health issues can have on diabetes care, only about one-third of individuals with diabetes are diagnosed and treated.[1] Without appropriate, timely identification and management of comorbid mental health issues, the patient's health and financial well-being can be significantly affected. Substantial cost to the health care system can also occur.

ANXIETY

The lifetime prevalence of generalized anxiety disorder in individuals with diabetes is approximately 20%.[3] Disease complications and progression, failing to meet glucose goals, fear of hyperglycemia or hypoglycemia, hypoglycemia unawareness, and insulin administration are commonly reported concerns.[4,5] Preexisting fears of needles and blood may be heightened with a diabetes diagnosis and may lead to severe anxiety or panic disorders.[1] Additionally, individuals exhibiting excessive diabetes self-management behaviors may have obsessive-compulsive disorder.[6]

Fear of hyperglycemia or hypoglycemia unawareness may compel some patients to purposefully maintain blood glucose levels above goals. Parents of children with type 1 diabetes (T1D) may also encourage this practice because of the same fear.[1] Furthermore, symptoms of hypoglycemia, such as heart palpitations, sweating, and tremors, can mimic symptoms of anxiety disorders, making it difficult for people with anxiety and diabetes to discern the difference.

DEPRESSION

Having type 2 diabetes (T2D) increases the risk of developing major depression disorder (MDD) and having MDD increases the risk for developing type 2 diabetes, which suggests they may have a bidirectional relationship.[1] Antidepressants and psychotherapy for depression treatment in individuals with diabetes have shown minimal effects on glycemic management and moderate effects on depression. The collaborative care model, a primary care model integrating behavioral health and general medicine, has shown significant positive effects on both depression and glycemic management.[1,7]

Table 1. Pharmacist's Checklist for Mental Health and Diabetes Management[7,9,12,15-18]

- Consider mental health professionals integral to the multidisciplinary team.
- Continue learning with mental health training.
- Discuss expected diabetes-related vs generalized psychological distress.
- Educate patients and their care teams regarding diabetes and mental health.
- Encourage developmentally appropriate steps.
- Encourage integrated behavioral and general health services.
- Include alerts in health records to prompt screening.
- Perform routine medication reviews, monitoring for medications that may contribute to weight changes or worsen mental health concerns.
- Provide blood glucose awareness training.
- Provide information resources for mental health services.
- Provide medication and therapy expectation education in the context of both diabetes and mental health treatment.
- Provide referrals to mental health professionals experienced in childhood diabetes, when appropriate.
- Recommend diabetes educators for problem-solving strategies.
- Refer metabolic surgery candidates to mental health professionals with obesity management expertise.
- Use validated tools to screen for anxiety, depression, eating disorders, diabetes distress, and psychosocial issues.

EATING DISORDERS

Women with T1D have a 2-fold increased risk for eating disorders.[1] Eating disorders, such as binge eating and caloric purging with insulin restriction, can be seen in 31% to 40% of women aged 15 to 30 years who have diabetes.[1,8] Comorbid diabetes and eating disorders increase the risk for poor glycemic management, hospitalizations, neuropathy, retinopathy, and premature death.[1]

DIABETES DISTRESS

Diabetes distress is significant psychological stress resulting from the emotional burden of managing the chronic, progressive disease without any "vacation days."[1,9] Over any 18-month period, approximately 38% to 48% of individuals with diabetes have diabetes distress.[10] High levels of diabetes distress can negatively affect diabetes management and quality of life, leading to poor dietary and exercise behaviors and medication adherence as well as declining glycemic management.[9,10] Mindful cognitive behavioral and social problem-solving approaches and self-compassion programs have been shown to decrease diabetes distress.[11]

Table 2. Screening Tools[16,19-21]

Anxiety	Generalized Anxiety Disorder-7 item scale (GAD-7)
Mixed anxiety/ depression	Diabetes Anxiety Depression Scale (DADS)
Depression	Patient Health Questionnaire-9 (PHQ-9)
Eating disorders	Diabetes Eating Problems Survey-Revised (DEPS-R)
Diabetes distress	• Diabetes Distress Scale (DDS) • Problem Areas in Diabetes (PAID) scale

SIDE NOTE

Metabolic surgery recipients may be at an increased risk of anxiety, depression, developing or worsening substance abuse, and suicide ideation. Clinicians and patients should address significant underlying mental health conditions before considering surgery.[12-14] Following metabolic surgery, the clinical team should assess recipients' mental health regularly.[14]

ISSUES IN CHILDREN

Profound developmental changes occur during the transition from childhood to adolescence and adulthood. Managing diabetes during this dynamic period can be challenging. Premature responsibility transfer from caregiver to child can result in suboptimal diabetes management and burnout.[15] Routine assessment of diabetes distress, psychosocial issues, and social determinants in patients and caregivers is necessary.

CONCLUSION

The pharmacist can play an active role in diabetes and mental health management (**Table 1**[7,9,12,15-18]). Appropriate screening tools can help identify those with or at increased risk for anxiety, depression diabetes distress, eating disorders, and diabetes distress (**Table 2**[16,19-21]). With timely intervention, pharmacists can positively affect diabetes and mental health outcomes. ■

Assisting Older Adults With Medication Use Can Reduce Errors

Areas of Focus Include Drug Discrepancies During Transitions of Care, Polypharmacy, and Promotion of Self-Management

By LYUBOV VILLANUEVA; JENNIFER CHEN, PHARMD, BCPS; AND SHANE P. DESSELLE, PHD, RPH, FAPHA

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OLDER ADULTS, GENERALLY DEFINED AS THOSE 65 YEARS OR OLDER, are projected to account for a quarter of the US population in the coming years and represent the fastest-growing age group in America.[1,2]

Pharmacists and pharmacy technicians are well known as some of the most accessible and frequently visited members of the health care industry.[3] Evidence suggests pharmacists interact with patients up to 10 times more frequently than primary care physicians.[4] With the continued expansion of the older adult population, pharmacists and technicians have the opportunity to play a major role in addressing their health care and medication-related needs. Some of these include medication discrepancies occurring during transitions of care, polypharmacy and the need to deprescribe, and promotion of greater self-efficacy through medication self-management, particularly for those who lack effective social support structures.

Older adults often face multiple chronic health conditions, which increases the likelihood of polypharmacy.[5] Polypharmacy, or the concurrent use of multiple chronic medications, has been widely linked to negative health outcomes.[6,7] A survey of 2206 community-dwelling adults of ages 62 to 85 years was conducted by in-home interviews and use of medication logs between 2010 and 2011. At least 1 prescription medication was used by 87% of participants. Five or more prescription medications were used by 36%, and 38% used OTC medications. Polypharmacy may contribute to an increase in drug-drug interactions, inappropriate combinations of medications, issues with medication adherence, and prescribing cascades. Technicians in all settings may help identify patients with polypharmacy who may benefit from a comprehensive medication review by their pharmacists. Pharmacists may then conduct a polypharmacy-targeted medication review and make recommendations for deprescribing to the patient's primary care physician. Deprescribing involves evidence-based systematic decisions in reducing unneeded medications that might contribute to deleterious health outcomes, rather than promoting positive ones.

Older adults are also more than twice as likely to require hospitalization compared with middle-aged adults,[8] which not only increases the risk of polypharmacy and medication errors. Transition points in care represent moments of increased risk for medication discrepancies and miscommunication. Seamless transitions of care are especially vital for multimorbidity older adults, who are cared for by multiple specialty providers, seen more frequently in the hospital setting, and often have complex medication regimens.[9] Medication reconciliation, a pharmacy-driven process, plays a key step in the identification of medication discrepancies and polypharmacy. Evidence has shown that trained technicians can obtain medication histories with accuracy and completeness.[10] A retrospective chart review conducted at a university hospital in New Jersey assessed 200 in-patients who received a technician medication history of prior-to-admission medications, followed by medication reconciliation of electronic health record (EHR) by a pharmacist.[11] Medication history–taking conducted by technicians included a brief interview of medication history with the caregiver or patient, which was then verified against objective data, such as prescribing data, prescription refill history, and prescription vials. Overall, 325 total medication discrepancies were identified, with medication omission the most frequently observed (64.7%). This study demonstrated the

utility of incorporating technicians into medication reconciliation programs.

In the community setting, there are additional measures that technicians can take to protect older adult patients. If feasible, technicians may encourage periodic so-called brown-bag checkups. They can instruct patients to bring in all their medications and among other things, check the expiration dates of these drugs. During these reviews, home medications brought in by patients may also be matched to their profiles in the EHR. This process can help identify patients who have medication discrepancies and use multiple pharmacies. A review of each patient's refill history may also shed light on medication adherence. Available methods to encourage adherence include having patients opt into automatic refills, providing medication charts, and using medication organizers. Because older adults tend to have multiple specialty providers, technicians may also encourage patients to transfer all their prescriptions to 1 health system or pharmacy, as this helps maintain an accurate and updated list of all outpatient medications prescribed to the patient. Finally, cognitive decline is highly prevalent among older adults and has been associated with poor medication self-management skills.[12] Technicians play a pivotal role in ensuring that patients leave the pharmacy with adequate resources for successful medication self-management. This may include printed prescribing information, ensuring patient materials are printed in legible font size, and verbal communication of medication changes to patients and their caregivers.

CONCLUSION

Technicians are a valuable resource for health systems and play a key role in working with older adult patients to reduce medication errors. In transitions of care, highly trained technicians can positively affect the workflow by conducting medication reconciliation upon admission. This process helps identify discrepancies in medication history and medication list and also identifies patients with polypharmacy. In the community setting, technicians interact with patients more frequently than pharmacists do, which make them the ideal candidates for recognizing difficulties with medication adherence.[13] Proactively reviewing patients' electronic records for dispensing history may help identify patients struggling with medication adherence and reveal an opportunity for technicians to alert and collaborate with pharmacists to share effective medication adherence strategies. Finally, communication of medication changes often falls on technicians when prescriptions are picked up. Ensuring clear, patient-friendly communication maintains an environment of trust and reduces medication errors. Trust is especially important especially for patient outcomes, but it also helps promote customer loyalty. ■

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CARDIOVASCULAR

Hypertension Watch

Maternal Deaths Caused by Chronic Hypertension Continue to Rise

CHRONIC HYPERTENSION is contributing substantially to maternal deaths in the United States, with a particular risk among Black women, according to new research results from Rutgers Robert Wood Johnson Medical School's Department of Obstetrics, Gynecology, and Reproductive Sciences in New Brunswick, New Jersey.[1]

The study analyzed data from more than 155 million births and 3287 hypertension-related maternal deaths among women age 15 to 49 years between 1978 and 2018 in the United States. The incidence of hypertension-related maternal deaths increased with age, with the highest being among women aged 45 to 49 years. Further, the research team found a substantial race disparity in the trends of maternal mortality rates because of hypertensive conditions.[1] The findings underscore the need to better identify and treat women with chronic hypertension and develop targeted prenatal interventions, such as reducing blood pressure and body mass index.

"We have gotten much better at treating women with pre-eclampsia/eclampsia during pregnancy, which has undoubtedly contributed to the decline in maternal death rates, but we haven't done as good [of] a job in treating women with chronic hypertension," study author Cande V. Ananth said.[1] "Part of that is because many of these women come in undiagnosed, and it's often problematic to treat women with drugs to reduce their blood pressure, particularly early in pregnancy, so there's a conflict of what's the right approach."—*Jill Murphy*

Hospitalization Rates Increase for Uncontrolled Hypertension

THE NUMBER OF PATIENTS HOSPITALIZED for a hypertensive crisis more than doubled between 2002 and 2014, according to investigators at Cedars-Sinai Medical Center in Los Angeles, California.

Furthermore, investigators found that although men are more likely than women to be admitted for a hypertensive crisis, women have similar hospital mortality rates.[1]

The findings, published in the *Journal of the American Heart Association,* showed that the increase in hospitalizations occurred at a time during which some studies reported overall progress in blood pressure control and a decline in related cardiovascular events in the United States.

For this study, investigators analyzed data from the National Inpatient Sample, including a subset of all hospitalizations across the United States. They found that annual hospitalizations for hypertensive crises more than doubled during a 13-year period. Hospitalizations related to hypertensive crises represented 0.17% of all admissions for men in 2002 compared with 0.39% in 2014. Hospitalizations related to hypertensive crisis represented 0.16% of all admissions for women in 2002 vs 0.34% in 2014.[1]

Based on their findings, the investigators estimated that between 2002 and 2014, 918,392 hospitalizations and 4377 in-hospital deaths related to hypertensive crisis occurred in the United States.[1]—*Aislinn Antrim*

Sleep Apnea During Pregnancy Is Linked to Hypertension Risk, Metabolic Syndrome

PRIMARILY OBSTRUCTIVE SLEEP APNEA, also known as sleep-disordered breathing, during pregnancy and in the years after delivery may be associated with an increased risk for hypertension and metabolic syndrome, new study results showed.[1]

Investigators conducted sleep apnea tests on 1965 women who were part of the nuMoM2b trial (NCT01322529) and experiencing their first pregnancy. They also evaluated 1222 women from the nuMoM2b trial who were examined 2 to 7 years after delivery.

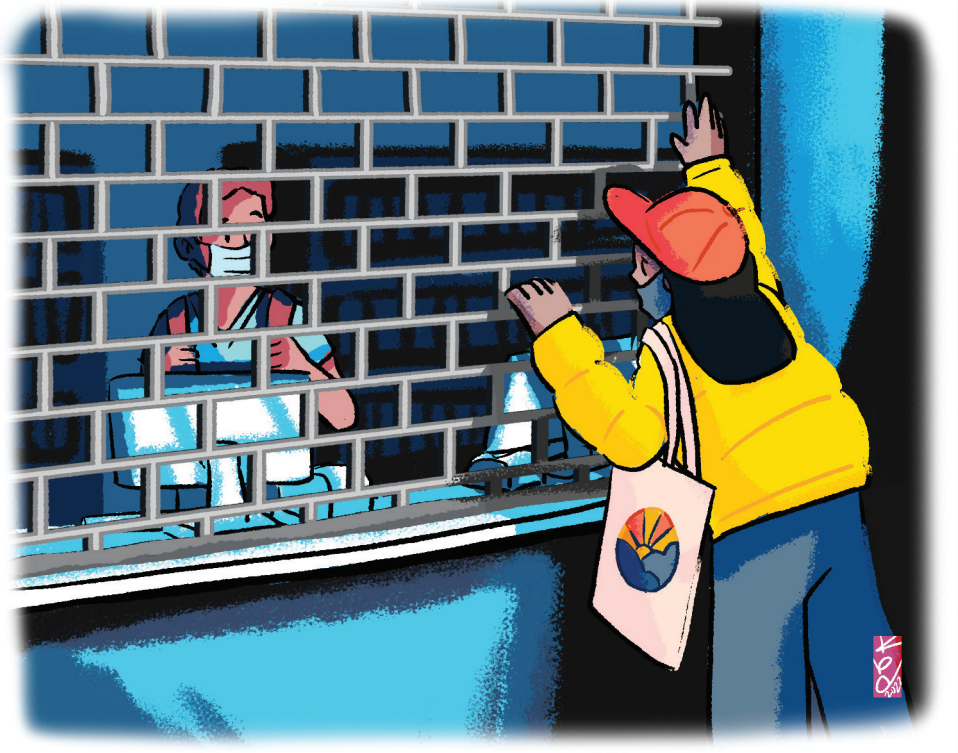
Participants in this study on sleep apnea in pregnancy were evaluated both during pregnancy and 2 to 7 years later, each using the same model of home sleep apnea test. The participants were considered to have sleep apnea if they experienced 5 or more breathing pauses or drops in oxygen during their estimated sleep period. The results showed that sleep apnea, measured during pregnancy and 2 to 7 years after delivery, was associated with the development of hypertension and metabolic syndrome.

"In addition, participants with sleep apnea that persisted during pregnancy and the 2-to-7-year follow-up visit were at more than 3-fold increased risk for incident hypertension and a more than 2-fold increased risk for metabolic syndrome compared [with] participants who never had an abnormal sleep study," said study coauthor Susan Redline,[1] MD, MPH, the Peter C. Farrell Professor of Sleep Medicine at Harvard Medical School, a professor of epidemiology at Harvard T.H. Chan School of Public Health, and the director of Programs in Sleep Medicine Epidemiology and Sleep and Cardiovascular Medicine at Brigham and Women's Hospital in Boston, Massachusetts.[1]—*Ashley Gallagher*

ILLUSTRATION BY KIRSTIE BELLE DIONGZON

Pet Peeves

BROUGHT TO YOU BY THE SASSY PHARMACIST



Impatient Patients

Individuals who ask whether the terminal is open when you have been open for 5 minutes.

Chatty Cathy

Customers in the passenger window who try to talk to pharmacy employers in the drive through.

Dr No

A physician submits a prescription with no directions, so the pharmacist calls to clarify the script, and the patient gets mad and says, "I've been taking this medication for 10 years, twice a day!"

Check Online

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

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Bossy patients, abandoned prescriptions, drive-through demands? We want to know! Send your pet peeves to **cmollison@pharmacytimes.com**. We'll share them here and online.

ILLUSTRATION BY KIRSTIE BELLE DIONGZON

Case Studies

By SUNERI AMIN, CHRISTOPHER EPPS, AND STEFANIE C. NIGRO, PHARMD, BCACP, CDCES

CASE 1

SA is a 54-year-old-woman with type 2 diabetes who is being discharged from the hospital following a hyperglycemic emergency related to diet and poor insulin adherence. The patient is highly motivated to control her diabetes with the help of a dietitian. Prior to discharge, the pharmacist is asked to counsel SA on calculating mealtime insulin dose at lunch using a correction factor. The patient receives 24 units of insulin glargine U-100 at bedtime and 8 units of regular insulin before each meal, 3 times per day. SA's prelunch glucose level consistently averages 240 mg/dL, and her target fasting plasma glucose is set at 120 mg/dL.

What correction dose should the pharmacist recommend?

CASE 2

GS has some concerns about his newly prescribed medications. He is a 56-year-old Hispanic man who was recently discharged from the hospital after experiencing a myocardial infarction with stent placement. GS was instructed to begin taking aspirin 81 mg daily, atorvastatin 80 mg daily, metoprolol tartrate 25 mg twice daily, pantoprazole 40 mg daily, and ticagrelor 90 mg twice daily. Two days after starting these new medications, he began experiencing bloating and diffuse stomach discomfort. GS is gluten- and lactose-intolerant and is concerned that these new medications may be contributing to these symptoms. He wonders whether he can stop taking them all together to avoid feeling sick.

What steps can the pharmacist take to ensure these medications do not have gluten or lactose excipients?

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Answers

CASE 1: The "rule of 1500" can be used to determine SA's correction factor (CF):

CF = 1500/total daily dose of insulin
(eg, 1500/48 = approximately 31)

This means for every 1 unit of regular insulin, SA's blood glucose (BG) level is expected to be lowered by 31 mg/dL. Next, the difference between the prelunch BG and the target BG should be calculated (eg, 240 mg/dL – 120 mg/dL = 120 mg/dL). To find how much insulin to add to the lunch dose, divide the BG amount above target by the CF (eg, 120/31 = 3.9). Therefore, SA will add 4 extra units of regular insulin to her prelunch dose, bringing the total to 12 units. Inform SA that this calculation is necessary to avoid hypoglycemia. SA should also keep track of her pre- and postprandial BG levels for the next week to determine what changes, if any, may be made at a follow-up appointment.

Reference

Howard-Thompson A, Khan M, Jones M, George CM. Type 2 diabetes mellitus: outpatient insulin management. *Am Fam Physician*. 2018;97(1):29-37.

CASE 2: The pharmacist should first verify which drug was dispensed to GS and by which manufacturer, then they can check the package insert or call the manufacturer to verify the inactive ingredient list. If GS's medications contain gluten or lactose, alternative drug entities or manufacturers can be explored. Several resources can help. One such resource is GlutenFreeDrugs.com.[1] However, this list is limited to a select number of drugs and manufacturers, and it is unclear how often it is updated. The National Library of Medicine's Daily Med is also useful.[2] The advanced search offers the querent the ability to screen drugs by the absence or presence of active or inactive ingredients. Once a specific manufacturer or product is identified as gluten- or lactose-free, the pharmacist can inform the prescriber. The ultimate goal is for GS to continue to take his medications as prescribed to avoid further cardiac complications.

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THIS ACTIVITY IS SUPPORTED BY AN EDUCATIONAL GRANT FROM AMERICAN REGENT.

Optimizing Treatment Approaches for Iron Deficiency in Heart Failure

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DISCLOSURES

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- Speakers Bureau: AstraZeneca, Boehringer Ingelheim

INTERVIEW VIDEO FACULTY
Christopher Chien, MD, FACC, has the following relevant financial relationship with a commercial interest to disclose:
- Grant/Research Support: American Regent

The following contributors have no relevant financial relationships with commercial interests to disclose:

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Video clips from an interview with Dr Chien highlighting answers to key questions in the management of iron deficiency in heart failure can be found at **pharmacytimes.org/ID-HF**

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.[1,2] More frequently, the rate of ID in the HF population is reported as approximately 40% to 50%.[3-6] 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 with anemia (hemoglobin <12.0 g/dL for women and <13.0 g/dL for men) and 45% of patients without anemia.[6] ID in patients hospitalized for acute HF has been documented to occur in as many as 50% to 80% of patients.[5]

As with other chronic inflammatory conditions such as chronic kidney disease (CKD), cancer, and inflammatory bowel disease, patients with HF are at an increased

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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 peak oxygen consumption (VO_2), decreased ventilatory response to exercise, and shorter 6-minute walk distance (6MWD).[4,12,13] An analysis of 552 patients with HF assessed the impact of ID on health-related QOL (HRQOL) as determined by the Minnesota Living with Heart Failure questionnaire (MLHFQ) and found that, even when adjusting for other factors that are known to limit HRQOL, ID was independently associated with worse MLHFQ scores. Notably, anemia was not independently associated with worse HRQOL in this analysis.[14] Lastly, ID is consistently demonstrated to independently increase mortality and hospital readmission in patients with HF regardless of baseline hemoglobin (Hb) status.[3,6,15] Data from 1506 international patients with HF published by Klip and colleagues even suggest that ID may be a more accurate prognostic marker than anemia.[6]

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% (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

TABLE 1. MANAGEMENT OF IRON DEFICIENCY PER CURRENT HEART FAILURE GUIDELINES[16-19]

	Screening	Diagnosis	Treatment recommendations	Class (level of evidence)
ACC ECDP on patients hospitalized with HF (2019)	Evaluate for underlying etiology of anemia	N/A	IV ferric carboxymaltose or non-dextran IV iron	Low-to-moderate quality evidence
ESC guidelines (2021)	Routine screening for comorbidities such as ID should occur in all patients All patients should be screened for ID before discharge from an AHF admission or at the first follow-up visit	Ferritin <100 ng/mL OR ferritin 100-299 ng/mL with TSAT <20%	LVEF ≤45%: IV ferric carboxymaltose	2a (A): should be considered based on data derived from multiple RCTs or meta-analyses
			LVEF ≤50% and recently hospitalized for HF: IV ferric carboxymaltose	2a (B): should be considered based on data derived from a single RCT
AHA/ACC/HFSA guidelines (2022)	Anemia screening as routine baseline assessment for all patients	Ferritin <100 ng/mL OR ferritin 100-300 ng/mL with TSAT <20%	Intravenous iron (only data from ferric carboxymaltose trials are included)	2a (B-R): is reasonable based on moderate quality evidence from 1+ RCTs or meta-analyses of moderate-quality RCTs

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.

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 DEFICIT[7,24]

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

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

Answer below.

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.[23,29,30] Contrary to the 2017 ACC/AHA/HFSA Focused Update, which did not

Answer: 1088 mg

address EF as a criterion for qualification, the 2022 AHA/ACC/HFSA Guideline specifically notes this recommendation is for patients with HFrEF but does cite the EF <50% criteria used for enrollment in AFFIRM-AHF.[16,23,25] Additionally, though a specific IV iron product is not endorsed, ferric carboxymaltose (FCM) was used for the treatment arms in all referenced studies.[16,23,27,28]

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.[18] 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.[19]

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.[28] 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).[23] 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.[17]

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.[16-18] 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.[16,17]

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.[31]

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.[32] 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.[33] 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.[34]

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.[24] 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, but no severe allergic reactions were reported.[27]

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.[27,28]

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 HFrEF 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, MLHFQ score) were all significant.[35] 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.[29] 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.[23] A post hoc analysis of AFFIRM-AHF also demonstrated that IV FCM improved HRQOL by week 4, which then persisted until week 24.[36]

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 VO_2 at 3 months was seen in patients receiving IV iron sucrose, with no significant change in exercise capacity for the oral iron group.[37] The IRONOUT-HF trial also sought to determine the potential role for oral iron replacement therapy in HF. Patients with HFrEF 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 assess the impact of IV FCM on 6MWD at 24 weeks.[44]

STAR*

★ The data and guidelines strongly support IV iron replacement for ID in HF with very minimal risk involved, especially with newer agents such as FCM. How can HF teams leverage these benefits to optimize outcomes most effectively in these patients?

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

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[17,23,25,27-29,33-37,40,45-51]): 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.[51] 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.[54]

When considering patient populations beyond HF, anaphylactic reactions and other hypersensitivity-type reactions are a

TABLE 2. INTRAVENOUS IRON PRODUCTS[17, 23, 25, 27-29, 33-37, 40, 45-51]

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

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

TABLE 2. INTRAVENOUS IRON PRODUCTS [17, 23, 25, 27-29, 33-37, 40, 45-51] (*continued*)

Iron dextran (INFeD)	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	• 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 • 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.

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.[55,56] 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.[47,48,52] 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.[55,57] Several reports support the safe use of iron sucrose in patients who have previously had infusion-related reactions with iron dextran products.[58-60] Hypersensitivity reactions in patients receiving FCM were low (0.8% vs 2.4% in patients receiving iron dextran, sodium ferric gluconate, or iron sucrose).[61]

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.[2,8,52]

STAR

★ Given FCM is widely regarded as the preferred agent for treating ID in patients with HF, are there still potential barriers to its use? Are there specific scenarios where the characteristics of other IV iron products may provide a benefit even if their supporting literature is not as vast?

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.[62-65]

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.[66] 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.[67]

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.[68] 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.[69,70]

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.[17] 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.[17] 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

Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(17):e263-e421. doi: 10.1016/j.jacc.2021.12.012

Rocha BML, Cunha GJL, Menezes Falcao LF. The burden of iron deficiency in heart failure: therapeutic approach. *J Am Coll Cardiol*. 2018;71(7):782-793. doi: 10.1016/j.jacc.2017.12.027

McDonagh TA, Metra M, Adamo M, et al; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726. doi: 10.1093/eurheartj/ehab368

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,

Video clips from an interview with Dr Chien highlighting answers to key questions in the management of iron deficiency in heart failure can be found at **pharmacytimes.org/ID-HF**

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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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.

THIS ACTIVITY IS SUPPORTED BY AN EDUCATIONAL GRANT FROM VIATRIS.

Incorporating Biosimilar Insulin in the Pharmacy: Updates on Interchangeability and the Role of the Pharmacist

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Patient Counseling Video Vignettes

Patient counseling video vignettes featuring a pharmacist providing education and recommendations to patients about biosimilar insulin and important counseling points are highlighted at **pharmacytimes.org/insulin-biosimilars**.

EDUCATIONAL OBJECTIVES

At the completion of this activity, the pharmacist will be able to:
- Analyze the regulations and approval pathways for biologics and biosimilars
- Explain requirements for an interchangeable biosimilar
- Explore advancements of biosimilar insulin in reducing barriers affecting insulin use, access, and adherence for patients with diabetes
- Identify the role of the pharmacist in addressing patient barriers with insulin treatment and counseling on newest available treatment options

At the completion of this activity, the pharmacy technician will be able to:
- Review the regulations and approval pathways for biologics and biosimilars
- Outline requirements for an interchangeable biosimilar
- Discuss advancements of biosimilar insulin in reducing barriers affecting insulin use, access, and adherence for patients with diabetes
- Express the role of the pharmacy technician in addressing patient barriers with insulin treatment and referring patients to the pharmacist as appropriate

TARGET AUDIENCE: Pharmacists and pharmacy technicians
ACTIVITY TYPE: Application for pharmacists; knowledge for pharmacy technicians
RELEASE DATE: May 31, 2022
EXPIRATION DATE: May 31, 2023
ESTIMATED TIME TO COMPLETE ACTIVITY: 2.0 hours
FEE: This lesson is offered for free at www.pharmacytimes.org.

Overview of Diabetes

In the past 100 years, there has been a plethora of advances in the understanding and treatment for diabetes. Unfortunately, simultaneously there has been an increase in the number of people diagnosed with diabetes. Currently about 1 in 10 people in the United States (37.3 million) have diabetes and in 2019, about 1.4 million new cases were developed.[1,2] There are 7.4 million people in the United States who use one or more formulations of insulin, with most using at least 1 vial each month while some people with diabetes may require multiple vials or multiple types of insulin. In a survey conducted by the American Diabetes Association (ADA), 27% of respondents stated insulin cost affected their use of insulin in the past year.[3]

The Role of Insulin in the Management of Diabetes

Last year, 2021, was the 100-year anniversary of the discovery of insulin. In some people with diabetes, insulin is the only option to manage hyperglycemia and could be the difference between life and death.[4] Over the past century, insulin therapy has advanced tremendously, including development of different types of insulins created to more optimally mimic endogenous insulin, creation of insulin analogs, finding different ways to deliver insulin, and refining the formulations to minimize hypoglycemia.

In people with type 1 diabetes, the β cell function is absent or near absent, which results in the inability of the body to produce insulin, thus requiring exogenous insulin. Most people

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with type 1 diabetes require a combination of basal and prandial insulins delivered either as multiple daily injections or via continuous subcutaneous infusion.

The pathophysiology of type 2 diabetes is complex with at least 11 pathways identified that can contribute to hyperglycemia.[5] The treatment guidelines recommend a person-centric approach when selecting the appropriate medications to address hyperglycemia and to take other issues than HbA1c into account when creating a treatment regimen for patients. Factors to consider when choosing a medication include comorbidities such as atherosclerotic cardiovascular disease (ASCVD) or high risk for ASCVD, heart failure, and chronic kidney disease. Management needs include minimizing hypoglycemia, weight gain or promoting weight loss, and cost considerations. Comprehensive lifestyle modifications remain a foundational part of the treatment plan.[6]

The role of insulin in a person with type 2 diabetes is dependent on the person's clinical presentation. Insulin should be considered early on when there is evidence of catabolism (weight loss), presence of hyperglycemia symptoms including polyphagia, polydipsia, or polyuria, or, if labs indicate, an HbA1c greater than 10% or blood glucose levels at or above 300 mg/dL. If these criteria are not met for early insulin use, a patient typically initiates metformin and/or other medications depending on the aforementioned factors and glycemic needs. For example, certain glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter 2 inhibitors are appropriate for patients with ASCVD, high risk for ASCVD, heart failure, or chronic kidney disease. Eventually, due to the progressive nature of type 2 diabetes, insulin may become necessary to optimize blood glucose levels and health outcomes.[6]

Insulin Supply Chain: How Is Cost Determined?

To further understand the complexity of insulin affordability, the ADA convened an Insulin Access and Affordability Working Group, whose objectives were to learn all factors that may contribute to the cost of insulin for the patient. The Working Group published a summary of their findings and recommendations. By conducting interviews with the various stakeholders involved in the insulin supply chain, it was concluded that while the path of how insulin gets to the patient from the manufacturer is clear, the pricing aspect is much more complex and much less transparent. The list price of insulin is set by the manufacturer, who usually sells their medication to wholesalers close to the list price with a fixed percentage of the list price as the handling fee. Then the wholesaler sells the insulin, with little to no markup, to pharmacies, but the wholesaler may sometimes charge a higher list price. In turn, pharmacies dispense the medication to the patient and submit a bill to the insurance plan, if the patient has one. The pharmacy may be reimbursed by the insurance plan for the cost of the medication dispensed and dispensing fee minus the cost-sharing that was collected (ie, co-pay). If the patient does not have or use insurance, typically pharmacists will charge the patient their cost plus a markup. Although it may appear that there is a direct path for the flow of money, depending on the patient's insurance, the way these costs may be determined is not always transparent or uniform, partly due to negotiated payments and rebates, which may be a contributing factor to the patient's cost. This lack of transparency has resulted in the average list cost of insulin to increase over the past 20 years and tripled between 2002 and 2013.[3]

The Insulin Access and Affordability Working Group concluded that the price of insulin has increased steeply due to various reasons including the current pricing and rebate system, lack of transparency through the insulin supply chain, and market power of pharmacy benefit managers. They also stated lack of competition in the insulin manufacturing sector, and the regulatory burden of developing biosimilars contribute to the cost. The latter has been addressed by the Biologics Price Competition and Innovation (BPCI) Act. The recommendations were multifactorial and directed at all the different entities involved to encourage innovation, continue streamlining the process for biosimilars, choosing lower cost insulin options when appropriate, creating accessible guidelines and standards of practice, and making information related to all aspects of insulin easily available for people with diabetes.[3]

The ADA *Standards of Care* 2022 also describe the substantial and disproportionate increase in insulin prices over the past 20 years.[6] It is advised that clinicians consider the impact of cost on patients and recommend cost-effective options such as follow-on biologics for insulin glargine and insulin, the interchangeable insulin glargine product, and authorized generic versions of analog insulins.[6]

TABLE 1. IMPORTANT DEFINITIONS[8-14]

Drug	Small molecule made through chemical synthesis
Brand	A drug that is originally discovered and developed by the manufacturer
Generic	A drug that is bioequivalent (similar to a branded or reference listed drug in terms of dosage, administration, and performance) to the brand-name product
Biologic product	A large complex molecule manufactured in a living system via biotechnology
Reference/originator product	FDA-approved single biological product with which a proposed biosimilar is compared
Biosimilar product	A product that is highly similar and has no clinically meaningful differences from a reference biologic product
Interchangeable product	A biosimilar product that meets additional requirements for substitution for the reference product without intervention of a health care provider
Safety	Relative freedom from harmful effects, direct or indirect, when a product is prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time
Purity	Relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product; this includes "relative freedom" from residual moisture, volatile, and pyrogenic substances
Potency	Ability or capacity the products need to produce a given result, determined by laboratory analysis
Immunogenicity	Ability of a foreign substance to provoke an immune response
Public Health Service Act	Provides authorization to the Department of Health and Human Services to respond to public health emergencies as well as the requirements for applying for a Biologics License Application (BLA)
Federal Food, Drug, and Cosmetic Act (FD&C Act)	Protects and promotes public health by ensuring the safety and effectiveness of human and veterinary drugs, biological products, and medical devices; and ensuring the safety and security of our nation's food supply; provides the pathway for generic drug approval
Biologics Price Competition and Innovation Act of 2009 (BPCI Act)	Created an abbreviated pathway for approval of biosimilar and interchangeable biological products
New Drug Application (NDA)	The vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the United States
Biologics License Application (BLA)	Request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce

STAR*

★ What are the key differences in the approval requirements for biologic versus biosimilar products?

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

What Are Biologics?

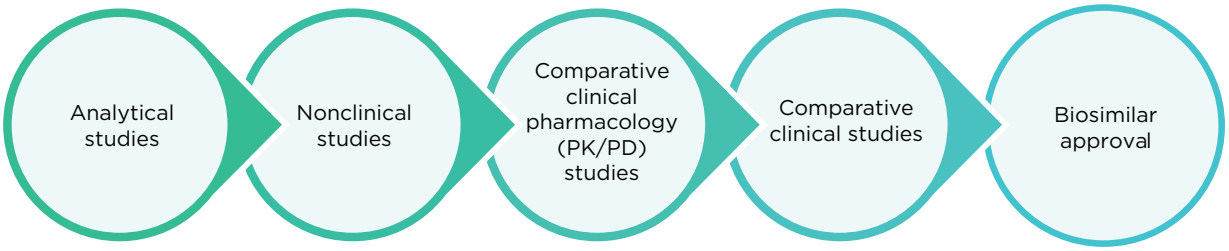
The purpose of all types of drugs is to either diagnose, prevent, treat, and/or cure diseases and medical conditions.[7] A biological product is a large complex molecule manufactured in a living system such as a microorganism, plant cell, or animal cell by using biotechnology.[8] Examples of types of biologic products include vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins such as rituximab (Rituxan), etanercept (Enbrel), and adalimumab (Humira).[9] The definition of a biological product is found in the Public Health Service Act and also meets the definition by the Federal Food, Drug, and Cosmetic Act (FD&C Act).[10,11] Additional important terms and definitions are listed in TABLE 1 for reference.[8-14]

Biologics differ from small-molecule drugs in molecular weight, complexity, manufacturing processes, handling, and storage. The chemical structure is much larger and more complex, ranging from approximately 18 to 150 kDa.[15] Insulins, glucagon, and human growth hormone, while more chemically in line with biologic products, are regulated as drugs under the FD&C Act.[10,11]

Categorization of Insulin Products

Despite insulin being a complex molecule made from

FIGURE 1. "TOTALITY OF EVIDENCE" TO DETERMINE BIOSIMILARITY[10,11]



PK/PD, pharmacokinetic/pharmacodynamic.

living cells, it has been categorized as both a drug and a biologic. Original insulin products available on the market were approved through a regulatory path for drugs. Because insulin products were not approved through the biologic path, drug companies could not introduce biosimilar insulin or interchangeable products. Insulin was placed into a biologic regulatory framework on March 23, 2020.[16] Currently, there is a single interchangeable biosimilar insulin product for the treatment of diabetes, insulin glargine-yfgn (Semglee), which is biosimilar to insulin glargine (Lantus) and was approved on July 28, 2021.[17]

What Are Biosimilars?

A biosimilar product is very similar to a biologic product with no clinically meaningful differences in terms of safety, purity, and potency.[13] Please refer to TABLE 1 for further explanations of these terms. Biosimilars are not identical to the approved biologic agent due to their complex nature and production in living systems.[15] There might be minor differences between biologic and biosimilar products in clinically inactive ingredients, but the manufacturer is required to demonstrate that no differences in terms of safety, purity, and effectiveness exist through clinical studies. Examples of possible differences include the glycosylation pattern of the protein, batch-to-batch consistency, and product stability.[18] Some examples of biosimilars include rituximab-arrx (Riabni), pegfilgrastim-apgf (Nyvepria), and infliximab-axxq (Avsola).[19]

Because biosimilars are approved through different regulatory pathways, they are not considered to be generic medications, which are manufactured and usually synthesized from chemicals and use ingredients that are standardized among lots. For approval, the manufacturer must prove that the generic is bioequivalent to the brand-name drug, also known as the reference product.[8] There can be more than 1 biosimilar for a reference product.[20]

Regulatory Process for Biologics

Biologics are a subset of drugs so they are regulated under both the FD&C Act and the Public Health Service (PHS) Act. The regulatory process is similar to that of drugs under the FD&C Act; however, biologics require different forms to be completed in the marketing application process. The product, manufacturing process, and facility must meet the requirements to ensure continued safety, purity, and potency to obtain a biologics license. Considering the complex nature of biologic products, the PHS Act outlines a system of controls for all aspects of the manufacturing process rather than relying on the standard chemical and molecular biology characterization techniques, which may not be able to detect important changes that can occur to the biologic product if the manufacturing process changes.[11]

Biosimilar Development and Regulation Process

A "totality of the evidence" approach is meant to be taken when developing a biosimilar product. This process is outlined in FIGURE 1.[10,11] Rather than independently establishing the safety and efficacy of the proposed biosimilar, the goal is to compare to the reference product by conducting an extensive analytical comparison to show both products are highly similar in structure and function. In addition to the analytical data, animal, human pharmacologic, immunologic, and additional clinical data may be added to show biosimilarity. The structure and function of the biosimilar has to be similar in purity, molecular structure, and bioactivity of the reference product.[21]

Regulation Requirements

Premarket approval and oversight for therapeutic biological products come from the FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).[22]

Naming Biological Products

The FDA has a naming policy for biological products to contain a core name and a unique 4-letter suffix that is attached with a hyphen to the core name of each product. The core name is the shared component that contains the drug substance and the suffix are 4 lowercase letters that are unique and do not have any meaning. Older biological products may not follow this nomenclature.[23]

Biologics Price Competition and Innovation Act of 2009 (BPCI Act)

On March 23, 2010, the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was signed into law which created a statutory pathway relating to approval of biologic-related products.[24] The BPCI Act sets criteria for approval of biologic, biosimilar products, and interchangeable products (FIGURE 1).[10,11] Under this law, a biosimilar should be evaluated against a single reference biological product.[25]

The BPCI Act requires that a biological product is biosimilar to the reference product based on[26]:

- Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components
- Animal studies (including the assessment of toxicity)
- A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which license is sought for the biological product
- Biosimilar and the reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use, the route of administration, and the dosage form
- The strength of the biological product is the same as that of the reference product
- The facility in which the biological product is manufactured, processed, packed, or held meets standards designed to ensure that the biological product continues to be safe, pure, and potent

Purple Book

The Purple Book began as 2 lists that kept track of the licensed biological products approved by the CDER and the CBER. As of February 2020, the FDA combined the lists and created a searchable, online database. All of the FDA-licensed biological products regulated by CDER and CBER are contained in the "Purple Book" database. This includes any biosimilar and interchangeable biological products, allergenic, cellular, and gene therapy, hematologic, and vaccine products. Features within the Purple Book include data download options, links to product labels, glossary of terms, and ability to search for pertinent information. For example, when the name insulin glargine is searched, the biosimilar, reference, and interchangeable products will be shown.[27] The card will include the proprietary and brand names and have icons that one can hover over to obtain additional product information. The Purple Book will link to Drugs@FDA to get the prescribing and labeling information.[19,28]

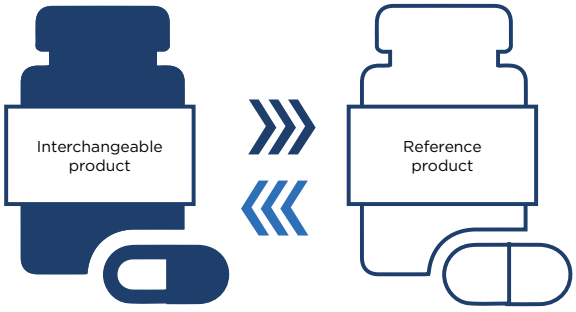
Clinical Study Requirements for Biosimilars

Required studies to demonstrate biosimilarity include comparative pharmacokinetic/pharmacodynamic (PK/PD) studies and comparative clinical studies (refer to FIGURE 1).[15,26] PK/PD studies include exposure and response assessment in either healthy subjects or patients having a particular disease.[29] Considerations for PK studies include parallel design for products with long half-life elimination and a crossover design for products with a short elimination half-life.[29] Route and dose of administration should be sensitive to detect differences in the biosimilar and reference product. Key parameters for PK similarity include maximum drug concentration, area under the concentration-time curve, and the concentration before next dosing.[29]

When assessing PD similarity, FDA guidelines recommended to consider the time of onset of change in the PD biomarker relative to dosing and its return to baseline with discontinuation of dosing. Also, the dynamic range of the PD biomarker over the exposure range to the biological product, the sensitivity of the PD biomarker to detect differences between the proposed product and the reference product, and the relevance of the PD biomarker to the mechanism of action of the drug should be considered.[29]

Furthermore, clinical efficacy studies do not have the same requirement for biosimilars as for a Biologics License Application or New Drug Application submission for an originator or a small molecule drug.[29] The goal of biosimilar clinical studies is to demonstrate that there are no significant clinical differences between the reference product and a biosimilar rather than to demonstrate safety and efficacy of the product versus placebo.[29] Clinical studies for biosimilar development should consider the study population to represent the approved therapeutic indication of the reference product. Sample size and end points should

FIGURE 2. RELATIONSHIP BETWEEN REFERENCE PRODUCT AND INTERCHANGEABLE PRODUCT[30]



be adequate to allow for the detection of clinically meaningful differences between the 2 products.[29] It is recommended that the analysis involves the equivalence design with symmetric inferiority and superiority margins.[29] It is recommended that both intention-to-treat and per-protocol analyses are conducted for biosimilar trials.[30] There is no requirement for a clinical trial for each indication for which the reference product was approved.[29] The FDA may extrapolate clinical data for the use of biosimilar studies for one indication to support approval for other indications.[30] Furthermore, another important aspect for obtaining the approval of the biosimilar is the ability to use data generated from clinical trials involving non–US-licensed originator products.[30]

Interchangeable Products

An interchangeable product is a biosimilar product that meets additional requirements for substitution as laid out in the BPCI Act of 2009. Per the PHS Act, an interchangeable product is "expected to produce the same clinical result as the reference product in any given patient" and "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product [must not be] greater than the risk of using the reference product without such alteration or switch."[13] Per the Act, the biosimilar product information is needed to show that an interchangeable product is expected to produce the same clinical result as the reference product in any given patient.[13] Manufacturers are required to show equivalence of the identity, strength, quality, purity, and potency as well as that there are no adverse effects, including immunological events, expected when patients are switched between the products.[24] The trial should establish the safety of switching back and forth between the interchangeable biologic and the reference product, as demonstrated by FIGURE 2.[30] The criteria for approval of interchangeable products involve studying all indications for use of the reference product. Depending on the product complexity and the likelihood of having significant immunogenic events, it may be required to pursue biosimilarity first and then use the postmarketing data to support interchangeability designation.[30] Unlike biosimilar clinical studies, interchangeability studies should be conducted only against the FDA-approved reference product, whereas biosimilar products can use data from approved products in other countries.[30]

Insulin glargine-yfgn

Insulin glargine-yfgn is the first FDA-approved, interchangeable biosimilar insulin glargine; it was approved on July 28, 2021. Other formulations of insulin glargine are listed in TABLE 2.[31-35] Insulin glargine is a recombinant human long-acting insulin analog. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and 2 arginines are added

TABLE 2. VARIOUS INSULIN GLARGINE PRODUCTS[31-35]

Insulin (brand name)	Approval	Availability	Interchangeability with Lantus
Insulin glargine (Lantus)	2000	10-mL vials and 3-mL prefilled pen	Reference product
Insulin glargine (Basaglar)	2015	3-mL prefilled pen	No → approved as follow-on insulin product
Insulin glargine (Toujeo)	2015	1.5-mL prefilled pen	No → different concentration
Insulin glargine-yfgn (Semglee)	2021	10-mL vials and 3-mL prefilled pens	Yes
Insulin glargine-aglr (Rezvoglar)	2021	3-mL prefilled pens	No

to the C-terminus of the B-chain.[31] It has been described by the FDA as a "momentous day for people who rely daily on insulin for treatment of diabetes" and is indicated to improve glycemic control in adults and pediatric patients from 6 years old with type 1 diabetes and in adults with type 2 diabetes.[17] Patients can be switched from insulin glargine (Lantus) without having to consult the prescriber, if state law allows. It was approved based on the criteria that there is no clinical meaningful difference in terms of safety, efficacy, and purity between insulin glargine and insulin glargine-yfgn.[17]

Insulin glargine-yfgn is available as an injection in 100 units/mL (U-100) 10-mL multiple-dose vial and 3-mL single-patient-use prefilled pen. It should be administered subcutaneously into the abdominal area, thigh, buttocks, or upper arms once daily at any time of day, but at the same time every day. Insulin glargine-yfgn vials and pens that are unopened should be stored in the refrigerator between 36 °F and 46 °F (2 °C-8 °C) until the expiration date or at room temperature up to 86 °F (30 °C) for 28 days. Opened vials and pens should be stored in the refrigerator or at room temperature for 28 days. The product should not be stored in the freezer and should be protected from direct heat and light.[34]

Based on the PK and PD clinical studies, the median time to maximum effect of insulin glargine-yfgn (measured by the peak rate of glucose infusion) was approximately 11.3 hours. The PD profile of insulin glargine-yfgn following subcutaneous injection demonstrated sustained glucose lowering activity over 24 hours with no pronounced peak. The median time to maximum M1 plasma concentration was 12 hours after injection. The efficacy and safety of insulin glargine-yfgn versus insulin glargine was demonstrated in the randomized, double-blind, phase 3 INSTRIDE clinical trials.[36-38] The proposed biosimilar within the studies is called MYL-1501D and the reference product is insulin glargine. During the descriptions of the 3 clinical trials, the term proposed biosimilar will be used to describe the now-approved insulin glargine-yfgn and the term reference product will be used to describe insulin glargine.[34]

Bioequivalence Study

A double-blind, randomized, 3-way crossover study published in November 2019 compared the PK and PD characteristics of the proposed biosimilar with the reference product in 114 patients with type 1 diabetes. Participants either received the proposed biosimilar product, the US glargine reference product, or the EU glargine reference product. Among all 3 groups, PK and PD bioequivalence was demonstrated for all the primary end points.[39]

INSTRIDE 1 Study

The first INSTRIDE clinical trial tested the safety and efficacy of the proposed insulin glargine biosimilar (called MYL-1501D at the time of the study but now known as insulin glargine-yfgn).[36] The primary objective of this 52-week, open-label, randomized study in people with type 1 diabetes was to determine whether the biosimilar insulin was noninferior to the once-daily insulin glargine (reference product) when given in combination with the prandial insulin lispro 3 times daily. The efficacy was measured by the change in HbA1c from baseline to week 24.[36]

Results

A total of 558 patients were randomized 1:1 into the 2 groups (proposed biosimilar vs reference product). From baseline to week 24, the mean change in HbA1c was 0.14% (standard error [SE] 0.054; 95% CI, 0.033-0.244) for the proposed biosimilar and 0.11 (95% CI, 0.007-0.220) for the reference product, insulin glargine. Between the 2 groups (SE, 0.054; ps, the least squares mean difference in change of HbA1c was 0.03% [SE, 0.046; 95% CI, –0.066-0.117]), with the upper bound of the 95% CI within the inferiority margin of 0.4%. The results were similar at week 52, showing no statistically significant difference in actual HbA1c between the 2 groups. Secondary end points included changes in fasting plasma glucose (FPG), insulin dose, self-monitoring of blood glucose (SMBG), immunogenicity from baseline, and occurrence of hypoglycemia. For all end points, while at different times during the 52-week studies, statistically significant differences were found between the 2 groups; they were either deemed clinically insignificant or by the end of the trial, there were no significant differences found. In terms of weight gain, there was slight weight gain in both groups by the end of week 52 with no significant findings based on the change in weight between both groups. Additionally, basal insulin dose requirements increased from baseline to week 52 and there was a greater mean change of dose in the proposed biosimilar group (0.0128 U/kg vs 0.0043 U/kg). This is thought to have been because the average baseline dose in the proposed biosimilar group was lower.[36]

Safety

In terms of safety, the rates of adverse effects were similar

among both groups, where 80.4% of the participants in the proposed biosimilar group versus 86% of participants in the reference group experienced at least 1 treatment-emergent adverse event (TEAE) such as, but not limited to, hypoglycemia, upper respiratory tract infection, or a gastrointestinal-related event. Most of the TEAEs were rated mild and similar among both groups as were the TEAEs that were rated severe in intensity (8.2% in the proposed biosimilar vs 8.3% in the reference product group). In terms of deaths, 2 patients in the proposed biosimilar group died: 1 of unknown etiology but thought to be unrelated to the study treatment and 1 of hypoglycemia, considered to possibly be related to insulin lispro. One patient in the reference product group died, most likely unrelated to the study and due to a myocardial infarction.[36]

Overall, INSTRIDE 1 met the primary end point, showing that the mean change in HbA1c from baseline to week 24 was similar among both groups. The transient statistically significant differences seen between the 2 groups for certain outcomes were not there at week 52, and both groups had similar incidence rates of TEAEs. Limitations included the open-label design, and the population included were mostly White men from Europe or North America, which does not mimic the general population.[36]

INSTRIDE 2 Study

The INSTRIDE 2 study was a multicenter, open-label, randomized, parallel-group, phase 3 study comparing the efficacy and safety of the proposed biosimilar product with reference insulin glargine in patients with type 2 diabetes receiving oral antihyperglycemic drugs. The primary objective was to compare the efficacy, safety, and immunogenicity among the 2 products and the secondary end points focused on change in HbA1c from baseline to week 24. Changes from baseline in basal insulin dose, FPG, SMBG levels, and safety end points were also evaluated.[37]

Results

There were 277 participants in the proposed biosimilar product group and 283 participants in the reference product group for a total of 560 patients. Seventy patients (12.5%) discontinued the study with the rate similar among both groups. The baseline characteristics were similar as well between both groups with a mean age of 55 years, 53% to 58% men, 52% to 53% White, 80% North American, and 41% insulin naive, with approximately 70% of all taking metformin. The mean change in HbA1c from baseline to week 24 was –0.60% (95% CI, –0.78 to –0.41) in the proposed biosimilar group and –0.66% (95% CI, –0.84 to –0.48) for the reference insulin group. In terms of the secondary end points, no significant difference was observed in change in FPG between the groups, while the change within each group was –0.74 (3.11) mmol/L (–13.33 [56.04] mg/dL) in the proposed biosimilar group and –1.05 (3.04) mmol/L (–18.92 [54.77] mg/dL) for the reference group. In the proposed biosimilar group, the weight gain over 24 weeks was 0.67 (3.29) kg ($P = .002$) and in the reference group, the weight gain was 0.42 (3.31) kg; ($P = .046$). Additionally, the mean daily basal insulin dose increased in a similar way between both groups, at 0.12 (0.14) U/kg in the proposed biosimilar group and 0.12 (0.14) U/kg; ($P = .757$) in the reference product group.[37]

Safety

At least 1 TEAE was experienced in 64.1% of participants receiving the proposed biosimilar versus 58.2% in the reference product group ($P > .05$). Hypoglycemia was the most common adverse reaction in both groups and no statistically significant differences were observed in the rate of hypoglycemia. There were no treatment-related deaths in either group.[37]

INSTRIDE 2 met the primary end point of the study, with both groups demonstrating noninferiority with a similar reduction in HbA1c from baseline to 24 weeks. In terms of safety, both groups had similar adverse effects and rate of TEAE with no new safety concerns identified.[37]

INSTRIDE 3 Study

The INSTRIDE 3 study was a multicenter, open-label, randomized, parallel-group, phase 3 study in patients with type 1 diabetes. The primary objective of the INSTRIDE 3 study was to assess if patients can switch between the proposed biosimilar and reference insulin glargine by testing equivalence after 36 weeks between people who stay on the reference glargine versus those who switch between the 2 insulin products (proposed biosimilar and reference glargine). The primary end point was to compare the change in mean HbA1c between both groups from baseline to week 36. The other end points evaluated were similar to the previous INSTRIDE studies.[38]

The study included those patients from the INSTRIDE 1 study, excluding those who had a history of clinically significant infections, moderate insulin resistance, or planned for elective surgery during the study period. The participants were randomized 1:1 to either continuing the reference glargine for 36 weeks

or the treatment-switching group, who received the proposed biosimilar for 12 weeks, then received the reference insulin for 12 weeks, and then switched again to the proposed biosimilar for an additional 12 weeks.[38]

Results

A total of 127 participants were randomized to the 2 groups, 64 to the treatment switch group and 63 to the reference insulin group. A total of 93.7% completed the study, with discontinuation rates similar between the 2 groups. The baseline characteristics of the participants were similar to the ones described in the INSTRIDE 1 study. In the treatment switch group, the change in HbA1c from baseline to week 36 was –0.05 (0.032) and –0.06 (0.034) for the reference insulin glargine group, meeting its primary objective with the 95% CI within ±0.4% equivalence limits.[38]

Safety

Overall, the TEAEs were similar among both groups, with the most common TEAE being infection (upper respiratory tract infection and influenza); there were no discontinuations due to a TEAE. The rates of hypoglycemia were also similar between both groups with no statistically observed differences and there were not any incidences of severe hypoglycemia reported in either group.[38]

INSTRIDE 3 assessed the various factors required to demonstrate bioequivalence between the proposed biosimilar and its reference product. It compared end points including change in HbA1c from baseline to week 36, SMBG and FPG to assess glycemic control, changes in insulin dose and hypoglycemia incidence and severity. INSTRIDE 3 demonstrated similar safety and efficacy with the treatment switching group and reference groups with no meaningful differences in immunogenicity.[38]

Biosimilar Interchangeability Laws by State

Each state differs in their pharmacy laws and practices, and the ability to interchange a biosimilar is dependent on current pharmacy practice laws within the state. As of this publication, a majority of US states allow for pharmacists to substitute an interchangeable biosimilar to a patient without consulting the prescriber and generally use federal standards to define "interchangeable." Within most of the state laws allowing pharmacists to substitute a biosimilar are requirements that include the interchangeable biosimilar being of lesser cost and neither the prescriber nor the patient have expressed "dispense as written." However, there are stipulations to these laws that may differ from the standard generic substitution of other medications in many of the states that allow for this substitution. These include: (1) having to notify the prescriber within a certain period of time (48 hours to 5 days, depending on the state) of the substitution via electronic or other means and (2) some type of recordkeeping and labeling requirements that stipulate the amount of time that record of substitution needs to be retained or certain verbiage on the prescription label. Additionally, some states do not allow patients to refuse the interchangeable biosimilar if being paid by a government agency, requiring the pharmacist to pass on cost savings to purchaser or third-party payment, or requiring that if the pharmacy does not have the less expensive interchangeable biosimilar available, they need to dispense the prescribed biosimilar at that lower cost. Considering the specific verbiage in law and the differences among states, it is vital that pharmacists are aware of their state's specifications.[40]

Labeling for Biosimilars

In 2018, the FDA issued guidance on Labeling for Biosimilar Products that focuses on prescribing information and briefly addresses patient labeling. While similar to labeling expected with generic medications, there are certain differences that are specific requirements for biosimilar products. The statement, "[BIOSIMILAR PRODUCT'S PROPRIETARY NAME (biosimilar product's proper name)] is biosimilar* to [REFERENCE PRODUCT'S PROPRIETARY NAME (reference product's proper name)]." The asterisk should be linked to the definition of what biosimilar means and the conditions that have been met by the biosimilar product. The immunogenicity section that is under adverse effects should include describing what immunogenicity is and the potential implications or limitations. The labeling should use relevant information from the reference product and the biosimilar product proprietary name should be used in labeling text that is specific to the product or for directive statements for preventing, monitoring, managing, or mitigating risks, including in the following sections: indications and usage, dosage and administration, description, and how supplied/storage and handling, boxed warning, contraindications, warnings and precautions, and drug interactions. If the risk is applicable to both the biosimilar and the reference product, the core name can be used with the word products after it. The FDA recommends that the clinical data conducted to demon-

strate biosimilarity or interchangeability is not included in the labeling as those data are not meant to be designed to support independent demonstration of safety or efficacy.[41]

The FDA guidance for labeling interchangeable products is currently in draft form and has similar recommendations to labeling for biosimilars, including a statement about interchangeability: [INTERCHANGEABLE BIOSIMILAR'S PROPRIETARY NAME (interchangeable biosimilar's proper name)] is interchangeable* with [REFERENCE PRODUCT'S PROPRIETARY NAME (reference product's proper name)], with the footnote further defining interchangeability.[42]

STAR

★ A patient comes into the pharmacy with a prescription for insulin glargine (Lantus), which you change to insulin glargine-yfgn (Semglee). How would you explain this change to the patient?

The Role of Pharmacists and Pharmacy Technicians

Pharmacists and pharmacy technicians play a key role in advocating for patients with diabetes in a myriad of ways. Considering the complexity of diabetes care and all the components that are included for the comprehensive management of this chronic condition, each health care professional plays a key role in ensuring that the patient is empowered with knowledge and understanding of the condition and treatment. As health care professionals, pharmacists have the knowledge and skill to provide accurate and effective patient education.[43]

Within the community pharmacy, pharmacists are able to provide both proactive care as well as serve to answer questions the patient may have. In general, education about diabetes can include explaining the pathophysiology of diabetes, role of medications and insulin in the treatment of hyperglycemia, and describing how to treat hypoglycemia. Additionally, pharmacists should assess adverse effects from the medications or diabetes-related complications, provide recommendations on how to prevent or discuss what to do if adverse effects occur and how to better manage them, ask about medication-taking behavior, address barriers including accessing care or obtaining medications, and evaluate blood glucose levels and HbA1c levels. Beyond this, pharmacists should take on the responsibility to ensure patients are prescribed the appropriate medications based on individual factors and comorbidities. Often, it is the pharmacist the patient may see the most often, and pharmacists are in a position to have a holistic view of the patient's medication history as well as understand other factors through conversation.[43]

Pharmacy technicians are an integral part of the pharmacy team. There is strong evidence to support the expanding roles of pharmacy technicians to support patient care.[44] They can also play an important role in ensuring patients know their options for cost-effective medications. Oftentimes, pharmacy technicians are the ones interacting with the patient at both ends of the prescription process, from intake of the prescription to giving the medication as well as interacting with and hearing concerns from the patient. Technicians are also very knowledgeable about insurance coverage and options for payment. The more familiar pharmacy technicians are with understanding the costs of prescriptions and less expense alternatives a patient may have, it can help facilitate the process. This role can easily translate to the pharmacy technician's role in considering interchangeable biosimilars. By understanding the role of interchangeable biosimilars, the laws within their state, and proactively recognizing when a patient may benefit from the interchangeable biosimilar, it can help optimize patient care and facilitate the dispensing process.

The pharmacy staff's responsibility is to ensure that patients have access to their medications, and barriers such as cost need to be considered. The biosimilar and interchangeable landscape has allowed for patients to have access to medications that are less expensive but do not compromise care. Proactive conversations, especially with patients who do not have insurance or who may not qualify for patient assistance programs, are important to ensure patients know that they have options to optimize their diabetes management. When discussing these alternatives, avoiding words such as "cheaper" is important as it may incorrectly connote that the medication is of lesser quality.[43]

As pharmacy technicians are often conversing with patients and identifying concerns, if patients are noticing their insulin costs are rising or they are not able to afford their medication, the pharmacy technician can identify patients that may benefit from speaking to the pharmacist and refer the patient to the pharmacist to further discuss options to be given the appropriate counseling that may be required. Pharmacists can work with their team of technicians, interns, and students to ensure everyone knows their roles and how to best facilitate this interchangeability process.[44]

Explaining Biosimilar Medications to Patients

When a company develops any medication, they must go through a strict process where they first ensure the medication is safe and it works as intended. Once clinical trials are complete and if the medication is found to be safe and effective, then manufacturers must go through the FDA, the oversight committee to look at all the data they found and approve the medication. If this happens, the company gets a patent, which means no other company can make the same drug for a certain amount of time. Once that time period is over, other companies can create their own version of that same drug. This is generic, but if the drug is more difficult to make, such as insulin, it becomes biosimilar; additionally, if it is given the interchangeable title, then it can be substituted without having to call the prescriber who wrote the prescription. Co-pay cards at this time are limited to patients with commercial insurance.[45]

Conclusion

Researchers continue to gain a better understanding of all the pathways that contribute to hyperglycemia and new treatment options are being explored continuously. Once-weekly, hepato-preferential, oral, and glucose-responsive "smart" insulins are substantially different insulin options that are being evaluated in various clinical trials. The availability of these types of insulin can impact the person with diabetes and the current recommendations to potentially address clinical inertia, barriers to adherence, and adverse effects. Biosimilars and interchangeable insulin are a vital development in the diabetes medication armamentarium that are available now. As diabetes continues to impact millions of individuals, having accessible and affordable options to treat hyperglycemia is essential. Pharmacists are the health care providers that patients rely on to discuss these options and ensure optimal management of diabetes, while pharmacy technicians also play a crucial role to enhance the care of these patients.

Patient Counseling Video Vignettes

Patient counseling video vignettes featuring a pharmacist providing education and recommendations to patients about biosimilar insulin and important counseling points are highlighted at **pharmacytimes.org/insulin-biosimilars**.

ADDITIONAL RESOURCES

Name	Reference
APhA Biosimilar Basics for Patients	https://aphanet.pharmacist.com/sites/default/files/files/APhA_Biosimilar_Basics_for_Patients1.pdf
FDA Fact Sheets	• What Is a Biosimilar? www.fda.gov/media/108905/download • Overview of Biosimilar Products: www.fda.gov/media/151058/download • Biosimilar Regulatory Review and Approval: www.fda.gov/media/151061/download
Purple Book Database of Licensed Biological Products	https://purplebooksearch.fda.gov/
FDA video: The Basics of Biosimilars	www.youtube.com/watch?v=1s7W1EKUekk&list=PLey4Qe-UxcxbFinyBSntx188r2lvxqxak&index=5
FDA video: The Biosimilar Development Process	www.youtube.com/watch?v=lI0R_tvtMkI&list=PLey4Qe-UxcxbFinyBSntx188r2lvxqxak&index=3
Cardinal Health: Biosimilar Interchangeability Laws by State	www.cardinalhealth.com/content/dam/corp/web/documents/publication/Cardinal-Health-Biosimilar-Interchangeability-Laws-by-State.pdf
FDA video: The Concept of Interchangeability	www.youtube.com/watch?v=ooP7djSgtBE&list=PLey4Qe-UxcxbFinyBSntx188r2lvxqxak&index=4

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Go to **www.pharmacytimes.org/insulin-biosimilars** to access the online version of this activity.

Click "Proceed," then complete the online pretest.

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POSTTEST QUESTIONS*

1. **Which legislation created a statutory pathway to approving biological products?**
   A. Biologics Price Competition and Innovation Act of 2009
   B. Federal Food, Drug, and Cosmetic Act
   C. Public Health Service Act
   D. Biologics License Application Act

2. **Which of the following is a correct statement about biosimilars?**
   A. Biosimilars are the same as their reference biologic product.
   B. Biosimilars are interchangeable with their reference biologic product without prescriber authority.
   C. There can only be one biosimilar for every reference product.
   D. Biosimilars do not have any clinically meaningful difference from the reference product.

3. **Which criterion is a requirement for an interchangeable biosimilar?**
   A. Efficacy and safety data that exceed the data provided for the reference product
   B. Equivalence in strength, quality, purity, and potency
   C. Additional labeling that states product may be less effective than reference product
   D. No clinical meaningful differences compared with placebo

4. **Which database is used to find information about biosimilar products?**
   A. Orange Book
   B. Drugs at FDA
   C. Purple Book
   D. Micromedex

5. **Which statement is true regarding interchangeable biosimilars and the law?**
   A. The federal laws stipulate that pharmacies can dispense an interchangeable biosimilar without a prescription.
   B. State laws about interchangeable biosimilars differ regarding switching products without the consent of a prescriber.
   C. Interchangeable biosimilars and biologic biosimilars are synonymous in terms of regulatory pathways.
   D. Just hospital pharmacists are allowed to switch to an interchangeable biosimilar without consent of the prescriber.

6. **FP is a 42-year-old patient who presents with a prescription for insulin glargine. In his profile, he has received insulin glargine (Lantus) in the past before the availability of insulin glargine-yfgn. If the pharmacist works in a state that allows pharmacists to conduct biosimilar interchangeability, and the interchangeable biosimilar is the most cost-effective option, which of the following recommendations is the most appropriate?**
   A. Dispense the same insulin FP has been receiving to ensure effectiveness.
   B. Change to insulin glargine-yfgn and counsel FP about this substitution.
   C. Call the provider to ask for a new prescription for insulin glargine-yfgn prior to dispensing.
   D. Switch to a long-acting basal insulin because FP is now requesting it.

7. **JL is a 62-year-old patient concerned with the rising costs of her insulin glargine therapy. She has been purchasing and taking the insulin as prescribed; however, she is worried that she may not always be able to afford it. Which response to the patient's concern is optimal?**
   A. "There is another option for insulin glargine that is cheaper and is a generic for the insulin you are currently taking."
   B. "An interchangeable biosimilar is available for you. I need to call your provider to get permission before I change it."
   C. "Insulin glargine is available as insulin glargine-yfgn, which works the same way as your current insulin and is less expensive. I can get it ready for you."
   D. "I recommend you continue the insulin glargine you have for as long as possible because it is working for you."

8. **Which statement is true regarding how biosimilar insulin may impact accessibility for patients?**
   A. Biosimilar insulin will impact only patients with type 1 diabetes.
   B. Generic insulin is the preferred option to most brand-name insulins.
   C. Biosimilar insulin may enhance accessibility because of the decreased cost.
   D. There is unlikely to be any change in accessibility with biosimilar insulin coming to market.

POSTTEST QUESTIONS (continued)

9. **Which statement is correct regarding insulin glargine-yfgn?**
   A. It can be interchangeable with any insulin glargine product.
   B. It is available in a vial and prefilled pen formulation.
   C. Patients may have lower rates of hypoglycemia.
   D. It has worse HbA1c lowering efficacy.

10. **Interchangeable products require the following:**
   A. Same clinical result within 85% as the reference product in any given patient
   B. Alternating or switching between use of the biological product and the reference product should not alter the risk in terms of safety or diminished efficacy
   C. Equivalence of the identity, strength, and quality, but purity and potency may differ
   D. Equivalence in the way the product appears

* Pharmacy technician assessment questions available online.

SEE OUR AD ON PAGE 19

Florajen Digestion Probiotic

Manufactured by Clarion Brands, LLC

For patients seeking gastrointestinal support, Florajen's digestion probiotic has high potency to ensure stable, healthy, and thriving cultures. The multiculture probiotic supplement helps rebuild bacterial balance lost due to antibiotic use and can also help relieve occasional gas, bloating, constipation, and diarrhea. Furthermore, it supports immune health with once-daily capsules each containing 15 billion live cultures. Florajen also offers refrigerated probiotics formulated for women and children and is the No. 1 pharmacist-recommended refrigerated probiotic.

FOR MORE INFORMATION:
florajen.com

SEE OUR AD ON PAGE 33-35

Heplisav-B

Manufactured by Dynavax Technologies

Heplisav-B is the only hepatitis B vaccine given in 2 doses within 1 month. It is unanimously recommended by the Advisory Committee on Immunization Practices for the prevention of infection caused by all known subtypes of hepatitis B virus in adults 18 years and older. results of clinical trials among adults aged 40 to 70 years showed 94.6% protection, and trial results among individuals with diabetes aged 18 to 70 years showed 90% protection. The most common patient-reported adverse events reported within 7 days of vaccination were injection site pain, fatigue, and headache.

FOR MORE INFORMATION:
dynavax.com

SEE OUR AD ON PAGES 50-53

Shingrix

Manufactured by GlaxoSmithKline

Of the 99.5% of individuals 50 years and older infected with the varicella zoster virus, 1 in 3 will experience virus reactivation and shingles. Shingrix is indicated for the prevention of herpes zoster in older adults, and should be prioritized for this patient population, according to experts. Local adverse reactions in individuals aged 50 years and older included pain (78%), redness (38.1%), and swelling (25.9%). General adverse reactions included myalgia (44.7%), fatigue (44.5%), headache (37.7%), shivering (26.8%), fever (20.5%), and gastrointestinal symptoms (17.3%).

FOR MORE INFORMATION:
shingrix.com