Pharmacist-Administered Immunizations

VACCINES

PharmacyTimes.com
Chairman’s Note

INFECTIONOUS DISEASES

Vaccinations Are Major Contributors to Global Health

VACCINATIONS ARE A HUGE SUCCESS story in global health care and have helped to eliminate smallpox and nearly eradicate polio. According to the CDC, immunization against deadly diseases saves 2 million to 3 million lives per year.¹

The COVID-19 vaccines reduce the risk of contracting the virus, including severe disease, in fully vaccinated individuals by 90% or more.² Yet vaccine hesitancy or outright opposition is prolonging the pandemic.

According to the results of a survey conducted in August 2021 by Morning Consult, a data intelligence company, 18% of Americans are opposed to getting vaccinated and 10% are hesitant.³

Pharmacists can help combat hesitancy and opposition by providing patients with the facts about vaccines, including efficacy and safety data.

In this issue's Cover Feature, Kathleen Kenny, PharmD, RPh, discusses how the pharmacist-administered immunization movement is propelling the profession forward. In addition, in the OTC Focus article, Yvette C. Terrie, BSPharm, RPh, provides information on whether patients should avoid taking pain relievers before getting the COVID-19 vaccine.

Meanwhile, Lisa Ruohoniemi, PharmD, offers information on travel vaccines in the Patient Focus article.

Look for coverage of flu season and influenza vaccines online at PharmacyTimes.com. In our influenza resource center, pharmacists can find information about flu season predictions, coadministration of the vaccine with routine immunizations, and the role pharmacy technicians play in this year’s influenza vaccine campaign.

Elsewhere in this issue, we provide tips on treating attention-deficit/hyperactivity disorder and dry eye disease.

In this issue we also are commemorating our finalists in the Next-Generation Pharmacist® Awards program, which recognizes exceptional pharmacists, pharmacy students, and technicians who have gone above and beyond in caring for patients and advancing the profession. The awards ceremony will be held October 8, 2021, in Charlotte, North Carolina. Since 2010, the program has been held with Parata Systems, the industry’s most comprehensive pharmacy technology solutions provider. Look for the list of winners in the October issue of Pharmacy Times®.

Thank you for reading!
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77 Optimizing Clinical Outcomes in Spinal Muscular Atrophy With the Use of Novel Disease-Modifying Therapies: A Review for Pharmacists

At the completion of this activity, the participant will be able to:
• Investigate the incidence, pathophysiology, types, and clinical presentation associated with spinal muscular atrophy (SMA)
• Examine the current management guidelines for SMA and the safety and efficacy of available and emerging therapies
• Explore the impact of SMA on patient and caregiver quality of life including physical and economic burden
• Identify the role of the pharmacist in educating patients on novel and emerging therapies for SMA and in making recommendations to improve clinical outcomes in this patient population

94 Decreasing Mortality Rates When Reversing DOAC-Related Bleeding: Examining Updated Recommendations, New Data, and Real-World Evidence Using Specific Reversal Agents

At the completion of this activity, the participant will be able to:
• Explain current recommendations and guidelines for the reversal of major bleeding associated with the use of direct-acting oral anticoagulants (DOACs)
• Examine up-to-date clinical data and real-world evidence comparing the safety benefits of specific reversal agents over prothrombin complex concentrates (PCCs) for reversing life-threatening DOAC-related bleeding
• Identify the role of health-system formulary committee members, pharmacy directors, and integrated delivery networks in improving clinical outcomes and decreasing mortality rates in those patients being treated for reversal of major bleeding related to the use of DOACs
Opioids may not always be necessary following surgery, according to results of a recent study. Here’s what you had to say about the finding.

Jess S.: I feel like you couldn’t make a blanket statement like this. I do not handle pain well. I couldn’t imagine not having an opioid after either of my surgeries!

Christian B.: Some pharmacies will even give you free ibuprofen and paracetamol for forgoing the opioid.

Akyianu G.: Wow, that’s a good approach. As [opioids] usage is reduced, it will definitely help reduce opioid addiction/dependence.

Leah S.: Everyone has different pain thresholds. It’s too patient specific to make clinical changes based on this study alone.
EDITOR'S NOTE

BACK TO SCHOOL, UP IN the airplane, and off to the restaurant: The United States has chosen to move forward now that an effective vaccine has been available for more than 10 months. In the face of some of the worst outbreaks of the pandemic, we are forging ahead. Mask debates rage on and vaccine resistance continues, but in large part, behavior has changed and likely for the long term. With 72% of respondents to a survey supporting mask mandates and 61% supporting vaccine mandates, a majority of Americans have decided that life must go on but with evidence-based interventions and precautions.1 Most of us get tested when we need to, wash our hands a little longer than we did before, and wear masks when we should.

Pop-Up Providers, Shopping Malls, Sports Venues
When President Joseph R. Biden set a goal of more than 1 million vaccinations per day, one would have thought the United States was girding for a world war on 2 fronts, calling in the Federal Emergency Management Agency and the National Guard, sequestering space and tens of thousands of volunteers, and enticing many of them with early access to the vaccine. The media was fixated on the idea that there were not enough vaccination sites for such a lofty goal. Administrators and politicians often ended up ignoring an existing and well-scaled vaccine administration infrastructure, governors freaked out, and hospital lobbyists called in favors to receive their vaccine bounties. Makeshift vaccine providers, shopping malls, and sports venues, having never cared for patients before the pandemic, became primary venues for getting shots into arms. Never mind that more shots go into arms during school vaccinations and well-child efforts alongside influenza season and at a quicker pace than the COVID-19 rollout for many weeks during the vaccination push this past spring.

Let's Use the Current System and the Trust Built Over Many Decades
The vaccine supply is ample. So the country should focus on using the existing vaccine administration infrastructure of pharmacies and primary care providers, which together represent more than two-thirds of annual influenza vaccine
administration, alongside the special role of health departments for assisting underserved populations and advising on policy. Why would a patient need, want, or be required to drive past tens, if not hundreds, of existing providers, some of whom already maintain their health records, to get a first, second, or third dose? Why should patients receive health care services from someone they have never met and will never meet again rather than highly trusted, locally based, frontline health care providers in their own neighborhoods? And we wonder why we have hesitancy and trust issues over the COVID-19 vaccinations.

The Next Wave(s): Multiple Tests and Vaccinations, OTC Counseling
Unlike the past fall, winter, and spring, during which a few thousand lab-confirmed positive tests countrywide defined a nearly absent influenza season, the upcoming seasons have many anticipating a trifecta of cold, COVID-19, and flu symptoms at pharmacies. We are launching a booster shot program, and testing and vaccination requirements will grow exponentially for patrons of concerts, gyms, institutions, and restaurants. Pharmacies will likely retain much-needed authority to test for infectious diseases, a capacity problem we have not solved in this country. If Delta leads to another variant that is better at getting around the complement of COVID-19 vaccines, we may have a crisis that exceeds or matches what we experienced in March 2020 and the months following with fear, a high demand for curbside and hand delivery services, and too few regularly scheduled physician visits not related to COVID-19. Pharmacies will be busy, regardless, as patients will continue to need medications.

Pop-Up Clinics Fill an Important Gap
Mass vaccination clinics did play an important role in filling the gap for those individuals who don’t usually access health care. The healthy and young, without an established connection to the health care provider community, often rely on events or work site drives for health care screenings and vaccinations. Individuals who are confined at home, marginalized, and/or very ill comprise the gap on the other side of the spectrum, with accessibility, cognition, and travel barriers. In both instances, pop-up clinics staffed by a known entity in the neighborhood or workplace can fill this gap without renting out the speedway 30 miles away.

Rolling Demand, Multiple Systems of Care, Plenty of Capacity
With a relatively steady half million newly vaccinated individuals per day, and rolling demand created by the 8-month federal guidance on “booster” shots, pharmacies should expect a very manageable but steady stream of residents accessing local vaccine providers over the next 6 months. Pharmacies and primary care providers should play a major role in vaccination administration. There is no need to disrupt the existing infrastructure by creating clinics that are unnecessary and have the potential to erode the already festering government and institutional mistrust simply to create “vaccine theater.” Hundreds of millions of tests and vaccines are carried out each year as part of the frontline health care infrastructure, and there is plenty of capacity, both at clinics and pharmacies.

Community-Based Pandemic Response Most Effective
Much like the lakes of Minnesota, which boast a longer shoreline than California, Florida, and Hawaii combined, smaller bodies of water (community-based providers) that are much more plentiful (10,000+ lakes) are superior to the flashy beaches of the Atlantic and Pacific oceans. Only in America would we spend trillions of dollars on a health care system and then create an alternative system of access when a pandemic ensues. By 2 to 1, patients prefer to use a pharmacy or primary care clinic as their main source of vaccination services.² Many experts predict that COVID-19 will become endemic and that, like influenza, we will be chasing variants and similar pathogens indefinitely, perhaps seasonally. With many developing countries just now receiving their first sizeable shipments of COVID-19 vaccinations, we can assume we will be in this for the long haul.

Countless Service Opportunities as Essential Community Providers
For pharmacies, the ongoing pandemic will offer continued opportunities to serve their communities, both as health care providers and leaders, in concert with the care team. Counseling and education opportunities, tests, and vaccinations will number in the billions over time, and pharmacists and primary care providers should prepare for and welcome this. Providing superior community-based care, they will demonstrate that the 60,000-plus pharmacy locations and nearly half a million primary care providers in the United States are part of the essential infrastructure.

REFERENCES

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## FDA Approvals

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<th>Drug name</th>
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<tr>
<td>Anifrolumab (Saphnelo)</td>
<td>Indicated for the treatment of adults with moderate to severe systemic lupus erythematosus who are receiving standard therapy</td>
<td>AstraZeneca</td>
<td>8/2/21</td>
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<td>Pembrolizumab and lenvatinib</td>
<td>Indicated as a combination therapy for the first-line treatment of adult patients with advanced renal cell carcinoma</td>
<td>Merck</td>
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<td>Belzutifan (Welireg)</td>
<td>Indicated for the treatment of patients with some type of Von Hippel-Lindau disease-associated tumors</td>
<td>Merck</td>
<td>8/13/21</td>
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<td>Tick-borne encephalitis vaccine (Ticovac)</td>
<td>Indicated for active immunization to prevent tick-borne encephalitis in individuals 1 year and older</td>
<td>Pfizer</td>
<td>8/13/21</td>
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<td>Insulin lispro-aabc injection (Lyumjev)</td>
<td>Indicated to improve glycemic control in adults with type 1 and type 2 diabetes, including administration via continuous subcutaneous insulin infusion with an insulin pump</td>
<td>Lilly</td>
<td>8/16/21</td>
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<tr>
<td>Dostarlimab-gxly (Jemperli)</td>
<td>Indicated for the treatment of adult patients with mismatch repair deficient recurrent or advanced solid tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options</td>
<td>GlaxoSmithKline</td>
<td>8/17/21</td>
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<td>Empagliflozin (Jardiance)</td>
<td>Indicated for use in adults living with heart failure with reduced ejection fraction</td>
<td>Lilly</td>
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<td>Nivolumab (Opdivo)</td>
<td>Indicated for the treatment of patients with urothelial carcinoma who are at high risk of recurrence following radical resection, regardless of prior neoadjuvant chemotherapy, nodal involvement, or programmed death-ligand 1 status</td>
<td>Bristol Myers Squibb</td>
<td>8/20/21</td>
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<td>COVID-19 vaccine (Comirnaty)</td>
<td>Indicated for the prevention of COVID-19 in individuals 16 years and older</td>
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<td>Rivaroxaban (Xarelto) plus aspirin</td>
<td>Indicated for the treatment of patients following lower-extremity revascularization due to symptomatic peripheral artery disease</td>
<td>Janssen</td>
<td>8/24/21</td>
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<td>Ivosidenib tablets (Tibsovo)</td>
<td>Indicated for the treatment of adult patients with previously treated, locally advanced, or metastatic cholangiocarcinoma with an IDH1 mutation</td>
<td>Servier Pharmaceuticals</td>
<td>8/25/21</td>
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<tr>
<td>Brivaracetam (Briviact)</td>
<td>Indicated for the treatment of partial-onset seizures in pediatric patients 1 month and older</td>
<td>UCB</td>
<td>8/30/21</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>Indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are ineligible for any platinum-containing chemotherapy</td>
<td>Merck</td>
<td>8/31/21</td>
</tr>
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For the full FDA approvals list, go to pharmacytimes.com.
Mild to Moderate Adverse Effects From Pfizer Vaccine Are Seen in Youth at Risk of Complications

**RESULTS FROM A NEW** study published in the Archives of Disease in Childhood show that the adverse effects (AEs) of the Pfizer-BioNTech vaccine against COVID-19 are likely to be mild to moderate and clear up quickly in 12- to 15-year-olds at high risk of complications from the infection because of certain co-existing conditions.

The data represent teens most likely to benefit from the vaccination and are meant to offer reassurance to clinicians and patients, even with small study numbers, according to the study authors.

Although healthy children with COVID-19 infection generally have a mild illness, some coexisting conditions, such as neurological conditions, are associated with severe disease. The high-risk children were then protected to reduce their risk of infection and would not have been included in the early vaccine safety studies.

Because there were unknown AEs of vaccination in the group, the study authors requested that the parents of 27 of these children report any AEs of subsequent COVID-19 vaccinations for each child. The children were between 12 and 15 years of age: 16 were male and 21 were White, with 3 hospital inpatients.—*Jill Murphy*

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**Vaccination, Previous Infection Offer Reduced Protection Against Some Variants**

**BLOOD SERUM DRAWN FROM** individuals who have previously been vaccinated against or naturally infected with COVID-19 have significantly reduced defense against 2 widely circulating variants of SARS-CoV-2, according to a study published in *Nature Communications*.

Investigators from Oregon Health and Science University (OHSU) emphasized the importance of vaccinations and public health measures.

“We know that the virus continues to evolve for its own advantage,” said co-senior author Fikadu Tafesse, PhD, assistant professor of molecular microbiology and immunology in the OHSU School of Medicine, in a statement.

The investigators found that 2 variants of concern—the Alpha variant and the Beta variant—show reduced neutralization by antibodies in the blood of nearly 100 people who were either vaccinated with the Pfizer vaccine or previously infected with SARS-CoV-2. In terms of vaccine response to the Beta variant, in particular, they found a 9-fold reduction in efficacy compared with the original virus. However, it was interpreted as a positive development that vaccination and earlier infection offered some protection against these 2 variants.

The reduction in antibodies was particularly noticeable in adults older than 50 years of age, according to the study.

“The people who surround our older and more vulnerable populations need to get vaccinated and minimize exposure to the virus,” Bill Messer, MD, PhD, assistant professor of molecular microbiology and immunology and medicine (infectious diseases) in the OHSU School of Medicine, said in the statement.—*Skylar Kenney*

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**COVID-19 Causes Severe Disease, Disrupted Treatment in Children with Cancer**

**A LARGE, INTERNATIONAL RESEARCH** effort has found that 20% of children with cancer who were diagnosed with COVID-19 developed severe infections compared with between 1% and 6% of children without cancer who have COVID-19.

In addition to more critical or severe infections, pediatric patients with cancer were more likely to be hospitalized and die than were other children. The pandemic also caused major disruptions to cancer treatments, with effects observed more significantly in low- and middle-income countries. Notably, these countries also had nearly 6-times higher risks of critical or severe Acritical disease from COVID-19.

“The results clearly and definitively show that children with cancer fare worse with COVID-19 than children without cancer,” corresponding officer Sheena Mukkada, MD, of the St. Jude Departments of Global Pediatric Medicine and Infectious Diseases, said in a statement. “This global collaboration helps clinicians make evidence-based decisions about prevention and treatment, which, unfortunately, remain relevant as the pandemic continues.”

This is the first multinational study analyzing the outcomes of a large cohort of adolescents and children with cancer or hematopoietic stem cell transplantation and laboratory diagnosis of COVID-19, according to the statement.

The study used the Global Registry of COVID-19 in Childhood Cancer, which gathers data on the pandemic’s impact on this patient population. The registry remains open and is enrolling children younger than 19 years of age.

Investigators looked at 1500 children from 131 hospitals in 45 countries between April 15, 2020, and February 1, 2021. This time frame is prior to the availability of vaccinations for older children and is also before the emergence of some variants, including Delta.

The investigators found that 65% of patients were hospitalized and 17% required admission or transfer to a higher level of care. Furthermore, 4% of patients died from COVID-19 infections compared with a mortality rate between 0.01% and 0.7% among general pediatric patients.—*Aislinn Antrim*
CARDIOVASCULAR

**Experts Urge Caution, Education About Opioid Use for Individuals With Heart Disease**

_A NEW AMERICAN HEART_ Association Presidential Advisory outlined the ongoing opioid epidemic and the advancing science on opioid use, including its effects on brain and heart health through evidence-based research, according to a statement from the American Heart Association (AHA).

The advisory notes different strategies for addressing the issue, such as improving education and training for the public and health care professionals on how to safely manage pain and opioid overdose and support treatment for opioid use disorder, including creating and developing partnerships with federal, local, state, and employer-based programs. — _Jill Murphy_

MENTAL HEALTH

**Study Finds Short Naps Do Not Relieve Sleep Deprivation**

**RESULTS FROM A RECENT** study from Michigan State University’s (MSU) Sleep and Learning Lab showed that a nap during the day will not restore a sleepless night. “We are interested in understanding cognitive deficits associated with sleep deprivation. In this study, we wanted to know if a short nap during the deprivation period would mitigate these deficits,” study author Kimberly Fenn, director of MSU’s Sleep and Learning Lab, said in a statement.

“We found that short naps of 30 or 60 minutes did not show any measurable effects,” she said. This study was among the first to measure the effectiveness of shorter naps, according to the study authors. “While short naps didn’t show measurable effects on relieving the effects of sleep deprivation, we found that the amount of slow-wave sleep that participants obtained during the nap was related to reduced impairments associated with sleep deprivation,” Fenn said.

The deepest and most restorative stage of sleep is known as slow-wave sleep (SWS), which is marked by high amplitude, low frequency brain waves, and is the sleep stage when the body is most relaxed. “SWS is the most important stage of sleep,” Fenn said. “When someone goes without sleep for a period of time, even just during the day, they build up a need for sleep; in particular, they build up a need for SWS,” she said.

Fenn and her research team recruited 275 college-aged participants for the study who completed cognitive tasks when arriving at MSU’s Sleep and Learning Lab in the evening. They were then randomly assigned into 3 groups: the first group was sent home to sleep; the second stayed in the lab overnight and had the option to take either a 30- or 60-minute nap; and the third did not nap at all in the deprivation condition.

The next morning, participants resumed in the lab for cognitive tasks when arriving at MSU’s Sleep and Learning Lab showed that a nap during the day will not restore a sleepless night. “We are interested in understanding cognitive deficits associated with sleep deprivation. In this study, we wanted to know if a short nap during the deprivation period would mitigate these deficits,” study author Kimberly Fenn, director of MSU’s Sleep and Learning Lab, said in a statement.

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The next morning, participants resumed in the lab to repeat the cognitive tasks, which measured attention and placekeeping, or the ability to complete a series of steps in a specific order without repeating or skipping them even after interruption. — _Jill Murphy_

DIABETES

**Experts Recommend Diabetes Screenings for Overweight Adults Beginning at Age 35**

**OVERWEIGHT ADULTS SHOULD BE** screened for diabetes beginning at aged 35 years, according to an updated recommendation from the US Preventive Services Task Force. The new recommendation is 5 years earlier than previous recommendations.¹

The new recommendation cited CDC data that approximately 13% of all US adults have diabetes and 34.5% meet criteria for prediabetes. Of those with diabetes, 21.4% were not aware of or did not report it, and just 15.3% of those with prediabetes reported being told by a health care professional that they meet the criteria.²

“Clinicians can prevent serious health complications by screening adults with overweight or obesity for prediabetes and diabetes,” task force member Chien-Wen Tseng, MD, MPH, MSEE, said in a statement. “With appropriate screening, diabetes can be detected and treated earlier to improve overall health.”²

Estimates of the risk of progression from prediabetes to diabetes vary greatly, and the authors said this could be because definitions of prediabetes differ. A large cohort study of 77,107 patients with prediabetes reported that the risk for developing diabetes increased with higher body mass index and hemoglobin A1C levels.¹

Diabetes also has significant risks for other conditions. For example, it is the leading cause of kidney failure and new cases of blindness among adults in the United States and is associated with increased risks of cardiovascular disease, nonalcoholic fatty liver disease, and nonalcoholic steatohepatitis. It was also estimated to be the seventh-leading cause of death in the United States in 2017.¹

Screening asymptomatic adults for prediabetes and type 2 diabetes (T2D) may allow earlier detection, diagnosis, and treatment, with the ultimate goal of improving health outcomes, according to the recommendation. The recommendation applies to nonpregnant adults between age 35 and 70 years who are obese or overweight with no symptoms of diabetes.¹

Being obese or overweight are the strongest risk factors for developing prediabetes and T2D in adults, according to the recommendation. — _Aislinn Antrim_
Help Patients Combat Dry Eye

Doctors and Pharmacists Discuss OTC and Prescription Treatment Options and Use During Webcast

By JILL MURPHY

WITH NEW FDA-APPROVED TREATMENTS available for dry eye and other therapeutic agents being developed, health care experts continue to emphasize that this condition should not be taken lightly by patients or overlooked by health care professionals.

During a Pharmacy Times® webcast, experts discussed several topics related to dry eye, including OTC and prescription treatment options and how to advise patients on proper use. The panel comprised moderator Abhiruchi Mehta, PharmD, outpatient pharmacist at Massachusetts General Hospital in Boston, and panelists Monazzah Akbar Sarwar, PharmD, assistant director of Taylor Street Pharmacy in Chicago, Illinois; Lisa Nijm, MD, JD, an assistant clinical professor of ophthalmology at the University of Illinois Eye and Ear Infirmary, Department of Ophthalmology and Visual Sciences in Chicago and founder and medical director of Warrenville EyeCare & LASIK in Warrenville, Illinois; and Brian Walker, RPh, a community pharmacist at Walgreens Pharmacy in Warrenville.

Nijm started the conversation by explaining that dry eye disease is an imbalance in homeostasis, or a disruption in homeostasis of the tear film, that usually occurs because of inflammation. The condition causes an inflammatory waterfall that results in the symptoms that patients often experience.

“It’s much more common than one would think,” Nijm said. “An estimated 16 million people in the United States have diagnosed dry eye disease, and another 16 million have underdiagnosed or undiagnosed dry eye disease, so about 32 million people in the United States experience dry eye.”

Some of the symptoms associated with dry eye include dryness, a foreign-body sensation, or a gritty, sandy feeling, she said. Additionally, fluctuating vision and tearing from the eye are common symptoms that people do not tend to associate with dry eye.

Pharmacists can see patients who have this condition and be proactive asking open-ended questions, before these patients visit physicians, Walker noted.

“Many times, people see you as being busy and may not want to bother you, so they’re not going to want to answer those questions,” he said. “However, you want to spend time with them to ask those questions as opposed to simply pointing to the aisle with all the preparations, especially since those things can be quite confusing to people who don’t exactly know what they’re looking for.”

Akbar Sarwar agreed with Walker, adding that there could be consequences of not seeking treatment, because tearing protects the eye surface from infection.

“If it’s left completely untreated, dry eye can lead to other things, like eye inflammation, abrasion of the corneal surface, and, in extreme cases, vision loss. There’s a definite risk of progression, so catching it early on is important,” Akbar Sarwar said.

Walker pointed out that applying warm compresses for approximately 10 or 15 minutes can help loosen the glands that produce tears. Akbar Sarwar recommended informing patients about avoiding excess dust, smoke, or wind; tak-
ing breaks from screen time; and using humidifiers in the house to improve symptoms.

The COVID-19 pandemic has not helped patients with dry eye. Nijm mentioned the increased screen time resulting from remote schooling and working as a culprit behind an uptick in dry eye among younger people.

“Often, we think of dry eye disease in older patients, but it’s actually across the board,” she said. “It’s becoming more frequent among younger patients, because we have other triggers that we’re looking at with the effects of the pandemic: increased screen time and greater use of electronic devices, along with all the normal things that go on [such as allergies, inflammatory disease, and wind].”

Walker noted that he has seen an increase in medication use since COVID-19, which has caused more people to develop dry eye. Antianxiety medications and antidepressants have been associated with dry eye because they contain antihistamines, which cause dryness.

Mask-associated dry eye syndrome has increased dry eye for many individuals during COVID-19, as wearing masks causes air to recirculate from the mouth and hit the eyes, according to Nijm.

The multitude of OTC products to treat dry eye, such as artificial tears, gels, and ointments, causes confusion for both health care professionals and patients according to Walker. He suggests artificial tear products as a first-line treatment for individuals with mild eye dryness.

“Something that you could use 2 to 4 times a day [includes] Blink, Biotrue, Clear Eyes, Systane, Theratears, Refresh, Rohto, or Soothe by Bausch + Lomb,” he said. “Those are products that are going to be thinner or liquidy. They can be put in while a person is driving or wearing contacts.”

Patients who need stronger products should try GenTeal or Refresh, and those who have specific issues with screen time could opt for Refresh Digital or Rohto Digi-Eye, he suggested.

When analyzing preservative-free products versus preserved products, Akbar Sarwar tries to get an idea of how long the patient needs to use it.

“If it is for chronic use, we know that [benzalkonium chloride] can be somewhat toxic to the surface of the eye because it does break down that corneal epithelium, and that will increase the permeability of the cornea. It changes that ocular surface and the epithelial cells, which becomes a concern to us,” she said.

“For long-term use, the good news is there are a lot of alternative preservatives on the market, like oxidizing agents such as sodium perborate,” she continued. “You find that in things like GenTeal and TheraTears; chelating agents like EDTA [ethylenediaminetetraacetic acid]; oil-based products like Soothe and Systane, which help to ensure that moisture is retained in the eye; and a lot of other oil-based products.”

Getting the best use of a medication involves gentle eyelid closure, Akbar Sarwar noted. Patients with eye crusting and pain who unsuccessfully try OTC treatment should seek the advice of a physician, Walker said.

Nijm is a fan of artificial tears, particularly those that are preservative free, but they offer only limited and temporary relief for patients with serious dry eye. In terms of prescription solutions, FDA-approved dry eye treatment Eysuvis is a 2-week regimen taken 4 times daily.

“Before, there were very limited options for treatment of dry eye disease, and I think that’s where artificial tears became our mainstay,” Nijm said.

“Then we got Restasis, which was great, but that was it for the longest time,” she continued. “We’ve evolved so much with Xiidra [and] Eysuvis and with what we understand about the pathophysiology of dry eye and the underlying inflammation that if patients have a lot of symptoms and have tried 1 or 2 artificial tears and aren’t getting relief, then they should be seen.”

Eysuvis can be used either as a standalone or for patients who need it as induction therapy, Nijm said. In addition to the treatment meeting all end points in the STRIDE 1 (NCT02813265) and STRIDE 3 (NCT03616899) trials, the data surrounding instillation site pain were important to analyze.

“It was very low, which is great because we know a lot of treatments that we have, especially for patients with dry eye disease who are suffering at the time of those drops, can be difficult to start with it,” Nijm said.

“The IOP [intraocular pressure] increased, which is always good to ask about when we’re talking about a steroid, but there were only 3 of 1400 patients in the Eysuvis trial that demonstrated increased pressure in the eye,” she said. “That’s extremely significant and very comforting for eye care professionals utilizing Eysuvis, that they can prescribe it and have a very low incidence of increased pressure or any adverse effects.”
Pharmacist-Administered Immunization Movement Propels Profession Forward

Although Most Americans Live Close to a Pharmacy, Vaccination Rates Remain Suboptimal

by Kathleen Kenny, PharmD, RPh

Pharmacists have been involved in vaccines since the distribution of the smallpox vaccine in the mid 1800s.
The Washington State Pharmacy Association designed the first formalized training program for pharmacist-administered vaccines in 1994. In 1996, the American Pharmaceutical (now Pharmacists) Association launched its nationally recognized training program.1

Fast-forward to 2021 and all 50 states, as well as the District of Columbia and Puerto Rico, have given pharmacists the authority to administer vaccines, although this authority differs from state to state. Some state-specific restrictions include age of patient, requirement of a prescription, and type of vaccine. The profession has made great strides in the vaccination arena, but pharmacists can still advocate for nationwide standards as opposed to different regulations and rules for every state.

Although most people live close to a pharmacy, vaccination rates are still suboptimal. The CDC estimates that influenza-related hospitalizations in the United States have ranged from 140,000 to 710,000 since 2010. Influenza-related deaths ranged from 12,000 to 56,000 over the same period.2

Approximately 320,000 people contract pneumococcal pneumonia every year, leading to more than 5000 deaths and 150,000 hospitalizations.2 Between 700,000 and 1.4 million people have chronic hepatitis B, which can cause complications, such as liver cancer.1

Human papillomavirus (HPV) causes more than 27,000 cancers in both men and women each year. Approximately 4000 women die every year from cervical cancer.2

Common vaccine-preventable diseases include:

**Chickenpox (varicella):** Causes symptoms including headache, fever, an itchy rash with blisters, and tiredness. Chickenpox is typically mild but can lead to encephalitis, pneumonia, severe skin infections, and even death.2

**Diphtheria:** Produces a toxin in the body that can cause low-grade fever, sore throat, swollen neck glands, and weakness. The effects of this toxin can also lead to swelling of the heart muscle and heart failure. Severe cases can result in coma, paralysis, and death.2

**Influenza:** Causes chills, dry cough, headache, joint and muscle pain, runny nose, sore throat, and sudden high fever. Extreme fatigue can last from days to weeks. The disease can lead to hospitalization or even death.2

**Hepatitis A:** Often spreads through contaminated food. Hepatitis A can cause abdominal discomfort, dark urine, fever, jaundice, loss of appetite, nausea, and tiredness. People who are infected with this disease may have no symptoms, mild symptoms, or severe illness.2

**Hepatitis B:** A blood-borne disease that causes influenza-like symptoms such as jaundice, joint pain, loss of appetite, nausea, rashes, and vomiting. This virus can stay in the liver of some individuals for the rest of their lives, causing severe liver diseases, including fatal cancer.2

**HPV:** Especially prevalent among individuals in their teens and early 20s. HPV is a major cause of anal cancer or genital warts in both men and women and of cervical cancer in women. Some other types can cause cancers of oropharynx and penis.2

**Measles:** A respiratory disease often brought to the United States by international travelers. This virus can cause cough, rash, and persistent fever. It can also cause brain damage, pneumonia, seizures, or in some cases death.2
Meningococcal disease: A bacteria-caused illness that is the leading cause of bacterial meningitis. It can cause confusion, nausea, photosensitivity, sleepiness, and vomiting. It also causes blood infections. Meningitis has about a 10% mortality rate, and survivors may become deaf or developmentally disabled, develop nervous symptom difficulties, lose limbs, or experience seizures or strokes.2

Mumps: Causes fever, headaches, loss of appetite, muscle aches, and swelling of salivary glands. Severe complications can include encephalitis, meningitis, permanent hearing loss, and swelling of the testes, leading to sterility.2

Pneumococcal disease: A bacterial illness that can spread from the nose and throat to ears or sinuses and generally causes mild infections. Serious health problems typically occur when the bacteria spread into other parts of the body, such as the blood (bacteremia), the lining of the brain and spinal cord (meningitis), and the lungs (pneumonia). Severe disease may result in brain damage, hearing loss, limb loss, or even death.2

Rubella: A viral disease, often called German measles. It usually causes mild illness with fever, a rash, and swollen glands. Severe disease can lead to encephalitis in adults. If a pregnant woman becomes infected, it can result in miscarriage or serious birth defects, such as blindness, deafness, heart defects, and intellectual disability.2

Shingles (herpes zoster): Varicella zoster virus that causes chickenpox, shingles causes a painful rash that blisters, then typically scabs over and clears up. Other symptoms can include chills, fever, headache, and an upset stomach. If shingles affects the eye, it can cause loss of vision.2

Tetanus: A serious bacterial disease that causes painful, serious tightening of the muscles, leading to spasms and stiffening of all the muscles in the body. This can lead to lockjaw to the point of being unable to breathe, open the mouth, or swallow. Tetanus has approximately a 30% mortality rate.2

Whooping cough (pertussis): A highly contagious, bacterial respiratory infection that causes prolonged cold symptoms leading, to choking and violent coughing. It is most severe for babies, even leading to hospitalization or death. Babies typically contract this disease from a caregiver, parent, or relative.2

TRAVEL VACCINES
In some states, pharmacists are also authorized to administer travel vaccines. Examples of diseases covered by such vaccines include cholera, Japanese encephalitis, rabies, typhoid, and yellow fever. The CDC has a complete list of recommended and required vaccinations based on age, destination, season, and vacation duration.

The profession has made great strides in the vaccination arena, but pharmacists can still advocate for nationwide standards.

REFERENCES

The profession has made great strides in the vaccination arena, but pharmacists can still advocate for nationwide standards.
GREAT STRIDES HAVE BEEN MADE in understanding, preventing, and treating severe COVID-19 infections.

The emergency use authorization by the FDA for the available COVID-19 vaccines and the recent full FDA approval of the Pfizer COVID-19 vaccine were monumental moments in the fight against this relentless virus. As the COVID-19 pandemic persists, pharmacists continue to be instrumental in providing patients with reliable information about the prevention, detection, treatment, and management of COVID-19. Pharmacists can be influential in dispelling common misinformation and myths about the COVID-19 virus, its variants, and the available vaccines. In the beginning of the pandemic, there were initial concerns about the safety of individuals with COVID-19 taking ibuprofen, but these claims originated from anecdotal and low-quality evidence.1 Major public health organizations around the globe do not advise against using ibuprofen to ease COVID-19 symptoms or the adverse effects (AEs) associated with the vaccine.1 As accessible health care providers, pharmacists are likely to encounter patients seeking counsel on the use of nonprescription analgesic/antipyretics, such as acetaminophen, and the non-steroidal anti-inflammatory agents (NSAIDs), such as ibuprofen and naproxen sodium, for the symptomatic relief of some of the common mild to moderate symptoms associated with COVID-19 that may be amenable to self-treatment and to manage AEs, such as fever and pain, associated with the COVID-19 vaccines.

In a recent publication on the Medical News Today website, the author indicates that the CDC recommends consulting a health care professional about taking analgesics/antipyretic to manage the AEs of the COVID-19 vaccine.1

The CDC stated, "It is not recommended you take over-the-counter medicine, such as ibuprofen, aspirin, or acetaminophen, before vaccination for the purpose of trying to prevent vaccine-related side effects. It is not known how these medications might affect how well the vaccine works. However, if you take these medications regularly for other reasons, you should keep taking them before you get vaccinated. It is also not recommended to take antihistamines before getting a COVID-19 vaccine to try to prevent allergic reactions."2

In response to the early concerns about the use of NSAIDs and the evolving information about these issues, GlaxoSmithKline (GSK), a leading manufacturer for OTC analgesics issued a statement about the use of ibuprofen and COVID-19 vaccines, saying, "The appropriate use of antipyretics/analgesics, like Advil (ibuprofen), is recommended by public health authorities for the COVID-19 vaccine.3-5 This is consistent with the fact that in the COVID-19 vaccine studies, participants were allowed to use antipyretics/analgesics to treat symptoms."5

Additionally, GSK posted information on its Advil product website about a patient education initiative referred to as #AfterMyShot, which provides...
patients with valuable information about COVID-19 and the vaccines.6

On August 12, 2021, the manufacturer, Janssen also issued a statement about the use of antipyretics and analgesics and the COVID-19 vaccine. In its response, the manufacturer indicated the following:7

- **Pre-vaccination:** There are no robust clinical data on how pre-treatment use of antipyretics affects COVID-19 vaccine-induced antibody responses.7
- **Post-vaccination:** There is no clinical evidence that the use of antipyretics post-vaccination has a negative effect on COVID-19 vaccine efficacy.7
- During the Janssen COVID-19 Vaccine clinical trial program, antipyretics were recommended post-vaccination for symptom relief as necessary. Prophylactic antipyretic use was not encouraged. However, in some instances, it could have been considered for participants with special circumstances and/or comorbidities.7,8

Bayer Consumer Health, the manufacturer of the OTC NSAID marketed as Aleve also has information on its website about the COVID-19 virus and the use of the product, stating: “To date, public health authorities, including the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration, the European Medicines Agency and the World Health Organization, are not aware of any scientific evidence supporting a link between the use of non-steroidal anti-inflammatory medicines (NSAIDs), such as Aleve, and worsened outcomes from COVID-19.”9

### CLINICAL STUDIES

Available clinical evidence regarding other vaccines indicate that analgesics/antipyretics are commonly used around the time of vaccination to ameliorate fever and pain, and the use is primarily post-vaccination.10-12 Although the results of several studies show that prophylactic analgesic/antipyretic administration decreases post-vaccination adverse reactions, there are also study results showing that their use may decrease the antibody responses to several vaccine antigens.13

In a recent 2021 publication, Etminan et al, indicated that several regulatory bodies have made statements regarding the use of antipyretics around the time of vaccination. In 2015, the World Health Organization stated that use of antipyretics is not recommended before or at the time of vaccination but approved in the days after vaccination, and the CDC concurs with these recommendations.14,15 Etminan et al, noted that to date, there are no clinical data on this issue with regard to the COVID-19 vaccines, and the data provided in clinical trials for the mRNA vaccines only mentioned that the use of antipyretics was increased with increasing dose concentrations and dose number, but data on immunogenicity were not given.14, 16,17 Finally, Etminan et al, indicated that moving forward, clinical trials need to urgently investigate and answer 4 questions:14

- Do either acetaminophen or ibuprofen affect antibody response by COVID-19 vaccines, and if so, is there a difference in antibody titers between the 2 agents?
- Does a potential interaction with antipyretics vary with different vaccine types (mRNA vs non-mRNA vaccines)?
- Does the timing of antipyretic administration (before vaccination or immediately after) affect antibody titers?
- Does a possible negative interaction only affect antibody titers for the first dose, second dose, or both? 14

### CONCLUSION

As clinicians and patient educators, pharmacists can educate patients about the benefits of vaccines and provide patients with facts and dispel common myths and misconceptions about vaccines particularly the COVID-19 vaccine. Until more clinical data become available, patients should be directed to adhere to CDC recommendations, and when in doubt they should consult their primary health care providers before taking any medications, including OTC drugs.
Infants’ Pain & Fever
Manufactured by Genexa
An oral liquid containing acetaminophen, Genexa’s new fever and pain medication for infants is the newest in its clean medicine lineup. In addition to acetaminophen, it contains organic agave syrup, blueberry flavor, and citrus extract, as well as non–genetically modified organism flavor and purified water. The product joins the company’s other medicines for infants and newborns, including probiotics, saline nasal drops and spray, and vitamin D.

FOR MORE INFORMATION:
genexa.com

Nervive
Manufactured by Procter & Gamble
Nervive is a line of daily supplements designed to address nerve care and pain. It includes Nerve Health to fortify overall nerve health, as well as Nerve Relief and Nerve Relief PM for occasional aches, discomfort, and weakness related to aging. Nerve-related discomfort is especially common in aging adults because of natural structural changes in the nervous system, including loss of myelin and slowed signaling. To help address these changes, the supplements are specially formulated with ingredients to support patients’ fundamental functions and needs.

FOR MORE INFORMATION:
pg.com

Apple Cider Vinegar Supplements
Manufactured by Bragg Live Food Products
Designed to deliver apple cider vinegar in capsule form, Bragg Apple Cider Vinegar supplements offer 750 mg of acetic acid—the equivalent of 1 tbsp of liquid apple cider vinegar—in 3 capsules. Benefits of apple cider vinegar include appetite control and maintenance of healthy blood glucose and cholesterol levels. The supplements also include vitamin D and zinc and are available in 90-count bottles, according to a company statement.

FOR MORE INFORMATION:
bragg.com

Curated Combinations
Manufactured by Nature’s Bounty
With a line of 4 personalized nutrition packs to address specific health and wellness concerns, Nature’s Bounty aims to make daily supplement intake simple. Each pack contains 3 to 4 pills that are taken daily and are available in 4 varieties. A Good Night includes melatonin, L-theanine, and magnesium; Daily Essentials features an advanced multivitamin, high-dose vitamin C, and L-theanine; Master the Day includes Ginkgo biloba leaf extract, high-dose vitamin C, and super B complex; and Set the Foundation includes coenzyme Q10, Ginkgo biloba, and vitamin D. The supplements are available on Amazon and will be on retail pharmacy shelves later in the year.

FOR MORE INFORMATION:
naturesbounty.com
Diabetes

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

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Q

CASE 1: Continuous Glucose Monitoring

MD is a 59-year-old woman who is looking to replace her glucose monitor. It has been 5 years since she last purchased a monitor, and she would like to upgrade to a continuous glucose monitor (CGM). MD has a 10-year history of diabetes and takes Lantus 10 U at bedtime and metformin 1000 mg daily. She does not take other medications. MD is technology-savvy. What should the pharmacist recommend?

A

Let MD know that most insurance plans have strict guidelines regarding the use of a CGM instead of conventional glucose testing. CGM products have proven to beneficial at reducing A1C levels and hypoglycemia events. CGM products allows patients to track glucose levels day and night and alert them if they have hyperglycemia or hypoglycemia. Glucose monitors should be selected based on multiple factors, such as ease of cost and insurance coverage, flexibility, information retrieval, and of course, use. Certain CGM products also connect to insulin pumps, but because this is not a factor for MD, she can consider any product. CGM products in the United States include the Dexcom G6, Freestyle Libre system from Abbott, and Medtronic’s Guardian Sensor 3. Because MD uses insulin only at bedtime, most insurance companies will not cover CGM products. However, she has the option to select a CGM product and pay out of pocket if her insurance company does not cover it. According to Healthline, out-of-pocket prices for CGM supplies can range from $160 to $500 per month.

CASE 2: Diabetes Neuropathic Pain

RM is a 58-year-old woman who is complaining of neuropathic pain related to diabetes. She has had diabetes for the past 15 years and her A1C levels usually range between 9 and 10. RM takes metformin 1000 mg twice daily but does not want to add additional prescription medications. Her doctor recently gave her a diagnosis of neuropathic pain, but she declined to add medications at the time. RM’s friend said she started taking alpha-lipoic acid, which has helped reduce her pain. RM is hesitant to add a supplement, because she is worried about drug interactions. What recommendations should the pharmacist make?

A

RM should discuss the addition of alpha-lipoic acid with her prescriber. One study followed 460 patients over 4 years and found that alpha-lipoic acid was useful in preventing progression of neuropathy. RM could benefit with the addition of alpha-lipoic acid to prevent further progression. A meta-analysis evaluated the addition of alpha-lipoic acid and found improvements in neuropathic pain, when given intravenously. The study authors concluded that the benefit with oral administration is unclear. RM can see if it is beneficial but should also be advised that multiple prescription medications can also be beneficial with diabetic neuropathy.

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OTC Cases

CASE 3: Diabetes Cold

Q

CS is a 38-year-old man who is looking for pseudoephedrine to clear his congestion. CS has been sick for the past 2 days with some congestion, but he does not have a cough or fever. His medical history includes diabetes and hypertension. CS takes lisinopril 10 mg daily, metformin 1000 mg twice daily, and regular insulin 10 U with each meal. He does not have seasonal allergies and has not tried any medications to relieve his congestion. What recommendations should the pharmacist make?

A

All OTC decongestants come with a caution label for patients who have diabetes or hypertension. Pseudoephedrine can increase blood pressure (BP), so patients are recommended to monitor their BP when taking a decongestant. In addition, patients with diabetes or insulin must monitor their BP more often and adjust diabetes medications if needed. In addition to using a nasal decongestant, CS can consider trying a dehumidifier or nasal saline to see if his congestion improves.

CASE 4: Diabetes and Quitting Smoking

Q

YI is a 45-year-old man who wants to quit smoking. He has smoked 2 packs of cigarettes per day for the past 15 years. YI has tried to quit cold turkey a few times but has never succeeded. He has diabetes and takes metformin 1000 mg twice daily and regular insulin 20 U with each meal. YI wants information on OTC nicotine replacement products, such as the patch. What advice should the pharmacist give him?

A

Nicotine replacement products have been beneficial for patients who are trying to quit smoking. Because YI smokes 2 packs per day, his recommended dose would be 21 mg for 4 to 6 weeks, followed by 14 mg for 2 weeks, and completion of 7 mg for an additional 2 weeks. The most common adverse effects associated with the patch are skin reactions, such as burning or redness. YI should apply the patch to a clean, dry place on the upper arm or body every 24 hours. The patch should be applied to a different part of the skin each day to prevent skin reactions. One patch should not be used for more than 24 hours. YI can shower and swim with the patch on. Let him know that when he quits smoking, he should monitor his blood sugar more often, because nicotine can alter cells that block insulin action, and hypoglycemia can occur. YI can also receive additional support by attending community smoking cessation support groups.
ADHD Is Not Likely to Go Away
But the Good News Is Treatments Can Be Tailored for Patients With the Chronic Behavioral Condition

By JEANNEtte Y. WICK, MBA, RPH, FASCP

AS THE MOST COMMON BEHAVIORAL condition and the second most common chronic illness in children, attention-deficit/hyperactivity disorder (ADHD) affects approximately 9% of children in the United States. 1

Because ADHD is chronic, it usually requires lifelong care and coordination of interventions from education, medical, and mental health providers.

DIAGNOSIS
The Diagnostic and Statistical Manual of Mental Disorders describes ADHD in behavioral terms,2 so clinicians diagnose the condition using a clinical evaluation. No objective tests can confirm the diagnosis. In addition to a comprehensive history and physical examination, clinicians also use parent- or teacher-reported behavior rating scales in children.3 In adults, self-reporting and descriptions of behaviors from family members can help.

Animal models, neuroimaging studies, and pharmacologic studies suggest adrenergic and dopaminergic alterations in ADHD.4,5 Approximately 76% of individuals with ADHD may be genetically predisposed, but investigators have not isolated specific genetic patterns.6 Environmental factors, such as childhood lead exposure, head trauma, maternal alcohol intake or smoking, or prematurity, increase risk.7

TREATMENT
Behavioral treatment and medication do not cure ADHD but can control symptoms, which include hyperactivity, impulsivity, and inattention. Behavior-modifying interventions, such as parent behavior management training and school behavior management programs, have been shown to help.8 They are considered first-line treatments.

The results of the multisite National Institute of Mental Health’s Multimodal Treatment of ADHD study showed that behavioral interventions and stimulant medication were effective over 14 months with follow-up at 10 years.9 Stimulant medication had the strongest effect on core ADHD symptoms. Families found behavioral interventions most acceptable, but behavioral therapy combined with medication was most effective. This was especially helpful when children had comorbid health concerns or family dysfunction. The investigators had difficulty demonstrating long-term benefits, because families did not necessarily receive the same level of behavioral interventions or medication once they left the active trial.9

Regardless, rigorous studies have consistently confirmed medication’s efficacy and safety when taken in the therapeutic dose range for ADHD.10 Table 111 has clinical tips about FDA-approved nonstimulants and stimulants that can reduce ADHD symptoms and improve functioning in children 6 years or older.

AUTHOR BIO
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Other interventions, such as cognitive or neuropsychological training interventions, diets, electroencephalographic training, or supplements, lack empiric support. Conclusions

Table 2 lists common questions and information to help pharmacists with patients who have ADHD.

## Table 1. Medications Used for ADHD

<table>
<thead>
<tr>
<th>Medications</th>
<th>Proposed mechanisms</th>
<th>Practice points to remember</th>
</tr>
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<tbody>
<tr>
<td><strong>Stimulants</strong></td>
<td></td>
<td></td>
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<tr>
<td>Amphetamine and methyphenidate</td>
<td>Increase dopamine levels in the brain to improve attention and movement</td>
<td>• Long-acting psychostimulants are first-line pharmacologic treatments.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If switching is needed, do so during summer vacation or after the first report card period in the school year.</td>
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<tr>
<td></td>
<td></td>
<td>• Schedule drug holidays during the summer; using weekends for drug holidays may paradoxically increase adverse effects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• When abused, stimulants may mask fatigue but will not significantly improve academic performance.</td>
</tr>
<tr>
<td><strong>Nonstimulants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Selectively inhibits presynaptic norepinephrine reuptake</td>
<td>• May benefit patients with anxiety disorders or enuresis along with ADHD. If Tourette syndrome is comorbid, it tends not to worsen symptoms.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patients may tolerate daily doses differently than twice-daily doses.</td>
</tr>
<tr>
<td>Clonidine, guanfacine</td>
<td>α-2 agonists</td>
<td>• Minimizing caffeine and other sympathomimetic agents sometimes eliminates or reduces adverse effects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• When discontinuing, taper doses because of the significant risk of withdrawal, such as hypertensive crises.</td>
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</tbody>
</table>

ADHD, attention-deficit/hyperactivity disorder.

## Table 2. Questions About ADHD

<table>
<thead>
<tr>
<th>Questions</th>
<th>Facts</th>
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</thead>
<tbody>
<tr>
<td>Do children outgrow ADHD?</td>
<td>• Two studies have documented that approximately 30% to 60% of children who receive a diagnosis of ADHD either no longer met diagnostic criteria for this disorder by late adolescence or stopped treatment. The reasons are complicated; adolescents may have chosen employment that works around their limitations or developed coping skills.</td>
</tr>
<tr>
<td>In what areas do we need to focus discussion?</td>
<td>• The primary finding of a retrospective, longitudinal cohort study (N = 423) was relatively low rates of monitoring for sexual activity and no evidence of discussion of the risks of medication diversion.</td>
</tr>
<tr>
<td>Are certain populations overlooked?</td>
<td>• Children who are Black or raised in households where English is not the primary language are less likely than similar White children to receive a diagnosis of ADHD; these children are as likely as White children to have ADHD.</td>
</tr>
<tr>
<td></td>
<td>• Girls with ADHD tend to be forgetful and inattentive; boys tend be disruptive and hyperactive; 2.5 boys for every girl receive a diagnosis.</td>
</tr>
<tr>
<td></td>
<td>• Women with ADHD consistently receive a misdiagnosis; they are underrecognized and understudied.</td>
</tr>
<tr>
<td>What's new in ADHD treatment?</td>
<td>• The FDA approved a prescription-only medical device to treat ADHD in April 2019: the Monarch external Trigeminal Nerve Stimulation System.</td>
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<tr>
<td></td>
<td>• This device is indicated for patients aged 7 to 12 years who are not currently taking prescription ADHD medication.</td>
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<tr>
<td></td>
<td>• Common adverse effects include drowsiness, an increase in appetite, trouble sleeping, teeth clenching, headache, and fatigue.</td>
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ADHD, attention-deficit/hyperactivity disorder.

CONCLUSION
Pharmacists must manage patients’ expectations about medication and explain that individuals respond differently. Many prescribers fail to counsel patients with ADHD and their families about drug abuse and diversion, and pharmacists can fill that gap.
Empagliflozin (Jardiance)
Marketed by: Eli Lilly and Company
Breakthrough results confirmed that the EMPEROR-Preserved phase 3 trial (NCT03057951) of empagliflozin met its primary end point, establishing the drug as the first therapy to significantly reduce the risk of cardiovascular death or hospitalization for heart failure (HF) with preserved ejection fraction. When added to results from the EMPEROR-Reduced trial (NCT03057977), these findings demonstrate the efficacy of empagliflozin in all forms of HF and in patients both with and without diabetes, according to a statement from Eli Lilly and Company. Empagliflozin is not approved for the treatment of HF in the United States, though a supplemental new drug application has been submitted to the FDA. The indication would be to reduce the risk of cardiovascular death, heart failure, or hospitalization in adults with HF with reduced ejection fraction. A decision is expected later in 2021.

FOR MORE INFORMATION:
lilly.com

Finerenone (Kerendia)
Marketed by: Bayer Healthcare
The FDA has approved finerenone to reduce the risk of cardiovascular death, hospitalization for heart failure (HF), kidney failure, kidney function decline, and nonfatal heart attack in adults with chronic kidney disease associated with type 2 diabetes. Clinical trial results showed that the treatment led to a reduction in the risk of cardiovascular death, hospitalization for HF, and nonfatal heart attack among patients in the investigational arm. Adverse effects can include hyperkalemia, hyponatremia, and hypotension. Individuals with adrenal insufficiency and those receiving simultaneous treatment with strong CYP3A4 inhibitors should not receive finerenone.

FOR MORE INFORMATION:
bayer.com

Upadacitinib (Rinvoq)
Marketed by: AbbVie
Significantly more patients receiving upadacitinib achieved the primary end point of clinical remission in a 52-week phase 3 maintenance study of patients with moderate to severe ulcerative colitis. Upadacitinib is a reversible and selective Janus kinase inhibitor being investigated for the treatment of several immune-mediated inflammatory diseases. All secondary end points were also met, including the achievement of corticosteroid-free clinical remission at week 52, endoscopic improvement, and histologic-endoscopic mucosal improvement. No new safety risks were identified, and the most common adverse events observed in the upadacitinib groups were blood creatine phosphokinase increase, exacerbation of ulcerative colitis, and nasopharyngitis.

FOR MORE INFORMATION:
abbvie.com

Tezepelumab
Marketed by: Amgen Pharmaceuticals
The FDA has granted priority review to tezepelumab for the management of asthma. The biologics license application from Amgen is based on results from the PATHFINDER clinical trial program, which includes results from the pivotal NAVIGATOR phase 3 trial (NCT03347279). In this trial, tezepelumab demonstrated a clinically meaningful and statistically significant reduction in the annualized asthma exacerbation rate among this patient population. Investigators found no meaningful differences in safety results between the placebo and tezepelumab groups in the NAVIGATOR trial. A breakthrough therapy designation was granted to tezepelumab in 2018 for the treatment of patients with severe asthma without an eosinophilic phenotype.

FOR MORE INFORMATION:
amgen.com
Ponvory From Janssen Pharmaceuticals, Inc

By MONICA HOLMBERG, PHARMD, BCPS

THE FDA HAS APPROVED PONVORY (ponesimod; Janssen) for the treatment of relapsing forms of multiple sclerosis (MS) in adults, including active secondary progressive disease, clinically isolated syndrome, and relapsing-remitting disease.1

MS occurs when immune cells damage or destroy myelin. Common symptoms include problems with balance, bladder, bowel, and vision, along with dizziness, fatigue, numbness, tingling, vertigo, and weakness.2

PHARMACOLOGY AND PHARMACOKINETICS

Ponvory is a sphingosine 1-phosphate (S1P) receptor modulator. How its mechanism treats MS remains unknown but may involve the reduction of lymphocyte migration into the central nervous system.

Steady-state plasma concentration is observed after 3 days of oral maintenance dosing. Ponvory reaches maximum plasma concentration 2 to 4 hours after an oral dose and displays an elimination half-life of approximately 33 hours.3

DOSAGE AND ADMINISTRATION

The following clinical assessments are required before beginning treatment with Ponvory: cardiac evaluation, complete blood count, confirmation of antibodies to varicella zoster virus, evaluation of current or prior medications with immune system effects, liver function tests, ophthalmic evaluation, and vaccination status. After assessments are completed, treatment with Ponvory begins with a 14-day once-daily oral dose titration that is supplied in a starter pack. The titration schedule consists of 2 mg on days 1 and 2, 3 mg on days 3 and 4, 4 mg on days 5 and 6, 5 mg on day 7, 6 mg on day 8, 7 mg on day 9, 8 mg on day 10, 9 mg on day 11, and 10 mg on days 12, 13, and 14. Beginning on day 15, the recommended maintenance dose is 20 mg orally once daily. Ponvory should be swallowed whole with or without food. First-dose monitoring is recommended for patients with first- or second-degree (Mobitz type I) atrioventricular (AV) block, a history of heart failure or myocardial infarction, or sinus bradycardia.4

CLINICAL TRIALS

Ponvory was evaluated in an active-controlled, double-blind, parallel group, randomized superiority study in patients with relapsing forms of MS. The length of treatment was 108 weeks. Participants received either once-daily Ponvory, beginning with a 14-day dose titration, or teriflunomide (Aubagio) 14 mg once daily. The primary end point was the annualized relapse rate, which was statistically significantly lower in the participants who received Ponvory than in those who received teriflunomide. Additionally, the numbers of new gadolinium-enhancing T1 lesions and enlarging or new T2 lesions from baseline to week 108 were statistically significantly lower in participants who received Ponvory than in those who received teriflunomide.1,2

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

The use of Ponvory is contraindicated in patients who have experienced class III/IV heart failure, decompensated heart failure requiring hospitalization, myocardial infarction, stroke, transient ischemic attack, or unstable angina within the past 6 months. Ponvory is also contraindicated in patients with Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless the patient has a functioning pacemaker. Ponvory may increase the risk of infections. Patients should be monitored for infection during treatment and for 1 to 2 weeks after discontinuation, and patients with an active infection should not begin treatment. Ponvory may result in a decline in pulmonary function and a transient decrease in heart rate. Ponvory should be discontinued if significant liver injury occurs. Blood pressure should be monitored during treatment with Ponvory. Periodic skin examination is recommended to monitor for cutaneous malignancies. Women of childbearing age should use effective contraception during treatment and for 1 week after stopping Ponvory. S1P receptor modulators, including Ponvory, have been associated with an increased risk of macular edema, and this risk is greater in patients with diabetes mellitus and a history of uveitis. Administration of live attenuated vaccines during treatment with Ponvory and for up to 1 to 2 weeks after discontinuation should be avoided. Ponvory should not be taken with strong CYP3A4 and UGT1A1 inducers. Ponvory should not be used in patients with moderate or severe hepatic impairment.

The most common adverse reactions are hepatic transaminase elevation, hypertension, and upper respiratory tract infection.1

FOR REFERENCES, GO TO PHARMACYTIMES.COM/PUBLICATIONS.
Patients Report Confusion With Use of Alprostadil Urethral Inserts
Pharmacists Should Provide Both Verbal Education and Written Instructions, So Mistakes Do Not Occur
BY MICHAEL J. GAUNT, PHARMD

AUTHOR BIO
MICHAEL J. GAUNT, PHARMD, is a medication safety analyst and the editor of ISMP Medication Safety Alert! Community/Ambulatory Care newsletter at the Institute for Safe Medication Practices in Horsham, Pennsylvania.

PATIENTS OFTEN INCORRECTLY USE THE product called medicated urethral suppository for erection (MUSE), a urethral alprostadil suppository prescribed for erectile dysfunction.

The medication is available preloaded in an applicator system (see Figure) and is administered by inserting the stem into the urethra after urination to ensure the urethra is wet and pressing the applicator button. Each applicator system is wrapped in a foil pouch. Six applicator systems are packaged in a carton. Patients have reported confusion regarding how to properly use this product, resulting in ineffective medication and sometimes leading to urethral hemorrhage.

One factor contributing to these errors has been the lack of adequate verbal patient education. Patients have reported that neither the prescriber nor the dispensing pharmacist explained how to administer the medication. In 1 case, the patient used the product with the protective cover still in place.

Another factor for confusion has been a breakdown in providing written instructions for use.

Despite the professional package insert stating that “a patient package insert [PPI] must be given to each patient at the initiation of therapy,” patients are not always given one.

This gap can be attributed to several issues. First, the manufacturer’s information intended for patients, including step-by-step patient
instructions for administration, is printed at the end of the professional package insert meant for health care professionals. Both patients and pharmacists could easily miss these essential patient instructions, and pharmacists may not give the patient what appears to be a professional package insert.

Also, this information is confusingly referred to as “patient information” and not a “patient package insert,” as stated in the professional package insert.

Another issue is that not all prescriptions are written for a quantity of six applicator systems, resulting in patients being dispensed individual foil pouches and not the full carton. As there appears to be just 1 package insert in the carton of 6 applicator systems, some patients will not receive the patient package insert when the carton contents are split. The professional package insert with the included patient information could substitute for a separate PPI if there were enough of them and they were handed to each patient.

Still, it would be far better if the “patient package insert” was a document separate from the professional package insert and there were enough copies of the patient document to accommodate situations when individual pouches are dispensed.

For patients who do not receive the patient information, there are instructions on the back of each foil pouch that direct patients to external manufacturer resources for information: a phone number to the company’s medical information center and the product-specific website (muserx.net). However, at press time, this website did not appear to be working, and the phone number did not lead to a direct line that walks patients through the administration process. Also, the website for the manufacturer listed in the product labeling, Meda Pharmaceuticals of Somerset, New Jersey, does not include separate updated instructions identified as a PPI.

It is critical for prescribers and dispensing pharmacists to familiarize themselves with the administration process for MUSE. They must teach patients how to administer the drug safely and verify the patient’s understanding. They also must provide patients with the manufacturer’s professional package insert with the included patient information if it is available. Other than diagrams in the product labeling, the manufacturer does not appear to provide additional information to help patients properly use MUSE. YouTube, however, has several useful videos about MUSE, including this: youtube.com/watch?v=2sfOG6YBCM. But the instructions may be challenging to find on YouTube with the search feature, because other products and at least one musical artist use the name “Muse.” It helps to include something else about the product in the search, such as “MUSE suppository” or “MUSE alprostadil.”

The Institute for Safe Medication Practices has been in contact with the FDA about this product and the issues with the patient instructions. It is worth noting that there are other medications and dosage forms packaged in cartons containing multiple units that may not be accompanied by an adequate number of PPIs if the carton is split to accommodate prescriptions for quantities less than a full carton. For products that are routinely dispensed in quantities less than a full carton, including MUSE, manufacturers should consider including additional copies of patient instructions for each individual drug product that might be dispensed. The FDA should take this into account when interacting with manufacturers.
Desipramine Hydrochloride Tablets
Marketed by Alembic Pharmaceuticals

Compare To: Norpramin
One of 2 recently approved generics from Alembic Pharmaceuticals, desipramine hydrochloride tablets have been approved in strengths of 10, 25, 50, 75, 100, and 150 mg. The tablets are used to treat depression and may improve appetite, energy levels, mood, and sleep by balancing norepinephrine levels in the brain. Common adverse effects include blurred vision, constipation, dizziness, drowsiness, dry mouth, headache, increased appetite, nausea, nervousness, trouble sleeping, and weight gain. The tablets are not recommended for children younger than 18 years because of the risk of serious adverse effects.

FOR MORE INFORMATION:
alembicpharmaceuticals.com

Fingolimod Capsules
Marketed by Zydus Cadila

Compare to: Gilenya
The FDA has granted tentative approval to a new strength of Zydus Cadila’s generic fingolimod capsules, now in a 0.25-mg strength. The capsules are an immunomodulating drug and a sphingosine 1-phosphate receptor modulator indicated for the treatment of patients 10 years and older with relapsing forms of multiple sclerosis, including those with active secondary progressive disease, clinically isolated syndrome, and relapsing-remitting disease. Adverse effects can include abdominal and back pain, diarrhea, hair loss, headache, nausea, and weakness. Zydus Cadila received approval for fingolimod capsules in a 0.5-mg strength in October 2020.

FOR MORE INFORMATION:
zyduscadila.com
Nitrofurantoin Capsules  
Marketed by Alembic Pharmaceuticals  

**Compare to:** Macrobid  
The FDA has approved Alembic’s nitrofurantoin (macrocrystals) capsules in strengths of 25, 50, and 100 mg. The drug is indicated for the treatment of urinary tract infections due to susceptible strains of Enterococcus, *Escherichia coli*, *Staphylococcus aureus*, and certain susceptible strains of the *Enterobacter* and *Klebsiella* species. Common adverse effects can include headache, loss of appetite, nausea, and vomiting. Nitrofurantoin is not recommended for children younger than 1 month because of the risk of hemolytic anemia.

**FOR MORE INFORMATION:**  
alembicpharmaceuticals.com

Fluvastatin Sodium Extended-Release Tablets  
Marketed by Lannett  

**Compare to:** Lescol XL tablets  
Lannett is introducing fluvastatin sodium extended-release tablets in a strength of 80 mg, indicated as an adjunct to diet to treat elevated cholesterol levels. Patients with heart disease may use them to lower the risk of heart problems and slow the buildup of cholesterol in the arteries. Serious adverse reactions can include acute renal failure and myopathy, liver enzyme abnormalities, and rhabdomyolysis with myoglobinuria. The tablets had a market value of approximately $10 million for the 12 months ended May 2021, though actual generic market values are expected to be lower.

**FOR MORE INFORMATION:**  
lannett.com

FROM PIPELINE TO PATIENT  

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We deliver peace of mind.
THE RESULTS OF A NEW report from the Association for Accessible Medicines showed that generic prescriptions are less available to patients with Medicare Part D plans than to those with commercial insurance plans.

Generic medications are an important option to improve health care access and reduce medical costs for patients, especially older adults who often have chronic conditions or take multiple medications.

Generics saved the national health care system $313 billion in 2019 alone and close to $2.2 trillion over the past decade, according to the report.

In 2020, 72 first generics were approved, increasing market competition and helping lower costs for many patients, according to the report.

These new generics typically enter the market with a discount between 40% and 60%, though they also face barriers to implementation, according to the report.

Earlier research results suggested that generic drugs approved by the FDA between 2016 and 2018 had significant delays in Medicare Part D formulary coverage compared with commercial insurance plans.

Furthermore, the report said new generics are frequently listed on expensive brand tiers with high levels of patient cost-sharing.

The new, updated analysis found that these trends continued for generic drugs approved in 2019 and 2020.

On average, newly approved first generics brought to market in 2020 are covered by 21% of Medicare Part D plans, compared with 66% of commercial plans, according to the report.

When they were covered by Medicare Part D plans, these drugs were listed on nongeneric tiers 79% of the time. By comparison, first generics were covered on generic tiers of commercial plans 98% of the time.

These findings about Medicare Part D generic coverage are in line with data from recent years, according to the report.

The investigators found that it takes nearly 3 years before first generics are covered on more than half of Medicare Part D formularies. Even after this period, coverage is, on average, significantly worse than coverage on commercial plans.

“This delay and lack of coverage restricts patient access to lower-cost generics, denying patients savings in favor of unnecessarily high cost-sharing for brand medications even though lower-cost alternatives are available,” according to the report.

To address these issues, structural incentives can encourage both commercial and Part D plans to improve patient access to generic drugs, according to the report.

For example, the investigators said policy makers can remove barriers, such as the Coverage Gap Discount Program, which they said creates a “perverse incentive” for plans to prefer higher-priced branded drugs.

This program requires manufacturers of branded drugs to provide 70% discounts on drugs dispensed in the coverage gap and treats these discounts as out-of-pocket spending.

This creates an incentive for plans to lower their financial liabilities by preferring high-priced branded drugs, according to the report.

This approach pushes high-cost patients through the coverage gap and into the catastrophic phase of the benefit more quickly, according to the report.

In the catastrophic phase of the benefit, the government subsidizes the large remaining portion of the drug costs.

“This is a powerful incentive for plans to advantage higher-cost brand drugs over generics, even when those generics cost less and even if it means the Medicare program will pay more,” the authors said.

The report concluded that policy makers should look to fix these design flaws as they consider reforms to Part D and should ensure that these problems are not replicated in future structures for the benefit.

“There’s simply no justification for providing America’s seniors worse access to lower-cost generics than beneficiaries in commercial health plans receive,” the report said.

“The system prevents seniors from getting the full value of their Part D benefit. Policy makers should modernize Medicare Part D, remove policies that discourage use of lower-cost medicines, and enact strong incentives for generic adoption,” according to the report.
State Uses Pharmacy to Supply Drugs for Lawful Lethal Injection

Identity of Business as Source of Medications Supply Can Be Kept Confidential, Supreme Court Rules

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

ISSUE OF THE CASE

A SOUTHERN STATE WHERE THE appropriate state agency administers court-ordered executions by lethal injection has declined to disclose the identity of the pharmacy supplying the medications for that use.

Does a limitation in the statute governing the public’s access to governmental information apply to support the agency’s position?

FACTS OF THE CASE

Three attorneys representing defendants convicted of capital crimes and residing on death row in a state penitentiary had concerns related to mismanagement of executions by lethal injection by staff of the state’s department of criminal justice. They submitted written requests for the following information from the department: execution protocol the department intended to use; the drug or drugs the department intended to use; the source of those drugs; the dates the drugs were ordered and received; and any testing of the drugs to ensure integrity, potency, and purity.

Agency officials eventually responded by releasing all the requested information except for the source of the drugs. State law dictated that if an agency declines to release some information, it must request a legal opinion from the office of the state attorney general. The focus of that review is whether release of the requested information falls under some exception in the relevant open records statute.

The agency justified its denial of the request on a statutory provision stating that “information can be withheld if public disclosure ‘would subject the employee or officer to a substantial threat of physical harm.’”

The attorney general agreed with the agency and ruled that the “physical-safety exception” applied to the situation and protected identifying information from being disclosed.

The 3 attorneys then turned their attention from the executive branch of government to the judicial branch. They went to state court, where each side—the 3 attorneys vs the state agency—filed motions for summary judgment, an action that asked the trial court judge to decide the matter without a full trial. The motions sought to have the judge declare that there was no genuine dispute regarding a material fact at issue and...
that the matter could be resolved by the judge ruling in favor of 1 party or the other based on the relevant law.

The judge reviewed evidence submitted by the state agency that it felt showed a substantial threat of physical harm. That included a blogger's post about the pharmacy and capital punishment, comments on the website of a pharmacy that formerly supplied the medications for this purpose and emails sent to the owner of that pharmacy, and an email message sent to a pharmacy in a neighboring state that supplied medications for such use.

The trial court judge agreed with the 3 plaintiffs when he ruled that the evidence did not establish “a substantial threat of physical harm,” and therefore, the exception in the statute was inapplicable.

The state agency took the matter to the state court of appeals, which affirmed the decision of the trial court. The matter then advanced to the state’s highest court.

THE RULING
The state supreme court reviewed the entire record and concluded that the physical safety exception in the statute did apply and the agency could withhold the identity of the source of supply of the medication.

THE COURT’S REASONING
The court began by emphasizing that the statute under review “embodies a powerful policy that ‘each person is entitled, unless otherwise expressly provided by law, at all times to complete information about the affairs of government and the official acts of public officials and employees.”

Further, the legislature had mandated that the statute “shall be liberally construed in favor of granting a request for information.”

However, it also noted that the legislature “had enacted more than 50 exceptions to the broad rule of disclosure.”

The court reviewed an earlier appellate decision, which noted that there is a “common law interest in freedom from physical harm, which extends to every person.”

The burden of establishing a “physical-safety exception that would justify withholding information” rests with the governmental agency issuing the denial of access.

The court pointed out that the target of any threats is “largely unknown. No one but the department and the pharmacy itself knows the identity of the source that supplies the lethal injection drugs to the state.”

The court emphasized that physical harm means to a person and does not include economic or harm to physical property or potential loss of business or employment. The threat must be “directed at a person or persons.”

The highest court of the state concluded that the statutorily established right of the public to information about governmental operations “must yield in this context because that right is superseded by other highly important interests” and that an earlier “firestorm of hate mail” directed at the pharmacy formerly supplying the medications demonstrated “a substantial threat of physical harm that is directly connected to the identity of the pharmacy providing lethal injection drugs.”
Legislative Focus

Florida Authorizes Use of Automated Dispensing Systems

New Legislation Allows Community Pharmacies to Improve Medication Access in an Outpatient Setting

By D. KELLY PORTER AND JOSEPH L. FINK III, JD, DSC (HON), BSPHARM, FAPHA

FOR YEARS, THE STATE OF Florida has authorized the use of automated pharmacy dispensing systems to provide medication to patients residing in hospice settings, long-term care facilities, and prisons.

To improve medication access in other outpatient settings, Governor Ron DeSantis recently signed legislation into law that gives community pharmacies authorization to use these systems. Automated dispensing has the potential to alleviate the access-related issues of a high prescription-volume location, as well as in rural areas that may not have community pharmacies nearby.

Like mail-order pharmacies, automated dispensing is designed to increase the convenience of acquiring prescriptions for medications. Although convenience can maximize pharmacy revenue and is preferred by patients, it is hotly debated whether it is correlated to positive long-term outcomes. By contrast, automated dispensing may significantly contribute to medication nonadherence, which is costly for the health care industry and a significant preventable public health burden.

Nonadherence is associated with approximately 125,000 deaths, 10% of hospitalizations, and a cost of up to $289 billion annually. Promotion of a patient’s medication education and an adherence assessment is often seen as a hallmark role of pharmacists. Unfortunately, this role is typically executed to a minimum in most community pharmacy settings because of the crushing workloads these pharmacists have. This has resulted in pharmacy staff members often resorting to distribution of printed handouts that likely won’t be read by patients or caregivers. Medication therapy management services are done by pharmacists in many pharmacies, but strict performance metrics may inhibit a thorough interview process. Decentralized automated dispensing may set a delicate precedent that further removes pharmacists from their role of adherence assessment and management.

The legislation enacted by the Florida legislature and signed by the governor allows community pharmacies to provide outpatient dispensing through automated pharmacy systems. The Florida Pharmacy Association prepared an information sheet on the proposed legislation, highlighting the changes that will result from the enactment and concerns with the proposal.

The automated pharmacy system must be under the control of the pharmacy, and there must be a means of communication for the pharmacist to provide consultation to the caregiver or patient. The availability of counseling is required prior to the medication being released by the system to the patient, but there is no mandate that counseling occur.

The pharmacy must notify the board of pharmacy about the location of the automated dispensing system, and that location may differ from the location of the pharmacy on record with the board. No controlled substances may be dispensed using this technological approach, so none...
may be in the machine. There must be a pharmacist identified as being responsible for verifying the accuracy of the system and its activities, and the automated system must operate in a fashion that ensures confidentiality of personal health information.

The state pharmacy association identified some perceived drawbacks with the proposed legislation. The automated dispensing machine may be located remotely, away from the location of the controlling pharmacy. The association felt that the automated pharmacy system should be within the confines of the pharmacy that has the pharmacy permit issued by the board of pharmacy. The prior law addressing automated dispensing systems authorized their use at facilities where other health care providers were present on the premises; such a requirement was not part of this expansion. In addition, concerns were expressed about the security of staff members engaged in restocking the inventory in the machine, especially if located in remote areas. The legislation also would allow a pharmacist holding a Florida pharmacy license but living out of state to oversee and be responsible for the integrity and operation of the automated pharmacy system.

Rep. Matt Willhite, sponsor of the version of the bill introduced in the Florida House of Representatives, had this to say about the goal of the proposal: “With the passage of this bill, we hope to expand an individual’s access to their prescription medication. These machines will only dispense generic medications. Nonetheless, this technology will make it easier for busy parents and people living in rural communities to safely access the medications that they need.”

Direct integration into the Centers for Medicare & Medicaid Services (CMS) 5-Star Quality Rating System could be the change required to motivate community pharmacies to update their practice models in ways that will meaningfully increase adherence. A general timeline of transitions from quantity-centered to quality-centered care in most health care settings closely coincide with the implementation of CMS’ star system. With this in mind, it is understandable from a business perspective that pharmacies are almost entirely volume driven because they are not incentivized by the quality-centered, pay-for-performance model.

Recent unrelated legislative developments also provide opportunities to maximize the opportunities of automated dispensing. As several states implement legislation allowing pharmacists to bill for nondispensing services, it is reasonable to hope that reduced strain on a team dispensing medication will result in more time and resources to apply to other facets of the pharmacist’s scope of practice. If automated dispensing increases opportunities for other forms of engagement, such as collaborative care agreements or medication therapy management, there may be a wealth of untapped potential.
IT IS HARD ENOUGH TO be a mom and a pharmacist outside of a pandemic. Crazy schedules, including late nights and holiday and weekend work, have always been an issue. But now women in pharmacy can factor in increased anxiety about sending kids back to the classroom, vaccination responsibilities, virtual learning, and working with at-risk populations, which is sending many into crisis mode. What can we do to help each other during this pandemic, and can it be a turning point regarding how our profession and maybe even society value motherhood?

Based on my discussions with moms and the millions of posts within the Facebook Pharmacy Moms Group over the past 18 months, I can say that many moms are still struggling. Many are still doing most of the childcare and housework, as well as working outside the home for hours on end. It has been extremely difficult to coordinate children’s schedules as well. Many pharmacist moms are at their breaking point. As pharmacists, we are supposed to know exactly what to do for our patients, and as moms, our children and partners also expect much from us. It is the current state of uncertainty that makes it most difficult for many pharmacy moms.

One goal for the Pharmacist Moms Group, and also one of mine, is to use this time during the pandemic to highlight the stress that women in pharmacy have faced and continue to face.

Here are some points to keep in mind:

1. It is important to remind each other that perfection is not attainable and doing what you can is acceptable.
2. Every working mother will have a sick child at home at some point, so we need to give these employees the opportunity to stay home.
3. When pharmacist moms are sick and need immediate coverage, let’s make sure we have backups.
4. We cannot forget the pregnant moms who are working and who need a place to rest.
5. Likewise, every pharmacy should have a designated place for nursing moms who need a place to pump.

Most importantly, during this time of stress and uncertainty, we need to stick together as pharmacists and be there for each other.
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Before contracting with companies, independent pharmacies should take a hard look at their third-party logistics providers of pharmaceutical drugs or wholesalers to ensure they are dealing with legitimate entities and do not get caught in the crosshairs of an investigation.

Consider Woodfield Distribution, LLC (WDSrx), and Woodfield Pharmaceuticals, LLC, also known as WDSrx, a third-party logistics provider of pharmaceutical drugs, including for manufacturers, and wholesalers of highly regulated opiates.

In a massive sting operation, the Drug Enforcement Administration (DEA) recently seized a large number of controlled substances from the wholesaler and suspended its operations. The agency seized 27 tractor trailer–loads of opiates. Assembling in the parking lot of the Houston Astros Triple-A baseball team at Constellation Field, dozens of DEA agents gathered in preparation for what would be one of the largest narcotic seizures in recent history.

“We are taking custody of product that has a high likelihood of diversion, and we are going to safely secure it in another location,” Erik Smith, associate special agent in charge of the DEA’s Houston, Texas, division, told Fox 26 Houston.

The DEA is no stranger to the diversion of controlled substances and has been dealing with this trend for a long time. Essentially, diversion entails the unauthorized routing of highly addictive and dangerous opiates into an illegal marketplace for illegal sale to individuals who do not need it for a legitimate medical purpose.

An ongoing DEA audit has tracked tens of millions of doses delivered to WDSrx over the course of the past 3 years, according to Smith. The volume of controlled substances that are unaccounted for is substantial and represents a clear and present threat to public safety, he said, adding, “This is really the foundation of the opioid crisis in the United States.”

Fox 26 Houston reported that WDSrx was unable to account for large quantities of pharmaceutical-grade amphetamines, as well as opiates, such as codeine; phenobarbital; and tramadol, according to the DEA.

It would be prudent for industry drug manufacturers and wholesalers to take proactive measures to ensure that drug diversion does not take place in the supply chain. To that end, various monitoring systems are available in the marketplace.

Typically, outsourced solutions for suspicious monitoring programs are either fully managed software programs or “homegrown” systems.
Many companies opt to choose a “home-grown” system for a variety of reasons, such as the amount of money already invested and concerns about data security. Fully managed software programs may either sit in the cloud or be on-premises software. The benefit of fully managed software programs is simple: Manufacturers and wholesalers are not tasked with developing new algorithms and capabilities to keep up with DEA expectations, federal or state regulations, or industry trends. An example of recent regulation changes includes the federal Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act, which requires that potentially suspicious or “flagged” orders must be investigated and dispositioned by a company within 7 days. If that does not occur, the order must be deemed suspicious and reported to federal and state authorities accordingly. DEA expectations and industry trends can be much more complex. For example, a more recent best practice is to programmatically analyze customer order history, instead of using thresholds, and use morphine milligram equivalent benchmarks when evaluating orders.4

“The task of effectively monitoring suspicious orders while keeping up with ever-evolving regulations and trends is a gargantuan task. Outsourced solutions for suspicious monitoring, like Pharma Solutions NavigateSOM [suspicious order monitoring], and for state compliance, like Pharma Solutions ATLAS, [give] drug wholesalers and manufacturers the ability to cost-effectively mitigate compliance risk,” Sumeet Singh, CEO of Pharma Solutions USA, Inc, said in an interview.

WDSrx released a statement in connection with the DEA action, saying, “Woodfield Distribution, LLC, has been [maintaining] and continues to maintain active discussions with the DEA to address areas of concern related to governance and oversight of business operations. The alleged violations are being taken seriously by Woodfield Distribution, LLC, and every effort and attention is being made to resolve this situation in a timely and efficient manner for our clients in the near term.”3

REFERENCES

Fully managed software programs may either sit in the cloud or be on-premises software.
THE COVID-19 PANDEMIC HAS PUT a strain on the health care system globally, particularly affecting patients with chronic conditions. Many patients with disease states such as chronic obstructive pulmonary disease, diabetes, and hypertension are at high risk of contracting severe COVID-19, so it is especially important for this population to have access to medication therapy management (MTM) services to improve health outcomes. Evidence shows that implementing innovative pharmacist-led MTM services using technology tools such as telehealth during COVID-19 can help patients effectively manage chronic conditions.

Aspen RxHealth and Tabula Rasa HealthCare (TRHC) are both innovative platforms for delivering MTM services (see FIGURE). TRHC’s RxCompanion and MedWise

TRHC developed the MTM software platform RxCompanion, which can be used by community and health system pharmacists and health plans. RxCompanion includes a variety of features that help pharmacists identify and resolve medication-related problems and improve patient outcomes. Additionally, MTM services can be performed face-to-face, through video-based consultations, or via telephone and include more than 1000 clinical algorithms that identify and predict potential medication-related problems.

TRHC’s MedWise, a unique evidence-based medication safety software that can enhance MTM services, uses a medication risk-mitigation matrix to prevent adverse drug events. Pharmacists can perform comprehensive medication reviews through it and use it to conduct a multidrug analysis of the complete medication profile. TRHC can also provide services for health plans and pharmacies via its in-house MTM clinicians.

In an email interview, Sandra Leal, PharmD, MPH, FAPhA, CDCES, executive vice president for the Health Plan/Payer Business Unit of TRHC and president of the American Pharmacists Association, discussed the company’s MTM platform.

“We believe an MTM platform should empower a pharmacist to practice meaningful clinical pharmacy, regardless of their practice setting,” Leal said. “Our technology is used by over 10,000 community pharmacists, health system pharmacists, health plan pharmacists, and other telehealth providers.

“The clinical science behind our platform is a critical differentiator. As more of our population takes more medications, our platform’s ability to complete a simultaneous multidrug analysis through the new integration of our MedWise science empowers pharmacists like never before. In fact, a recent publication validated that the relative
risk of experiencing adverse drug events identified by the MedWise risk score is predictive of premature death.\textsuperscript{5}

Leal added that the COVID-19 pandemic “really highlighted the importance of the pharmacist. We believe they are best suited to provide personalized and culturally competent care that drives better health outcomes, lower costs, and higher patient satisfaction if provided the best technology.”

**ASPEN RXHEALTH**

Aspen RxHealth is an application-based MTM platform that pharmacists can access through a mobile phone or tablet. This flexible platform can expand career opportunities by allowing pharmacists to perform MTM services from anywhere through the app as long as Health Insurance Portability and Accountability Act privacy laws are followed. The platform includes a variety of programs, such as medication reconciliation, MTM, quality measure initiatives, and specialty drugs. Pharmacists are matched to patients based on various factors, such as clinical expertise and geographical location. After pharmacists complete and submit their successful MTM consults, they receive payment directly, and Aspen RxHealth manages the administrative activities.\textsuperscript{6}

Pharmacists can sign up with Aspen RxHealth and will be contacted if there are MTM opportunities in the areas where they are licensed. Once opportunities are available, a one-time $75 membership fee covers the background check, application setup, and ongoing training.

Martine Ferullo, PharmD, MBA, BCGP, is a pharmacist consultant at Aspen RxHealth who performs MTM services for patients with a variety of disease states, including asthma, congestive heart failure, diabetes, hyperlipidemia, hypertension, and osteoporosis. In an email interview, she discussed her experience with the Aspen RxHealth platform.

“The platform allows a great connection between the pharmacist and the patient to discuss their medication plan and their intended treatment goals,” she said.

Ferullo documents patients’ OTC and prescription medications, evaluates them for potential problems, and develops and discusses the action plan.

“I feel that many patients really like it and appreciate [the service], and they feel that this is not just a collection of medications call. It is about building relationships and trust,” Ferullo said.

Jenn Cohen, senior vice president of marketing and communications at Aspen RxHealth, said in an email interview, “In recent years we have seen dissatisfaction among pharmacists reach all-time highs. The Aspen RxHealth model comes at a time when this profession is ripe for transformation, and we couldn’t be more proud to deliver the groundbreaking technology empowering pharmacists to regain control of their career and reach new levels of professional and personal satisfaction. We are a company built for pharmacists, by pharmacists and will continue innovating to ensure pharmacists are able to find purpose and joy in their careers.”

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

**Call the Shots on Travel Vaccines**

*Pharmacists Can Assess Patients’ Needs, Evaluate What Is Required for Specific Destinations, and Provide Relevant Resources*

*By LISA RUOHONIEMI, PHARMD*

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**AS COVID-19 PANDEMIC-RELATED RESTRICTIONS LOOSEN** and international travel reopens, pharmacists are in an optimal position to provide patients with information about travel vaccines.

Being vaccinated protects both travelers and the individuals with whom they come in contact during their time abroad and their return home. Many countries have a range of recommended, required, and routine vaccines for travelers. Yet results of a survey of 1254 individuals departing the United States for international destinations found that up to 80% of respondents did not have a health consultation before traveling.

The most common reason for declining a pretravel evaluation was a “lack of concern about health problems related to the trip,” according to the survey results.

Pharmacists can address this lack of concern and other issues related to travel vaccines by assessing travelers’ needs, evaluating specific destination recommendations or requirements, and providing travel medicine resources for additional information.

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**ASSESSING TRAVEL VACCINATION NEEDS**

Each patient’s vaccination needs vary depending on the destination, trip duration, and type of travel. **TABLE 1** provides questions that pharmacists should ask to assess a traveler’s particular requirements and the rationale for doing so.

---

**TABLE 1. Questions to Assess a Traveler’s Vaccination Needs**

<table>
<thead>
<tr>
<th>Question</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the risk of acquiring a vaccine-preventable disease at the traveler’s destination?</td>
<td>Knowing about ongoing epidemics or outbreaks can help determine which travel vaccines are appropriate.</td>
</tr>
<tr>
<td>What is the length of the trip?</td>
<td>Both the duration of a trip and the season in which it takes place can affect a traveler’s likelihood of acquiring a vaccine-preventable disease. Travel during a particular season may increase the risk for certain diseases. For any trip, the longer the period of travel, the higher the risk becomes.</td>
</tr>
<tr>
<td>What type of travel will it be?</td>
<td>The destination and nature of travel, such as luxury travel or rural backpacking, will affect the individual’s disease risk.</td>
</tr>
<tr>
<td>How much time does the traveler have before departure?</td>
<td>Many travel vaccines are administered in a series that follows a strict timeline. It takes time for travelers to develop sufficient antibodies, necessitating planning ahead to develop full immunity prior to a trip. Travelers should be vaccinated 4 to 6 weeks prior to travel.</td>
</tr>
<tr>
<td>Are there any contraindications to the vaccines?</td>
<td>Several travel vaccines are live vaccines, which may be contraindicated in immunocompromised or pregnant patients. Others may have harmful interactions with certain medications.</td>
</tr>
</tbody>
</table>

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**AUTHOR BIO**

LISA RUOHONIEMI, PHARMD, is a pharmacist at LewisGale Hospital Montgomery in Blacksburg, Virginia.
Patient Focus

EVALUATING RECOMMENDED, REQUIRED, AND ROUTINE VACCINES

Pharmacists should take the following steps when evaluating a traveler’s potential vaccine needs:

For recommended or required vaccines: Determine the recommendations and requirements specific to the traveler’s destination. Some diseases eradicated in the United States still exist in other countries, necessitating vaccination. Many countries in tropical climates require the yellow fever vaccine. Some also require proof of meningococcal meningitis and/or polio vaccination. TABLE 2 lists possible vaccines that are recommended and/or required by international destinations. The CDC provides an interactive tool at gten.travel/prep/prep to help identify a patient’s travel risks and needs based on destination.

TABLE 2. Vaccines That May Be Recommended or Required by International Destinations

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Risk Factors for Contracting Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typhoid fever</td>
<td>Travel to: South America, Southeast Asia, Sub-Saharan Africa</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Adventure travel: Travel in rural areas where Japanese encephalitis is endemic</td>
</tr>
<tr>
<td>Rabies</td>
<td>Travel in areas where rabies is endemic, Travel related to the care or study of animals, including agricultural and research work</td>
</tr>
<tr>
<td>Meningococcal meningitis</td>
<td>Travel related to work in education or health care, Travel to: African meningitis belt (Sub-Saharan Africa)</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Travel to: South America, Sub-Saharan Africa</td>
</tr>
<tr>
<td>Cholera</td>
<td>Travel related to aid work, including health care and refugee work involving displaced populations in areas where cholera is endemic or epidemic</td>
</tr>
</tbody>
</table>

For routine vaccines: Review routine immunizations that the patient has already received. Some routine childhood vaccines require repeat doses to provide an effective level of immunity, which might otherwise wane over time. Pharmacists should determine whether a traveler is up to date on all appropriate routine vaccinations and offer or suggest booster doses if needed. In particular, hepatitis A and B vaccines are recommended for all travelers. TABLE 3 lists available routine vaccinations for adults as specified by the CDC. Note that some vaccines may have age or indication restrictions.

TABLE 3. Available Routine Adult Immunizations

<table>
<thead>
<tr>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (inactivated [IIV], recombinant [RIV], or live attenuated [LAIV])</td>
</tr>
<tr>
<td>Tetanus, diphtheria, pertussis (Tdap, Td)</td>
</tr>
<tr>
<td>Measles, mumps, rubella (MMR)</td>
</tr>
<tr>
<td>Varicella (VAR)</td>
</tr>
<tr>
<td>Zoster recombinant (RZV)</td>
</tr>
<tr>
<td>Human papillomavirus (HPV)</td>
</tr>
<tr>
<td>Pneumococcal conjugate (PCV13)</td>
</tr>
<tr>
<td>Pneumococcal polysaccharide (PPSV23)</td>
</tr>
<tr>
<td>Hepatitis A (HepA)</td>
</tr>
<tr>
<td>Hepatitis B (HepB)</td>
</tr>
<tr>
<td>Meningococcal A, C, W, Y (MenACWY)</td>
</tr>
<tr>
<td>Meningococcal B (MenB)</td>
</tr>
<tr>
<td>Haemophilus influenza type B (Hib)</td>
</tr>
</tbody>
</table>

PROVIDING TRAVEL MEDICINE RESOURCES

Pharmacists also can direct travelers to resources provided by the CDC for more information. These resources include:

• Health notices (wwwnc.cdc.gov/travel/notices)
• Health recommendations by destination (wwwnc.cdc.gov/travel/destinations/list)
• Travel vaccine clinic locator (wwwnc.cdc.gov/travel/page/find-clinic)
Help Ensure Proper Medication Storage and Disposal

*Education Is Key to Providing Information About Proper Techniques and Bolstering Patient Safety*

By JOANNE CANEDO, PHARMD; AND SHANE DESSELLE, PHD, RPH, FAPHA

**PHARMACY HAS HELPED INCREASE THE** attention paid to the improper disposal of expired, unused, or unwanted medications that have accumulated in households. Improper disposal can have many negative consequences. For one, dumping medications or flushing them down the toilet can pollute waterways, damaging sometimes fragile ecosystems and perhaps introducing toxicity into certain species of animals and plants. Nondisposal can result in accumulation, which can lead to unintentional poisonings if the medicines fall into the wrong hands, such as children, as well as substance misuse and abuse for drugs such as opioids, when the nonprescribed user takes them or even them illegally to others.

Education is key in the efforts to mitigate these problems. Pharmacy technicians should seek additional education about these issues so they can pass that knowledge on to patients receiving medications.

These efforts are commensurate with other efforts aimed at bolstering patient safety.

Research on medication waste and disposal helps with the design and implementation of educational strategies and other interventions. Maeng et al examined patient characteristics and health care use patterns that may be associated with the reason behind unused medications among Medicare patients. They observed that medication nonadherence is a major factor when it comes to accumulated medicines. Nonadherence and accumulation are especially problematic for patients with complex medication regimens, as these are often discontinued and/or change with no education or direction regarding the handling of unused doses. Findings from another study by some of the same investigators showed that the majority of accumulated medications were antibiotics and those prescribed for hypertension and pain, many of which are controlled substances. Medications such as opioids are often stored improperly in homes, where they may be easily accessible to family members, specifically children. The results of another study showed that among calls to poison control centers regarding accidental ingestions, more than 60% of children involved were younger than 5 years. The evidence shows that drastic changes are needed in health care to implement proper education for the public about the risks associated with improper medication disposal.

West et al observed that though the environmental implications of inappropriate medication disposal have been reported, the public’s knowledge about medication waste is inadequate. In terms of disposal practices, the most common methods are discarding for garbage collection and flushing down toilets. Although communities throughout the United States have begun to implement medication disposal programs, more efforts are necessary. One helpful piece of legislation, the Secure and Responsible Drug Disposal Act of 2010, permits law enforcement agencies to provide year-round drug donation boxes for collecting unused prescription opioids from community members. Involvement from law enforcement and philanthropic organizations can be instrumental in assisting pharmacies and other health care providers. Such is the case with the California Product Stewardship Council, for example, which lobbied for local drug take-back programs.

**AUTHOR BIO**

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ordinances and worked with pharmacies throughout the state to implement hundreds of secure take-back bins. Based on these and other study results, it is clear that pharmacy employees are pivotal in closing the gap in patients’ lack of knowledge about this public health challenge.

The provision of education on proper medication storage and disposal is paramount. Because pharmacists and particularly technicians are often the last individuals whom patients encounter when receiving prescribed regimens, they play key roles in facilitating proper storage of used and disposal of unused medications, particularly opioids. Of course, greater technician knowledge around the entire issue of medication nonadherence would be helpful. Besides many of the well-known factors—such as adverse effects, the complexity of medication regimens, and drug costs—contributing to nonadherence, technicians would benefit from additional information about other related issues to further their role in patient care. These include patients’ intentional nonadherence to wait to see whether a condition is improved by not taking a prescribed medication, physician over-prescribing, and even a belief by some that taking any medications regularly leads to physician dependence, even for drugs such as cholesterol-lowering agents and diuretics. Understanding nonadherence helps contribute to knowledge about possible accumulation and improper disposal.

Pharmacists and technicians can seize opportunities when providing education to strengthen their relationships with their patients. For instance, the provision of edifying information that helps a patient solve a problem will likely make them loyal to the pharmacy. The medication use process is often thought of as consisting of prescribing, dispensing, and use.

Greater technician knowledge around the entire issue of medication nonadherence would be helpful.

However, it involves much more, beginning with the patient’s receiving a diagnosis to their being adherent with medication use, storage, and disposal. Technicians who take a more holistic view of the medication use process can become even more important partners in ensuring optimal health outcomes.

REFERENCES
condition state management

Pneumonia Watch

By AISLINN ANTRIM

Choosing Appropriate Antimicrobial for Nosocomial Pneumonia Can Reduce Use of Broad-Spectrum Antibiotics

USING INTERNATIONAL AND NATIONAL guidelines, local microbiology data, and stewardship programs to choose the most appropriate antimicrobial treatment for nosocomial pneumonia can help reduce the use of broad-spectrum antibiotics, according to a paper published in Expert Opinion on Drug Safety.

In the data review, investigators analyzed the safety profiles of the most common antimicrobials for treating nosocomial pneumonia, including aminoglycosides, β-lactams, fluoroquinolones, linezolid, and vancomycin. β-Lactams are used most often for nosocomial pneumonia infections, with between 6% and 25% of patients reporting allergy or hypersensitivity reactions. However, the investigators said exhausting evaluation is essential for β-lactams because delabeling as many as 90% of these prescriptions by proper assessment seems possible. Combinations including a β-lactam are recommended in patients with risk factors for drug-resistant microorganisms and septic shock.

Aminoglycosides are safe for between 3 and 5 days of therapy, though the authors said that renal function should be monitored. Fluoroquinolones must also be used with supervision because of the risk of collagen degradation and cardiovascular events, which consist mainly of aneurysm and aortic dissection. Linezolid or vancomycin can also be used for the treatment of methicillin-resistant Staphylococcus aureus, though linezolid is preferable, according to the authors.

With all these indications in mind, the investigators said, physicians must choose treatments carefully. Daily assessment for adverse events is also essential, according to the paper.

Experts Publish Call to Action to Prevent NVHAP

A TASK FORCE OF health care leaders recently published a national call to action, urging increased focus on the prevention of non–ventilator-associated hospital-acquired pneumonia (NVHAP). Most health systems do not have systems in place to track or report NVHAP, according to the experts. Furthermore, most do not have active prevention initiatives, even though NVHAP is the most common hospital-acquired infection and has significant negative patient outcomes, including extended hospital stays, an increased risk for hospital readmission within 30 days, 15% to 30% mortality rates, and unexpected intensive care unit admissions of up to 46%.

Unlike cases of pneumonia associated with ventilators and other device-associated hospital-acquired infections, NVHAP is not recognized as an indicator in the National Database of Nursing Quality, and the Centers for Medicare & Medicaid Services does not require hospitals to report cases to the CDC National Healthcare Safety Network. NVHAP is also not included in pay-for-reporting or performance programs.

“Adding NVHAP to these lists of high-stakes conditions is one way to draw hospitals’ attention to NVHAP, to catalyze the discovery of optimized prevention initiatives and implementation strategies, and drive down NVHAP incidence and morbidity,” the white paper said, according to a statement.

COVID-19–Related Disease Lasts Longer, Causes More Damage

NEW RESEARCH RESULTS suggest that instead of rapidly infecting large regions of the lung, SARS-CoV-2 establishes itself in multiple smaller areas, hijacking immune cells and using them to spread over days or even weeks. Investigators took cells from patients’ lung fluid and examined the proteins expressed by those cells and the RNA, allowing them to identify how these immune cells drive inflammation. The investigators identified important targets to treat SARS-CoV-2–related pneumonia and minimize damage. Macrophages and T cells could be 2 critical targets because the findings suggest that macrophages could be infected by SARS-CoV-2, thereby contributing to the spread of the infection throughout the lung.

An experimental drug being tested at Northwestern University may quiet the inflammatory response of the immune cells and allow initiation of the repair process, according to a statement. The investigators said their goal is to make COVID-19 a mild disease, similar to a bad cold, though they cautioned that the virus is unlikely to completely disappear.
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Last Minute Requests
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Supply and Demand
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Fun Facts

Q: Before the advent of modern anesthesia, what were some techniques to render patients unconscious?

A: Humans have tried multiple avenues over the centuries to effectively render patients unconscious before surgeries. As an alternative to whacking patients over the head, some physicians tried suffocation to render them unconscious, whereas others accidentally discovered a drug’s ability to work as anesthesia when investigating it for potential recreational use. Examples include hashish in ancient China and opium in ancient Egypt.

Q: How was “animal magnetism” used to treat illnesses and injuries in the 18th and 19th centuries?

A: In the 18th century, Franz Friedrich Anton Mesmer, MD, an Austrian physician and theologian, introduced the healing power of animal magnetism to Europe. Although it was initially a treatment using magnetic plates that were placed on top of patients’ bodies, gradually the practitioner’s hands alone were used to heal. By the early 19th century, animal magnetism had arrived in the United States, where Mesmer’s disciples taught about the power of moving hands over specific areas of the body to heal patients of all manner of illnesses. This was a pseudoscience based on the power of suggestion.

Q: Trepanning is one of the oldest known forms of surgery, but on what part of the body was it used?

A: The skull. Trepanning, also called trephining, comes from the Greek word trypanon, which means to bore or drill. Surgeons historically used flint, metal, obsidian, or shells to scrape, cut a square, or drill a circlet of holes into their patient’s skull. However, unlike what we now understand to be brain surgery, trepanning was not intended to touch the blood vessels, brain, or the meninges. Instead, trepanning was usually conducted to address issues pertaining to the skull, such as epilepsy, fractures or injuries, headaches, and mental disorders.
Case Studies
By CHRISTINE PAN AND STEFANIE C. NIGRO, PHARMD, BCACP, CDCES

CASE 1

MP is a 22-year-old woman who is sexually active and accidentally missed her daily birth control dose both yesterday and the day before, as she left her pills at home while traveling for work. She takes a monophasic combination oral contraception pill containing ethinyl estradiol 20 mcg and norethindrone acetate 1 mg per tablet. MP notes that her placebo pills start next week, and she takes a 28-day pill pack. She asks whether she should take the missed pills today. How should the pharmacist respond?

What is the explanation?

CASE 2

JF is a 55-year-old man who recently became homeless after losing his job, because of economic hardship. He has type 2 diabetes and has been on insulin glargine for the past 5 years. Now that JF does not have constant access to refrigeration, he is worried that his insulin will not be effective and his diabetes will worsen. He is terrified, because his grandfather had his leg amputated as a result of diabetes. What advice should the pharmacist give to JF?

What should the pharmacist tell her?

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Answers

FOR REFERENCES, GO TO PHARMACYTIMES.COM/PUBLICATIONS.
Optimizing Clinical Outcomes in Spinal Muscular Atrophy With the Use of Novel Disease-Modifying Therapies: A Review for Pharmacists

**INTRODUCTION**

Spinal muscular atrophy (SMA) encompasses a group of degenerative, inherited neuromuscular disorders. Historically, patients with this disease were managed solely with supportive care to alleviate the associated symptoms and sequelae. However, the recent approval of novel agents to treat this family of disorders has the potential to change the trajectory of the disease process.

**Clinical Spectrum of SMA**

SMA is a progressive, degenerative, inherited neuromuscular disorder. It is an autosomal, recessively inherited group of neuromuscular diseases. The genetic basis as well as the phenotype-genotype correlation of SMA is illustrated in FIGURE 1. SMA is caused by mutations in the survival motor neuron (SMN) gene. Most often, the mutation occurs due to a homozygous deletion located on the 5q13 region of the SMN1 gene, which is responsible for encoding functional SMN1 protein. This protein ensures the survival of the α motor neuron. Healthy individuals usually have 2 copies of the SMN1 gene. The SMN2 gene is closely related to SMN1 but differs in its production of protein. Both SMN1 and SMN2 play a role in the pathophysiology of SMA. The difference between SMN1 and SMN2 is a single nucleotide, but SMN2 produces less functional protein than its SMN1 counterpart. For that reason, clinical severity of SMA correlates to the number of SMN2 copies a patient possesses. A larger number of copies of SMN2 is associated with less severe manifestation of the disease (see TABLE 1).

The characteristic feature of SMA is the degeneration of large motor neurons in the spinal cord and brainstem. The result of this degeneration is a loss of motor function.
SMA: spinal muscular atrophy.
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FIGURE 1. COMPARISON OF A HEALTHY INDIVIDUAL AND A PATIENT WITH SMA AND SPECTRUM OF PHENOTYPES

(A) Healthy Individual

Gene

SMN1

Exon 6
Exon 7
Exon 8

mRNA

100% FL-SMN2

Protein

100% Normal SMN

SMN2

Exon 6
Exon 7
Exon 8

mRNA

100% FL-SMN2

Protein

100% Normal SMN

SMN1 deletion or mutations

SMA type

Lethal

0

1

2

3

4

Non-symptom

(B) SMN1 deletion or mutations

SMA type

Lethal

0

1

2

3

4

Non-symptom

Disease severity

SMA, spinal muscular atrophy.

tion for the patient, SMA is the leading cause of death from genetic disease in infants because patients with the most severe disease will ultimately develop respiratory failure. SMA does not cause neurocognitive degeneration.12,13

Within the diagnosis of SMA are multiple subcategories with variable levels of severity.1 Patients diagnosed with SMA type 1 will exhibit the most severe manifestations of the disease. These patients are typically symptomatic by 6 months of age and present with severe hypotonia, including the inability to sit and lack of head control. Historically, patients diagnosed with this category of disease would die by 2 years of age from respiratory failure, unless they were provided mechanical ventilation support. Patients with SMA type 2 present with less severe disease. Symptoms in this patient group typically manifest between 6 and 18 months of age. Though these patients will never be able to walk independently, they will be able to sit independently. Patients with SMA type 2 will continue to develop a progressive weakness and will ultimately be unable to move their arms and legs against resistance. Symptoms in patients with type 3 disease are even less severe, and patients will be able to both walk and sit. However, as the disease progresses in patients with SMA type 3, they may not retain their ability to walk. Onset of symptoms in patients diagnosed with SMA type 3 typically does not occur until the patient is older than 18 months. Patients with SMA type 4 will be diagnosed in adulthood and will exhibit the least severe form of the disease. Patients with SMA type 3 or 4 rarely require mechanical ventilation during their lifetimes.12,13

SMA affects approximately 10,000 to 25,000 children and adults in the United States.12,14 The estimated incidence of SMA is 1 per every 6000 to 11,000 live births. The estimated prevalence of SMA is 1 to 2 per 100,000 people.12,13,15,16 Because SMA is an autosomal recessive disorder most carriers do not realize they are carriers until they have a child affected by the disease. Carrier frequency is estimated to be 1 in every 25 to 50 people.17,18

Historically, SMA was diagnosed upon the onset of symptoms.19 Patients would typically present with proximal muscle weakness, motor delays, or regression in milestones. In current practice, there has been a shift to emphasize the importance of
genetic screening and earlier diagnosis. Diagnosis is confirmed with a series of genetic tests, including multiplex ligation-dependent probe amplification, quantitative polymerase chain reaction, and next-generation sequencing. If these tests confirm that a patient is lacking both functional copies of SMN1, a diagnosis of SMA can be made. If a patient is found to have only 1 functional copy of SMN1, additional testing will be conducted. In rare instances, patients may exhibit symptoms consistent with SMA but will possess 2 functional copies of the SMN1 gene. Clinicians should then conduct further testing to ensure the patient does not have a rarer form of SMA or an alternative neuromuscular disease.19

When diagnosis was dependent upon the presentation of symptoms, it was commonly delayed for patients to receive their formal diagnosis of SMA.20-22 The delay could take approximately 4 to 10 months in some patients. In the least severe patients, it could be years before a diagnosis was formalized. With the advent of disease-modifying therapy (DMT) for SMA, the importance of early diagnosis has been emphasized. Patients who have a delayed diagnosis of SMA will not see the same benefit from DMTs. Once α motor neurons degenerate, function cannot be regained because the damage is irreversible. For a patient diagnosed with SMA type 1, 90% of motor neurons will be lost by 6 months of age.20

In order to expedite the diagnosis of SMA, a new focus has emerged on testing for prenatal carriers and conducting newborn genetic screening. The goal of these new screening methods is to detect SMA earlier and initiate DMT as soon as possible in qualifying patients. SMA was added to the US Federal Recommended Uniform Screening Panel (RUSP) in 2018. At this time, 36 states have adopted and implemented this recommendation with 2 additional states currently progressing towards inclusion of SMA in their state’s newborn screening.20-24

### Caring for Patients With SMA

Traditionally, supportive care with a multidisciplinary emphasis was considered the gold standard for management of patients with SMA. This is outlined in the 2018 SMA Standards of Care. Specialists across a wide variety of disciplines, including but not limited to neurology, orthopedics, respiratory therapy, pulmonology, nutrition, pharmacy, and physical therapy, must be part of the patient care team. Many times, patients will have a care coordinator who works alongside family members to organize services and optimize care.19,25

Respiratory therapy is a critical component of care for these patients. With the progression of respiratory failure, many patients will require mechanical ventilation during their lifetime. Most patients will require airway clearance with manual chest physiotherapy and mechanical insufflation-exsufflation in order to manage respiratory illnesses, and it must be started proactively.19,25 Nutrition services and support are also very important as many patients will progress to needing nutrition support through a feeding tube throughout their lifetime. There is also a need for expertise in enteral nutrition products, including elemental formulas and probiotics. Multimodal bowel regimens may often be required as the autonomic nervous system degenerates.26 Orthopedic specialists are needed to manage progressive spinal deformities that occur secondary to the neuromuscular disease. They can provide interventions ranging from the creation of braces for the correction of spinal curvature to surgical intervention to correct deformities.19

### Assessment Scales for SMA

One important aspect of caring for patients with SMA has been quantifying and objectively measuring patients’ motor function. Numerous scales have been validated for use and have also been important with the development of novel DMTs as they play a crucial role in qualifying outcomes in the clinical trials. The tests outlined have all been utilized in the clinical trials for DMTs in SMA.27 The scales are summarized in Table 1.27,28

### DMT and Treatment for SMA

In 2018, a treatment algorithm that was created by 15 experts in the field of SMA and moderated by a neutral third party was...
published to provide guidance in the management of patients with SMA. Their algorithm was meant to provide direction to providers once patients received a positive newborn screen. The authors determined that because patients with SMA have a wide variety of severity, range in acuity, and variable time to onset of symptoms, guidance should be provided on time to treatment.

The group created guidance for treatment initiation based on SMN2 copy number. Infants with 2 or 3 copies of SMN2 should be provided immediate treatment. Patients with 1 copy of SMN2 should receive treatment if pre-symptomatic; when symptomatic, it is left to the physicians’ discretion. Patients with 4 or more copies of SMN2 should be watched closely, and treatment should begin once symptoms present. It was recommended for patients to be evaluated every 3 to 6 months and for parents to keep a watchful eye for any noticeable changes in their child, such as changes to movement, feeding, breathing, or cry. In 2019, this treatment algorithm was updated secondary to newly available data. Per the expert panel, there are now enough data to recommend treating patients including those with 4 copies of SMN2.

### TABLE 2. SCALES FOR SPINAL MUSCULAR ATROPHY

<table>
<thead>
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<th>Scale</th>
<th>Length</th>
<th>Key Considerations</th>
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| Bayley Scales of Infant Development Third Edition (BSID-III)          | 45-120 minutes | • Assessment of infants and toddlers aged between 1 and 42 months  
• Multiple sections, including behavior, language, and fine motor and gross motor development  
• When assessing motor function, patients will be asked to complete tasks, such as grasping, stacking blocks, and sitting  
• Items are scored as able or unable  
• Currently, there are no data to support the use of the BSID-III specifically in the spinal muscular atrophy (SMA) population |
| Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) | 15-40 minutes | • 16-item scale developed for patients with SMA type 1  
• Items scored from 0 (no response) to 4 (complete response)  
• Measures both deliberate muscular movements and reflexive movements  
• Infants with SMA type 1 typically score approximately a 20, whereas those with normal development will often score 40 or above |
| Hammersmith Functional Motor Scale-Expanded (HFMSE)                   | 10-30 minutes | • Evaluate older children (>24 months) with SMA types 2 and 3  
• 33 items scored from 0 to 2  
• Assessment is of motor function, and expansion of the exam with the items from the Gross Motor Function Measure allows for utilization in both ambulatory and nonambulatory patients |
| Hammersmith Infant Neurological Examination-Section 2, Motor Milestones (HINE-2) | 5-15 minutes | • Assess infant motor skills and can be utilized for patients with SMA aged between 2 and 24 months  
• Assesses cranial nerves, motor milestones, posture, tone, reflexes, reactions, and behavior  
• Not developed specifically to assess patients with SMA, but has been validated in this patient population and utilized in clinical trials |
| Motor Function Measure-32 (MFM-32)                                    | 30-50 minutes | • 52 tasks, patients are scored on a 4-point scale (0 meaning cannot initiate the task and 3 meaning they can complete the task fully)  
• Motor function is examined in 3 different dimensions in this test: axial and proximal motor function, distal motor function, as well as standing, and transfers  
• Patients younger than 7 years may struggle with the length and complexity of this test |
| Revised Upper Limb Module (RULM)                                     | 10-15 minutes | • Evaluates upper limb function among primarily nonambulatory children  
• Both upper limbs are evaluated on a 19-item test geared towards assessing activities of daily living  
• Each item scored on a scale of 0 to 2 (with one item being scored as can or cannot)  
• Items include pressing a button, picking up a token, and other aspects of everyday life |
of SMN2 from the time of positive newborn screen. The panel continued to recommend waiting and closely monitoring those patients with 5 copies of SMN2.29

DMTs for SMA are a novel therapeutic area. Studies are ongoing and data are evolving with new interim analyses and regular updates. As such, different sources and reference information may exhibit slight discrepancies depending on date of publication. This article has worked to include the most accurate and up-to-date information available.

**STAR*  
★ Which patient populations would be considered candidates for nusinersen therapy?  
*S = Stop; T = Think; A = Assess; R = Review**

**Nusinersen**

Nusinersen was the first available therapy specific to SMA. Nusinersen is an antisense oligonucleotide that works by causing pre-messenger RNA (mRNA) splicing of the SMN2 gene in order to increase exon 7 inclusion in SMN2 mRNA transcripts. Ultimately, this leads to an increase in the production of full-length SMN protein. Nusinersen was approved by the US Food and Drug Administration (FDA) in 2016 for adult and pediatric patients with SMA.30

Nusinersen is administered to patients via intrathecal injection. Each dose of nusinersen is 12 mg/5 mL. Treatment with nusinersen can be broken down into the loading dose regimen and maintenance therapy phases. When treatment is initiated for patients, 3 loading doses will be given every 14 days. This is followed by a fourth and final loading dose 30 days after the third dose. Once the 4-dose loading regimen is completed, patients can begin maintenance therapy with nusinersen and receive 1 injection every 4 months.30

**Nusinersen Clinical Trials**

The ENDEAR study evaluated the safety and efficacy of intrathecal nusinersen in 121 infants aged 6 months or younger with infant-onset SMA.31 Investigators looked at event-free survival and motor milestone response, which was measured using HINE-2. An interim analysis in this study showed that patients treated with nusinersen had higher HINE-2 score improvements (41%) than those in the control group (0%) (P <.001). Patients treated with nusinersen were also found to have a prolonged time to death or need for permanent ventilation when compared with the control group. The most common adverse reactions to nusinersen were found to be lower respiratory infection and constipation.30 ENDEAR was terminated early because the data showed overwhelming efficacy for nusinersen, and patients were enrolled in the open-label extension study, SHINE.31,32 An interim analysis of the SHINE study showed improved Hammersmith scores with nusinersen treatment both at day 1 and day 480. For patients treated with nusinersen, HFMSE scores were 26.5 and 26.1 on days 1 and 480, respectively. For those randomized to the sham procedure, scores were 21.5 and 21.2 on days 1 and 480, respectively.33

The CHERISH trial examined the use of nusinersen in patients with later-onset SMA, defined as symptom onset after 6 months of age. This study included 126 children aged between 2 and 12 years. Investigators used the HFMSE scoring system to quantify patients’ neuromuscular function. Interim analysis in the CHERISH trial showed that patients exhibited a 4-point increase in HFMSE score versus 1.9 mean decrease in score for those in the control group. Fever, headache, vomiting, and back pain were all found to be common adverse reactions to nusinersen.30 Similar to ENDEAR, CHERISH was also terminated early due to overwhelmingly positive results; patients from CHERISH were enrolled in SHINE.34,35

The SHINE open-label extension trial began in 2015. The estimated completion date for this trial is August 2023.32 All patients enrolled in SHINE received nusinersen 12 mg intrathecal injections every 4 months. Patients who received nusinersen in CHERISH and ENDEAR exhibited better motor function than those transitioned from placebo utilizing the HFMSE and RULM scores.36,37

NURTURE is an open-label, interventional study assessing the efficacy, safety, tolerability, and pharmacokinetics of nusinersen in genetically diagnosed pre-symptomatic infants with SMA aged 6 weeks or younger at the time of therapy initiation.38 As of February 2020, all 25 patients treated with nusinersen in this trial were alive and did not require permanent ventilation.39 Compared with historical controls, this is significant as patients with SMA type 1 who remain untreated rarely live beyond 2 years of age. The estimated completion date for this trial is February 2025.40

Study of nusinersen continues with the DEVOTE trial, a phase 2/3, controlled, dose escalating trial.41 The study will have 4 treatment arms. The first will include patients with later-onset SMA who will be given nusinersen 28 mg on days 1, 15, and 29, followed by maintenance therapy with 28 mg on days 149 and 269. The second arm will be patients with infant- or later-onset SMA who will receive nusinersen 12 mg intrathecally on days 1, 15, 29, and 64, followed by 12-mg maintenance doses on days...
183 and 279. The third arm will include patients with infant- or later-onset SMA receiving loading doses of nusinersen 50 mg intrathecally on days 1 and 15, followed by 28 mg on days 135 and 279. A sham procedure will be administered on days 29, 64, and 183 in this treatment arm. Finally, participants who have been receiving the approved 12-mg dose for at least 1 year prior to study entry will receive a single 50-mg bolus dose intrathecally on day 1 (4 months following their most recent 12-mg dose), followed by maintenance therapy of nusinersen 28 mg on days 121 and 241. The goal of this study is to determine if a higher dose of nusinersen will increase treatment efficacy. Efficacy will be measured utilizing the CHOP INTEND scoring system. This study is estimated to be completed by July 4, 2023.

In January 2021, an announcement of the phase 4 RESPOND trial was made regarding treatment of the first patient in the trial. RESPOND will assess the benefit of nusinersen for infants and children treated with onasemnogene abeparvovec who may have unmet clinical needs after treatment. RESPOND will be a 2-year, open-label study including 60 patients up to 3 years of age at the time of first nusinersen dose. It has been reported that up to 40% of patients in the long-term study of onasemnogene abeparvovec have been treated with nusinersen.

Of the available DMTs, nusinersen has been available the longest. There are many observational, postmarketing, and surveillance studies currently ongoing. Investigators are also continuing to publish based upon their real-world experience with nusinersen. As these data are published, further evidence is growing for treatment of adult patients, and the hypothesis that earlier treatment results in improved outcomes is being validated. One study found that, overall, nusinersen treatment resulted in improved HFMSE scores and that earlier intervention was associated with the best response to therapy. Of note, investigators did not see any improvement in the progression of scoliosis with nusinersen treatment. The effect of nusinersen in patients with all types of SMA was examined in a 12-month observational study. Investigators noted that clinical trial data may not apply to all patients eligible for treatment with nusinersen and cautioned that extrapolating data from infants may not apply to all patients eligible for treatment with nusinersen. Nusinersen is approved for the treatment of SMA in all ages. The clinical trials discussed have outlined much of the data in infants and children. For adult patients, there are some published reports regarding nusinersen use. Published results of an observational cohort study in patients with genetically confirmed SMA aged between 16 and 65 years found that mean

Hammersmith scores significantly improved from baseline with nusinersen treatment. Limitations of the observational study included study design and the natural functional decline of SMA. Another study found that nusinersen provided a mild treatment effect in adult patients with SMA type 3 as noted in the 6-minute walk test, RULM, and peak cough flow results. There are ongoing studies of nusinersen in adult patients with SMA.

**Onasemnogene abeparvovec**

Onasemnogene abeparvovec is an adeno-associated virus type 9 (AAV9) vector-based SMN1 gene therapy. Onasemnogene works to replace the SMN1 gene encoding human SMN protein. This therapy was approved in 2019 for the treatment of pediatric patients younger than 2 years with biallelic mutations in the SMN1 gene. FDA approval for this medication was determined based on the completed phase 1 and ongoing phase 3 clinical trials conducted in patients with infant-onset SMA. Onasemnogene is an intravenous infusion administered over 60 minutes. Onasemnogene is dosed by body weight, and the recommended regimen is 1.1 x 10^14 vector genomes/kg.

**Onasemnogene abeparvovec Clinical Trials**

START was a phase 1 clinical trial that included 15 infants with SMA type 1, with 2 copies of SMN2. This was a single-arm, open-label, dose escalating study. The goal of START was to establish the preliminary efficacy and safety of onasemnogene. The primary outcomes were focused on safety and included treatment-related adverse events (trAEs) of grade 3 or higher. Time until death and need for permanent ventilation were secondary outcomes. Due to observation of elevated serum aminotransferase in the first patient in cohort 1, an amendment was made to the protocol to require concomitant prednisolone administration. At 2 years post infusion, all patients in the high-dose cohort were free from permanent ventilation. Of the 12 participants, 9 in the high-dose cohort could sit independently, and 2 could stand and walk independently. CHOP INTEND scores increased by 9.8 points after 1 month and by 15.4 points after 3 months when compared with untreated controls with SMA type 1. Overall, results showed that a single dose of onasemnogene positively affected survival and motor function in patients diagnosed with infant-onset SMA. The trial also found 56 serious adverse events (AEs) reported in 13 participants across both cohorts, of which 2 were treatment-related grade 4 elevations in serum aminotransferase levels.
The NeuroNEXT trial also studied onasemnogene in untreated patients with SMA type 1. This trial exhibited a 100% survival rate for infants treated with onasemnogene compared with 38% in the NN101 cohort. Meaningful changes in CHOP INTEND scores were also identified. Patients treated with onasemnogene improved to a score of 56.5 from a baseline score of 28.2. Patients in the NN101 group exhibited decline to 5.3 from a baseline of 20.3. Those treated with onasemnogene also exhibited significant achievement in motor milestones, which was not documented in the NN101 group. The untreated patients in this study were a historical control group.

STRIVE-US was a phase 3, open-label, single-arm, single-dose trial that assessed the safety and efficacy of onasemnogene in symptomatic patients with SMA type 1. Participants in this trial included those younger than 6 months who had 1 or 2 copies of SMN2. The co-primary end point for efficacy was event-free survival at 14 months; 91% of patients met this end point. Additionally, 59% of patients met the end point of functional sitting for 30 seconds or longer at 18 months of age (P < .0001 vs natural history). Further, 81.8% of patients were free of ventilation at 18 months of age. This study was the first to introduce the concept of ability to thrive at 18 months of age, a composite measure defined as the proportion of infants able to maintain healthy body weight without nutritional support or intervention. In this measure, 40.9% of study participants exhibited an ability to thrive, including 19 participants not requiring a feeding tube, 14 being able to maintain good weight, and 12 able to tolerate thin liquids. The most common AEs noted in the study were pyrexia, upper respiratory infection, constipation, and scoliosis. All were considered manageable and consistent with the medication’s safety profile.

SPRINT was an open-label, single-arm, phase 3 trial evaluating the efficacy and safety of onasemnogene in pre-symptomatic infants with SMA. Patients enrolled were younger than 6 weeks with 2 or 3 copies of SMN2. In 2019, an interim data analysis was conducted on this trial. This analysis showed that 8 of 14 participants with 2 copies of the SMN2 gene could sit independently for at least 30 seconds. Additionally, 4 of 14 participants could walk independently. All patients with 2 SMN2 copies achieved or maintained CHOP INTEND scores greater than or equal to 50. Patients in the trial who had not yet achieved motor milestones during this analysis were found to still be within the appropriate age range for continued development.

START Long-Term Follow-Up (START LTFU) is an ongoing, observational, long-term, follow-up study from the patients who completed the phase 1 START trial and received onasemnogene. As of December 2019, 10 of 12 participants in the active treatment cohort were alive and did not require permanent ventilation. No previously achieved motor milestones were lost during the follow-up period. Two patients were able to achieve new milestones of standing with assistance. No new trAEs were noted during the follow-up study.

The STRONG study is a phase 1 clinical trial with the goal of studying onasemnogene administration intrathecally. This trial has been on hold since October 2019 secondary to inflammation found following the intrathecal administration of onasemnogene.

Overall, the cumulative safety analysis from the trials and postmarketing surveillance suggests that although patients experience AEs with onasemnogene, they are generally not serious. However, there is the potentially serious AE of liver injury. Liver transaminase elevations need to be monitored via liver function tests and should be managed with prophylactic prednisolone.

Prednisolone dosing is adjusted based on laboratory results. Prednisolone must be initiated 1 day prior to treatment with onasemnogene and should be continued for at least 30 days following therapy. ALT, AST, total bilirubin, and prothrombin time should all be assessed at the end of the 30-day treatment period for prednisolone. If a patient is found to have normal liver function, steroids can then be tapered over the next 28 days. If liver function abnormalities are noted, systemic steroids should be continued at treatment dosing until assessments have normalized and then steroids can be tapered. If liver function does not improve, a hepatologist should be consulted. It may be helpful to include a hepatologist on the patient care team as well. Liver injury and hepatotoxicity can be serious without appropriate monitoring and intervention. One study reported 2 cases of transient drug-induced liver failure following administration of onasemnogene.

Thrombocytopenia has also occurred in patients receiving onasemnogene. However, this has been found to be transient and will resolve without intervention. Close monitoring of platelet counts is still recommended. Postmarketing surveillance has shown heart rate changes and laboratory abnormalities that cannot be explained clinically. Patients receiving onasemnogene should have troponin 1 monitored. Other adverse reactions to onasemnogene can include elevated aminotransferases and vomiting.

The manufacturer recently released a statement regarding real-world experience with onasemnogene indicating significant clinical benefit following treatment with this medication. The experience now allows clinicians to see that the benefits can be observed more than 5 years post dosing.
**Risdiplam**

Risdiplam is the first oral agent to treat SMA and was FDA approved in 2020 for the treatment of patients aged 2 months and older. It is a small-molecule, SMN2 splicing modifier that increases functional SMN protein. It is available as an oral liquid (0.75 mg/mL) that can be administered by mouth or via feeding tube. Dosing for this agent is based on both on age and weight. Patients aged between 2 months and 2 years will receive risdiplam 0.2 mg/kg body weight. For patients aged 2 years or older, dosing is 0.25 mg/kg body weight, with a maximum dose of 5 mg. Risdiplam is dispensed in amber glass bottles for protection from light. Pharmacists will need to dispense the appropriate oral syringes for patient use alongside the medication.

**Risdiplam Clinical Trials**

FIREFISH was an open-label, 2-part, phase 2/3 trial in infants with SMA type 1 aged between 1 and 7 months. The primary efficacy end point was the proportion of infants sitting without support for 12 months of treatment and longer using the BSID-III and CHOP INTEND. Results of the trial showed that key motor milestones were met after 1 year of treatment with risdiplam. Published results from the second part of the FIREFISH study showed that with risdiplam therapy 95% of patients were able to retain the ability to swallow and 89% of patients were able to feed orally. The most common AEs noted for risdiplam were upper respiratory tract infection, fever, rash, and pneumonia. SUNFISH is a second phase 2/3, randomized, double-blind, placebo-controlled extension study. The goal is to assess the safety, tolerability, and effectiveness of risdiplam in patients with SMA types 2 or 3 aged between 2 and 25 years. Patients in this study are nonambulatory. Part 1 of this study showed that treatment with risdiplam resulted in a median 2-fold increase in blood SMN protein levels after 4 weeks. These changes were sustained for a minimum of 24 months. Another finding was significant change in baseline MFM-32 score between risdiplam-treated patients and those who received placebo. The greatest response was noted in patients aged between 2 and 5 years (78.1% vs 52.9% achieving ≥3-point increase in MFM-32 score). The most common AEs included upper respiratory tract infection, nasopharyngitis, pyrexia, headache, diarrhea, vomiting, and cough; fever and rash were also noted.

JEWELFISH is a phase 2, open-label, exploratory trial. Patients included have SMA types 1, 2, or 3 and are between the ages of 6 months and 60 years. These patients have also previously received therapy for SMA including nusinersen and onasemnogene. This study is ongoing and has an expected completion date of 2025. No drug-related safety events have led to withdrawal from JEWELFISH.

RAINBOWFISH is an ongoing, open-label, single-arm, multicenter study. The goal of this study is to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants from birth to 6 weeks of age with pre-symptomatic, genetically diagnosed SMA. Estimated study completion for this trial is 2026.

**Investigational Therapies**

In addition to the therapies outlined, there are other agents being considered in the treatment and management of SMA. Branaplam is a small-molecule RNA splicing modulator that is thought to increase SMN protein levels. The safety and efficacy of oral branaplam in patients with SMA type 1 is currently being studied. Preliminary data on this medication showed improvement in motor function after 86 days of treatment. Celecoxib has been shown to increase SMN in animal models, and phase 2 and 3 trials are examining use of celecoxib in patients with SMA. The antibiotics azithromycin and the aminoglycoside drug class have possible potential as SMN protein stabilizers. Aminoglycosides have shown possible in vivo efficacy, but toxicity has yet to be investigated. Intrathecal administration of azithromycin in mice exhibited promising data. Bortezomib therapy, though able to improve motor function, has not shown improved survival.

**Therapeutic Agents Not Targeting SMN**

Many of the medications discussed in this activity focus on SMN-dependent mechanisms of action. However, there can be benefit in therapies that do not utilize SMN-dependent mechanisms in the treatment and management of patients with SMA. Patients with advanced disease or who might require multimodal therapy may benefit from these alternative agents.

Myostatin inhibitors are a class of medications that fall under this category. Myostatin is produced in skeletal muscles to inhibit muscle growth. If myostatin is inhibited, patients should be able to gain muscle mass, increase strength, and improve motor function. As muscle weakness is a hallmark symptom of SMA, myostatin inhibitors show promise in the management of patients with SMA. Another mechanism that has been studied is skeletal muscle troponin activation. The agent reldeesemtiv has been shown to improve muscle function in patients with SMA through a calcium-sensitizing effect. The result is an increase in the force of muscular contractions in response to
nerve activity. Some investigators believe that pyridostigmine, an acetylcholinesterase inhibitor used in the management of myasthenia gravis, may offer benefit in SMA. Potential benefits include possible increased activation and strength in muscles. Finally, stem cell therapy for SMA has been investigated. Precise recommendations, therapeutic potential, mechanism of action, and therapy details regarding this treatment option are still pending.3

The Effect of SMA on Patients and Families
Traditional management of SMA is associated with significant cost and burden for patients and families, both financially and emotionally. Multiple hospital admissions and appointments are needed with a variety of specialists for the management of breathing difficulties, orthopedic specialty interventions, speech therapy, specialized nutritional care, and surgeries. Families need to maintain ventilators, feeding tubes, suction machines, wheelchairs, back braces, and other resources. Lack of appropriate treatment or interventions could lead to increased patient hospitalizations, with significant financial burden associated with interventions and hospitalizations.73

Caregivers and the health care system experience additional strain to provide continual care for patients with SMA. One study from 2015 outlined some of the burden families faced prior to the implementation of DMTs.24 Families reported stress and psychosocial impact of SMA throughout their experiences. First, there was the experience of significant diagnostic delays and the associated frustration from that process. Second, there was the impact of living with SMA. Families needed to confront a number of psychosocial issues associated with an SMA diagnosis, such as coming to terms with a premature death and lost expectations, considering difficult treatments, fear of loss of function, stress, uncertainty, and helplessness.24 The National Alliance for Caregiving found that caregivers for children with rare diseases spend on average 53 hours per week maintaining their caregiving responsibilities. This demand often requires caregivers to cut back on working hours, and up to 86% of caregivers for patients with SMA report financial hardship.73

An economic analysis confirmed the cost burden, both inpatient and outpatient, for patients with SMA is significant and much higher than for healthy counterparts. Patients with infant-onset SMA were found to carry the greatest burden as it correlated with their severe disease. Those with child and juvenile SMA were still found to carry a burden 50-fold higher than their control counterparts. For patients with the most severe disease, the primary driver for cost was inpatient admissions for respiratory infections and respiratory failure. For patients with less severe disease, outpatient expenses, including home health care services, contributed to cost.73

DMT for SMA is associated with significant financial burden for patients and families; however, pharmacists can assist with access to therapies and mitigating costs. Though these therapies offer new hope for patients and families, their economic value has been debated. Because the clinical trials for SMA therapies have limited numbers of patients, extrapolations were required to conduct economic analyses. Limitations to these extrapolations include variable disease duration in study participants and heterogenous patient populations. Just 1 economic analysis has examined the impact of newborn screening for SMA. The cost of therapy will remain the same for all patients, but those treated prior to symptom onset may exhibit minimal deterioration or handicaps in the future.

Access to these therapies is important for caregivers and patients with SMA. Cure SMA has made its website easy to

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**STAR**

What economic and psychosocial factors must be considered when providing care to patients and families after a diagnosis of SMA is received?

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Image: Multidisciplinary Approach to Managing Patients with Spinal Muscular Atrophy

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navigate for patients and families seeking treatment. Nusinersen, onasemnogene, and risdiplam all have dedicated pages on the Cure SMA website. These directories can help patients, caregivers, and providers navigate some of the logistics associated with these medications. For example, the nusinersen page provides education materials for pediatric and adult patients, insurance policies, payer information, and a map tool to find centers administering nusinersen. For onasemnogene, similar information can be found, including another map tool to facilitate patient access. For risdiplam, payer information and patient education is available. Accredo Specialty Pharmacy is currently the only specialty pharmacy preparing and shipping risdiplam to patients.

The Role of the Pharmacist in Caring for Patients With SMA

A multidisciplinary approach is essential to the management of patients with SMA and is summarized in FIGURE 2. The pharmacist is a key member of any patient care team managing novel or complex medication therapies. In 2016, an article was published discussing many of the key roles a pharmacist plays in caring for patients with diabetes. Many of the key concepts discussed in this article are applicable to pharmacists assisting in the management of patients with SMA, such as the importance of the pharmacist in facilitating and participating in issues surrounding transitions of care, polypharmacy, financial matters, and patient education. Education to patients with SMA and their caregivers should include but is not limited to providing instructions on proper handling and administration of medications, information and resources on the various SMA therapies, expected adverse effects of medication therapies, and expectations of medical care and medication access, as well as any emerging data as new studies become available.

Handling and Administration

Pharmacists practicing in health systems and specialty pharmacies will need to be aware of the preparation instructions for the current DMTs. Nusinersen must be stored in the refrigerator until use. Once ready to use, the medication vial should be allowed to warm to room temperature without use of any external warming devices. At the time of preparation, nusinersen should be examined to ensure no particulates or discoloration are noted. Each vial is a single-dose vial, and 5 mL should be removed for each dose. Any extra medication in the vial should be discarded. Nusinersen should be administered within 4 hours of preparation (removal from the vial). Filter needles are not needed for the preparation of nusinersen. Sedation needs should be determined by the administering provider. Prior to intrathecal injection of nusinersen, 5 mL of cerebrospinal fluid should be removed from the patient followed by the injection of medication given over 1 to 3 minutes as an intrathecal bolus injection.

Onasemnogene is available as a kit for the pharmacy. It is frozen prior to use and must be thawed. Pharmacists have the option of allowing the kit to thaw over 12 hours in the refrigerator or over 4 hours at room temperature. If thawed within a refrigerator, the medication should be removed from refrigeration on the day of dosing. Once at room temperature, onasemnogene should be a clear to slightly opaque liquid (color will vary from colorless to faint white). Onasemnogene should always be free from particles. Do not shake onasemnogene at any point in the preparation or delivery process. The medication should be drawn from the appropriate number of vials into a syringe and delivered for infusion in a capped, room temperature syringe to the infusion center. Onasemnogene must be infused within 8 hours of being drawn into the syringe. If a syringe still contains onasemnogene 8 hours after preparation, both the syringe and medication should be discarded. Pharmacists should not attempt to refreeze onasemnogene after the medication has been thawed. Onasemnogene is administered as a 60-minute intravenous infusion from a syringe.

Risdiplam is provided to the pharmacy as a powder for reconstitution. During reconstitution of risdiplam, those preparing the medication should wear gloves and avoid contact with the skin or mucous membranes. Any skin or eye contact with risdiplam should result in washing the area thoroughly. To reconstitute risdiplam, gently tap the bottom of the closed glass bottle to loosen the powder, remove cap, and pour 79 mL purified water into the bottle. Recap the bottle and shake for 15 seconds, then wait 10 minutes. After this time, risdiplam should be a clear solution. If it is not, shake well again for another 15 seconds.

Once reconstituted, risdiplam has a 64-day expiration. Pharmacists should make note of this on the bottle and inform patients and caregivers that any unused medication must be discarded after that date. Upon dispensing, the pharmacy should ensure appropriately sized oral syringes are provided to the patient or caregiver. Risdiplam should be stored in the refrigerator. The medication is removed from the bottle with an oral syringe.
and can be administered by mouth, via gastrostomy tube, or via nasogastric tube. Patients and caregivers should check to ensure there are no large air bubbles and that the correct amount of risdiplam has been drawn up prior to administration.

After administration of risdiplam, it is recommended to drink a small amount of water or flush the tube through which the medication was given with a small amount of water in order to ensure all of the medication has been delivered. Risdiplam should be administered once daily after a meal at approximately the same time every day. If a dose is missed, it is recommended that it be administered as soon as possible if still within 6 hours of the dose. If outside the 6-hour window, the dose should be skipped, and the medication should be given at the regularly scheduled time again the next day. If the patient vomits a dose or if a dose is not fully swallowed, patients and caregivers should not administer another dose to make up for lost medication.

**Multidisciplinary Care and Medication Management**

With the advent of DMTs, the need for pharmacist involvement in the care of patients with SMA has only grown. Outside of the management of DMTs, pharmacists managing patients with SMA can participate in reviews of complex medication regimens for patients requiring multimodal supportive care. One aspect where pharmacists can provide oversight is in the review of medication regimens to ensure appropriate bowel schedules are created. Pharmacists can also play a role in the development of nutrition support regimens, including making recommendations on medication interactions with formula and feeding schedules, medication compatibility with feeding tubes, and the provision of total parenteral nutrition. Guidance on the design of efficacious airway clearance treatments and direction of antibiotic therapies are also opportunities for clinical pharmacists to be involved in the care of patients with SMA.

Clinical questions surrounding the use of multiple concurrent medications for the management of SMA and comparing the individual SMA agents still exist. Given the variable populations and time frames of the existing clinical data, direct comparisons of SMA agents are difficult to make. In clinical practice, many SMA providers have worked to obtain access to both nusinersen and onasemnogene for their patients. Each medication has a unique mechanism of action, and, as previously discussed, there is the potential for nusinersen therapy to provide additive benefit on top of onasemnogene. Results of the clinical trial investigating this very question are anticipated, but in the meantime, many providers feel as though the potential impact of dual therapy on neuromuscular function is worth fighting to provide. As the first oral agent for SMA, risdiplam has promise to be combined both with SMN DMTs and SMN-independent therapies. The promise of using risdiplam in combination with a medication like nusinersen is the enhancement of full-length SMN expression from combination therapy. Pharmacists will continue to play a key role in the oversight of medication selection, dispensing, administration, and monitoring. Select considerations are summarized in Table 3.

As an SMA provider, it is important to tailor therapy to the individual patient. A neonate with newly diagnosed SMA type 1 is eligible for treatment with onasemnogene and nusinersen. Most providers would want to initiate therapy as soon as possible in this patient with one or both therapies. However, this patient would not be a candidate for risdiplam until older. In contrast, an adult patient with SMA type 4 who initially presented without any symptoms could be managed with watchful waiting until symptoms present. Once symptomatic, this patient would be a candidate for either nusinersen or risdiplam. Either medication could be selected depending upon the patient’s needs and preferences. For patients with limited transportation options, or in whom regular procedural sedation may be a risk, risdiplam may be the preferred drug. Some providers may consider fighting for a combination of risdiplam and nusinersen therapy for their adult patients with SMA symptoms. Each patient will present in a unique manner, and therapy should be selected to their exact needs.

**Patient Education and Counseling on Special Considerations**

When educating patients and caregivers on the DMTs, each has their own unique counseling points. For nusinersen, it is important to educate on the possibilities of thrombocytopenia, coagulation abnormalities, and potential renal toxicities. Monitoring for these AEs will require additional blood work and laboratory monitoring. Nusinersen also will require on-site administration, coordination of additional transportation, and possible procedural sedation. Patients and caregivers should be made aware of all of these items.

For onasemnogene, patients should be educated on the risk of liver injury and the need for laboratory monitoring. This also will involve having additional blood work done. Patients should also be counseled regarding vaccination timing as it pertains to the steroid requirements with onasemnogene. Adjustments to vaccination schedules may be necessary, and viral infections may be more serious during the duration of steroid therapy. Onasemnogene also carries a risk of thrombocytopenia and
thrombotic microangiopathy. Both of these should be reviewed with patients and caregivers, and families should be counseled to seek immediate medical attention if patients experience unexpected bleeding, bruising, seizures, and diminished urine output. One important and unique counseling point is that vector shedding will occur through body waste after administration. Caregivers should be counseled on the proper handling of patient feces after medication administration, including the need to wash hands thoroughly and to double-bag any disposable diapers at the time of disposal.48

For patients and caregivers being treated with risdiplam, pharmacists should educate patients that the medication may cause fetal harm for women of childbearing age who may come into contact with the medication. Appropriate handling techniques should be reviewed. Male patients should be advised that their fertility may be impacted during treatment with risdiplam. Finally, all patients should be counseled that risdiplam should be a liquid when obtained from the pharmacy, be administered with meals or breastfeeding/bottles, and be administered immediately after being drawn up in the oral syringe.65

Coordination of Care
Pharmacists can play an important role in the creation of appropriate workflows for administration of these medications at their respective practice sites. This includes both the logistical and financial aspects of utilizing these medications. For example, with intrathecal administration, nusinersen requires coordination of many specialties, including pharmacy technicians for medication preparation; anesthesia; and lab, operating room, or procedure room staff. Onasemnogene

| TABLE 3. CONSIDERATIONS FOR SPINAL MUSCULAR ATROPHY MEDICATIONS30,48,65 |
|-----------------------------|-----------------------------|-----------------------------|
| Nusinersen | Onasemnogene | Risdiplam |
| **Mechanism** | SMN2-directed antisense oligonucleotide | Adeno-associated virus vector-based gene therapy | SMN2 splicing modifier |
| **SMA indication** | Pediatric and adult patients | Age <2 years with biallelic mutations in SMN1 gene | Age ≥2 months |
| **Frequency and route of administration** | Initial loading doses, then maintenance doses once every 4 months, administered intrathecally | Single-dose intravenous infusion over 60 minutes | Once-daily oral solution |
| **Dosing** | 12 mg (5 mL) per administration | 1.1 × 10^{14} vector genomes (vg)/kg of body weight | 2 months to <2 years: 0.2 mg/kg |
| | **4 loading doses:** 3 doses at 14-day intervals; 4th dose administered 30 days after the 3rd dose | Provided as customized kit to meet dosing requirements | ≥2 years, <20 kg: 0.25 mg/kg |
| | **Maintenance dose:** once every 4 months thereafter | Requires systemic corticosteroids for at least 30 days | ≥2 years, ≥20 kg: 5 mg |
| **Warnings and Precautions** | Thrombocytopenia and coagulation abnormalities; renal toxicity | Boxed warning: acute serious liver injury | May cause fetal harm; women of childbearing age should be educated on proper handling |
| | **Warning and precaution:** thrombocytopenia; elevated troponin-I | Elevated aminotransferases and vomiting | Later-onset: fever, diarrhea, rash |
| | | | Infantile-onset: similar to later-onset, and upper respiratory tract infection, pneumonia, constipation, and vomiting |
| **Adverse effects** | Later-onset: pyrexia, headache, vomiting, and back pain | | |
| | Infantile-onset: lower respiratory infection and constipation | | |
| **Drug interactions** | N/A | Patient’s vaccination schedule may need to be adjusted to accommodate corticosteroid administration. | Avoid coadministration with drugs that are substrates of multidrug and toxin extrusion transporters (metformin). |
will require coordination with infusion centers regarding preparation and administration of the medication. Additionally, continued oversight of appropriate monitoring and use of these medications is important. Pharmacists have a key role in ensuring patients meet and receive appropriate laboratory monitoring for continued therapy and that they receive the necessary supportive care, such as prednisolone treatment with onasemnogene.\(^8\)

**Impact of COVID-19 Pandemic**

The COVID-19 pandemic has impacted many patients with chronic disease states across the care spectrum, including patients with SMA. There have been significant challenges in managing and maintaining the multidisciplinary appointments required for their continued progress. It has been a significant challenge for patients and families to continue to coordinate the care required for management of SMA secondary to appointment restrictions, capacity limitations, and remote evaluations. Interacting with a physical therapist or neurologist via interactive online portals is often not the same as an in-person visit. Additionally, for orthopedic procedures or coordination of medication infusions or intrathecal injections within the hospital setting, there were temporary restrictions placed on elective procedures in hospitals in early 2020. Those restrictions continued to adjust and change, but nonemergent care was downgraded to prioritize the urgency of the pandemic. For pediatric patients requiring hospital admission, many institutions implemented visitor restrictions and limitations, which can be emotionally challenging for patients and families alike. For all patients with chronic diseases, especially those requiring significant respiratory therapy and support, the pandemic has been a source of fear and emotional distress. Logistically and emotionally, the COVID-19 pandemic has made managing the care of a patient with SMA more challenging. Cure SMA has created a coronavirus information center for further information on the pandemic and its impact on families of patients with SMA: https://www.curesma.org/covid19/.

**Conclusion**

SMA is a group of neurodegenerative diseases that have significant impact on patients, families, and caregivers. The burden of SMA spans physical, financial, and psychosocial spheres. Starting in 2016, DMTs entered the market and have since changed the trajectory of this disease. Though there is still a need for clinical trials to compare therapeutic agents, treatment decisions and algorithms are already being devised. Pharmacists can play an integral role in the establishment of access, as well as the initiation, delivery, monitoring, and administration of these medications.

**ADDITIONAL RESOURCES**

- Cure SMA: curesma.org
- SMA Foundation: smafoundation.org/about/sma/26852
- Children’s Hospital of Philadelphia: chop.edu/conditions-diseases/spinal-muscular-atrophy-sma/health-resources
- C.S. Mott Children’s Hospital: mottchildren.org/conditions-treatments/brain-neurology/spinal-muscular-atrophy

**REFERENCES**

8. Govoni A, Galfiardi D, Comi GP, Corti S. Time is motor neuron: therapeutic window and its corre-


doi: 10.1016/j.nmd.2017.11.004


71. Roche’s risdiplam showed significant improvement in motor function in people aged 2-25 with type 2 or 3 spinal muscular atrophy. News release. Roche. February 6, 2020. Accessed April 9, 2021. roche.com/media/releases/med-cor-2020-02-06.htm
75. Spinraza. Cure SMA. Accessed April 9, 2021. curesma.org/spinraza/
77. Evrysdi. Cure SMA. Accessed April 9, 2021. curesma.org/evrysdi/

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POSTTEST QUESTIONS

1. PC is a 3-year-old boy recently diagnosed with spinal muscular atrophy (SMA). He presented with less severe disease, with his symptom onset beginning a month prior. He is able to sit, stand, and walk. He does not have any feeding, orthopedic, or respiratory complications. He has 4 \( SMN2 \) copy numbers, but other patients with his type of SMA may have 3. Which type of SMA is most likely associated with PC’s clinical presentation?
   A. Type 1
   B. Type 2
   C. Type 3
   D. Type 4

2. PC’s doctor recommends initiating nusinersen. Which statement is true regarding his new medication?
   A. The most common adverse effects in later-onset SMA are diarrhea and rash.
   B. The medication has 5 loading doses and is then administered once every 2 months.
   C. The goal of the DEVOTE trial is to determine if a higher dose of nusinersen will increase efficacy.
   D. The dose of the medication is adjusted based on the patient’s weight.

3. An economic analysis found that those with child and juvenile SMA were found to carry a burden how much higher than their control counterparts?
   A. 5-fold higher
   B. 10-fold higher
   C. 25-fold higher
   D. 50-fold higher

4. KJ is a 7-day-old infant being seen in the neurology clinic after a positive newborn screen for SMA. The neurologist is discussing disease-modifying therapies (DMTs) for SMA with KJ’s mother and asks the pharmacist in clinic for assistance in explaining the different DMT agents. When discussing agents for the treatment of SMA with KJ’s mother, which of the following would be an important counseling point to discuss?
   A. Nusinersen will require intrathecal administration, appointments in the procedural area, and possibly procedural sedation.
   B. KJ will qualify for therapy with oral risdiplam immediately based on his age, but it must be given with an oral syringe.
   C. KJ will have to wait to be able to receive onasemnogene because it is only approved in patients aged 2 months and older.
   D. Intrathecal administration of branaplam may be an option for KJ’s treatment.

5. The pharmacist should recommend and ensure prednisolone or an equivalent systemic corticosteroid is administered 24 hours before a patient receives an infusion of onasemnogene due to what boxed warning associated with this medication?
   A. Anaphylaxis
   B. Pain at the injection site
   C. Bronchospasm
   D. Acute serious liver injury
Decreasing Mortality Rates When Reversing DOAC-Related Bleeding: Examining Updated Recommendations, New Data, and Real-World Evidence Using Specific Reversal Agents

EDUCATIONAL OBJECTIVES

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

• Explain current recommendations and guidelines for the reversal of major bleeding associated with the use of direct-acting oral anticoagulants (DOACs)
• Examine up-to-date clinical data and real-world evidence comparing the safety benefits of specific reversal agents over prothrombin complex concentrates (PCCs) for reversing life-threatening DOAC-related bleeding
• Identify the role of health-system formulary committee members, pharmacy directors, and integrated delivery networks in improving clinical outcomes and decreasing mortality rates in those patients being treated for reversal of major bleeding related to the use of DOACs

The approval of direct-acting oral anticoagulants (DOACs) dabigatran, rivaroxaban, edoxaban, and apixaban in the United States has dramatically changed anticoagulation management for primary stroke prevention in patients with atrial fibrillation and treatment or secondary prevention of venous thromboembolism (VTE). Together, these agents have become primary anticoagulant therapy selection in patients with atrial fibrillation over vitamin K antagonists (VKAs) owed to their improved safety profile and ease of use compared with traditional therapy. Despite an enhanced safety profile of DOAC therapy over conventional VKAs with a reduced incidence of major and clinically relevant nonmajor bleeding, the risk of clinically significant hemorrhage while on anticoagulation remains.

Major hemorrhagic events have been reported to occur in up to 4% of patients receiving DOACs, with fatal hemorrhage occurring in up to 0.3% of patients. The incidence of major gastrointestinal bleeding (GIB) is estimated at 2.09% and intracranial hemorrhage (ICH) at 0.51%. Between 2013 and 2014, 17.6% of all adverse drug events resulting in emergency department (ED) visits were attributed to anticoagulation therapy, with DOACs implicated as the baseline anticoagulant in 12.0% of anticoagulation-related adverse drug events. Supportive care and temporary anticoagulation cessation may be appropriate for patients with minor bleeding, as DOAC anticoagulation effects are reduced within 24 hours of last administration in patients with normal renal function. However, those with life-threatening bleeding, critical site bleeding, or major bleeding who are nonresponsive to supportive care measures should be considered for anticoagulation reversal.
bleeding that warrants immediate reversal includes ICH or other central nervous system hemorrhage, pericardial tamponade, airway or posterior epistaxis, hemotherax, intra-abdominal, and retroperitoneal hemorrhage, as well as intramuscular and intraarticular bleeding. Furthermore, major bleeding that is unresponsive to supportive care measures should be considered for anticoagulation reversal to improve patient outcomes.

Prior to the approval of agent-specific reversal agents, a lack of DOAC reversal agents was a major disadvantage to use and cited as a main barrier to provider prescribing despite the overall enhanced safety profile of these agents. Two agent-specific reversal agents have since been approved by the Food and Drug Administration (FDA): idarucizumab (Praxbind) and coagulation factor Xa (recombinant) inactivated-zhzo (Andexxa, commonly referred to as andexanet alfa). The purpose of this review is to examine the evidence supporting agent-specific anticoagulation reversal in patients with major or life-threatening bleeding while on DOAC therapy and discuss strategies health care systems can utilize to optimize patient outcomes.

Meeting the Unmet Need in Management of Life-Threatening Hemorrhages on DOAC Therapy

Landmark clinical trials bringing current DOAC therapies to the market for stroke prevention in patients with atrial fibrillation and treatment or prevention of VTE provide important insights on the mortality risk associated with hemorrhagic complications in the absence of the availability of DOAC-specific reversal agents. The majority of patients with hemorrhagic complications while on DOAC therapy in clinical trials were treated with supportive care measures only, with few receiving any factor replacement therapy. In the ARISTOTLE trial, 30-day mortality occurred in 8.9% of patients with major hemorrhage while on apixaban. Similar results were observed in patients receiving dabigatran therapy in a pooled estimate of the RE-LY, RE-COVER, RE-COVER II, RE-MEDY, and RE-SONATE trials, where 30-day mortality was reported to be 9.1% in patients with major hemorrhage. All-cause mortality after rivaroxaban-associated major hemorrhage reached 20.4% in patients in the ROCKET-AF trial. In patients with ICH while on DOAC therapy, 30-day mortality was reported in 45.3% on apixaban, 48% on rivaroxaban, and 36% on dabigatran, highlighting a subset of patients who are most at risk of poor outcomes. All-cause mortality in clinical practice has been reported to occur in 16% to 40% of patients with DOAC-associated ICH.

The importance of anticoagulation reversal in the setting of major or life-threatening bleeding cannot be understated. In patients on VKA therapy presenting with ICH, treatment with prothrombin complex concentrates (PCCs) or fresh frozen plasma for anticoagulation reversal was associated with lower risk of mortality compared with no reversal. The benefit of reversal is expected to extend to all anticoagulant therapies, including DOACs. Withholding reversal in patients with DOAC-associated ICH was associated with approximately 1.5-fold increased risk of death and worse functional outcomes in the Swedish Stroke Register. Life-threatening and major hemorrhagic events while on DOAC therapy are significant risks for morbidity and mortality for patients requiring therapeutic anticoagulation. Institutions should proactively implement protocols to guide management in patients presenting with DOAC-associated major or life-threatening hemorrhages.

Review of Guideline and Society Recommendations

Available guidelines and societal expert consensus statements recommend preferential use of DOAC-specific reversal agents, when available, for patients in whom anticoagulation reversal is indicated. When DOAC-specific reversal agents are not available, off-label use of PCCs may be considered. These recommendations are endorsed by the American College of Chest Physicians, the American Society of Hematology, the American College of Emergency Physicians, the American College of Cardiology, the American Heart Association, the Heart Rhythm Society, the European Stroke Organization, and the Anticoagulation Forum. Regardless of anticoagulation reversal strategy utilized, all patients presenting with major hemorrhage should undergo supportive care measures, such as temporary cessation of anticoagulation therapy, volume resuscitative measures, blood transfusions, blood pressure control, and source control, if applicable.

Overview of Agent-Specific Reversal Agents

Idarucizumab

Idarucizumab was approved by the FDA in 2015 for reversal of the oral direct thrombin inhibitor dabigatran. It is a humanized monoclonal antibody fragment that binds to dabigatran and its metabolites with 350-fold higher affinity compared with dabigatran binding affinity for thrombin, effectively neutralizing dabigatran’s anticoagulant effect. Dabigatran is dosed as 2 consecutive 2.5-gram intravenous (IV) bolus doses. This dosing strategy was found to neutralize 99% of dabigatran concentrations associated with therapeutic dosing in patients with normal renal function. Major adverse effects reported with the use of idarucizumab include headache, hypokalemia, delirium, constipation, pyrexia, pneumonia, thromboembolic
events, hypersensitivity reactions, and risk of serious adverse reactions due to sorbitol excipient in patients with hereditary fructose intolerance.25

The efficacy and safety of idarucizumab for dabigatran reversal were evaluated in the RE-VERSE AD trial. This was a prospective, international, multicenter, open-label trial of patients with uncontrolled bleeding (n = 301) and patients undergoing an urgent procedure (n = 202).13 Of patients with uncontrolled bleeding, 88% were deemed to have major or life-threatening bleeding. The primary efficacy end point was the maximum percent reversal of anticoagulant effects within 4 hours of administration. Rapid and complete reversal of diluted thrombin time, ecarin clotting time, activated partial thromboplastin time, and unbound dabigatran concentrations were observed following administration of idarucizumab. The 5-day, 30-day, and 90-day mortality rates were 6.3%, 13.5%, and 18.8%, respectively, in patients presenting with uncontrolled bleeding. In patients with ICH, 5-day and 90-day mortality rates were 9.2% and 16.7%, respectively.13,28 In patients with GIB, of which 84% were classified as major or life-threatening bleeding, 30-day and 90-day mortality bleeding were 10.9% and 14.6%, respectively.29 Thrombotic events within 30 days occurred in 4.7% of patients with uncontrolled bleeding.13

When compared with pooled estimates, patients enrolled in the RE-VERSE AD trial with uncontrolled bleeding had higher mortality rates than those with major bleeding enrolled in the early dabigatran clinical trials (30-day mortality rate, 13.5% vs 9.1%).13,16 However, patients receiving idarucizumab for dabigatran-associated ICH were reported to have lower 90-day mortality rates compared with 30-day mortality rates of patients with dabigatran-associated ICH in clinical trials when a reversal agent was not yet identified (16.7% vs 36%).

Post-Clinical Trial Real-World Experience With Idarucizumab

The RE-VECTO surveillance program was developed to monitor idarucizumab utilization across 3 continents between 2016 and 2018.30 Idarucizumab was most commonly used for the management of dabigatran-associated GIB (44.4%; 92/207) and ICH (38.6%; 80/207). In clinical practice, the mortality rates of patients with major bleeding while on dabigatran have been reported to range from 0% to 36% in patients treated with idarucizumab.29,31-44 GIB and ICH remain the most represented patient cohorts across studies. Pooled mortality rate across 16 observational studies of idarucizumab use in clinical practice was 14% (66/472), similar to rates reported in the REVERSE-AD trial. Reported hemostatic effectiveness rates ranged from 60% to 100%. Across 12 studies, 10 of 413 (2.4%) patients were reported to have thromboembolic complications. The largest retrospective observational cohort study to date compared patients hospitalized with dabigatran-associated major bleeding who received idarucizumab (n = 266) with those who did not (n = 1345).41 Patients with GIB were not observed to have significantly reduced odds of in-hospital mortality (5.9% vs 3.3%) with idarucizumab therapy. Patients with dabigatran-associated ICH treated with idarucizumab were found to have a higher in-hospital mortality rate (11.6%) compared with those who did not (2.8%). Notably, patients with ICH who received idarucizumab were more likely to present with evidence of brain compression (12.5% vs 4.1%) and brain edema (21.4% vs 12.9%) than those who did not, suggesting the possibility of selection bias towards the decision to administer idarucizumab in patients presenting with more severe ICH and higher risk of in-hospital mortality. Available real-world data giving insight into the safety and effectiveness of idarucizumab are limited by significant heterogeneity, missing data on markers of severity at presentation in patients with GIB or ICH, and concurrent utilization of supplemental coagulation factors.

Although most patients had sustained dabigatran plasma concentrations below 20 ng/mL through the 24-hour evaluation period in the RE-VERSE AD trial, a subset of 23% of patients were found to have rebound of dabigatran levels above 20 ng/mL at least 12 hours after idarucizumab administration, which was associated with recurrent or continuous bleeding.13 In the RE-VECTO surveillance program, 2.4% of patients with life-threatening or uncontrolled bleeding required idarucizumab redosing based on clinical signs in combination with coagulation tests suggesting incomplete reversal.30 Patients with renal dysfunction appear to be particularly at risk for rebound phenomena.30 The decision to redose idarucizumab should be patient-specific and limited to those with concern for ongoing hemorrhage or need for emergent procedures with rebound coagulation abnormalities.

In one study, of the 21% of patients reversed for bleeding complications and found to have inappropriate use of idarucizumab, 72.7% of patients were identified to not have uncontrollable bleeding, 18.2% of patients with normal coagulation parameters had a last known intake that exceeded dabigatran clearance, and 1 patient was found to be on rivaroxaban at baseline.29 Limited real-world evidence of outcomes surrounding idarucizumab usage in patients with dabigatran-associated major and life-threatening hemorrhages may be due to the overall declining usage of dabigatran in favor of apixaban and rivaroxaban.36 Available evidence to date affirms outcomes
reported in the REVERSE-AD study, although optimization of appropriate use is prudent.

Idarucizumab Comparison With Off-Label Factor Replacement Therapy for Dabigatran Reversal

Prior to the approval of DOAC-specific reversal agents, off-label use of factor replacement therapy was considered a potential nonspecific treatment strategy for patients with dabigatran-associated hemorrhages. These agents act by supplementing levels of vitamin K-dependent coagulation factors, such as prothrombin, to increase thrombin generation. 47,48 In the case of dabigatran reversal, PCC or activated prothrombin complex concentrate (aPCC) replacement is thought to increase thrombin concentration to exceed that of unbound dabigatran levels to minimize the anticoagulant effect of dabigatran. 49

In vitro evaluations have found aPCC (25-75 IU/kg), PCC (70 IU/kg), and recombinant factor VIIa (rFVIIa) (120 mcg/kg) partially reversed the anticoagulant effects of dabigatran, whereas idarucizumab completely reversed dabigatran-induced anticoagulant effects on thrombin generation and thrombelastometric assays. 50,51 The procoagulant effects of factor concentrates have not been observed with idarucizumab, theoretically offering a reduced thromboembolic complication rate.

There is evidence from small case series that aPCCs may be effective in dabigatran-associated major bleeding. 52,53 Limited case reports suggest 4-factor PCCs (4F-PCCs) may offer therapeutic benefit in patients with GIB. 54 Anecdotal evidence suggests that aPCCs may be preferred over non-aPCC formulations, though further study is required to determine the optimal reversal agent in the absence of idarucizumab. 9,55

Most studies supporting factor replacement for dabigatran anticoagulation reversal have been conducted in vitro or in vivo using animal and healthy human volunteers, which may not be representative of response rates in patients presenting with major hemorrhage. Additionally, data are limited on the outcomes of patients with dabigatran-associated major hemorrhages who receive factor replacement therapies. The strongest evidence to suggest therapeutic or mortality benefits in patients with dabigatran-associated hemorrhage is largely limited to those treated with idarucizumab.

Andexanet alfa

Andexanet alfa, otherwise known as coagulation factor Xa (recombinant), inactivated-zhzo, is a recombinant modified human factor Xa (FXa) decoy protein approved by the FDA in 2018 for apixaban and rivaroxaban reversal. 56 Andexanet alfa exerts its therapeutic effect by binding to and sequestering FXa inhibitors with high affinity. 56,57 Andexanet alfa has been found to inhibit the activity of tissue factor pathway inhibitor and, as a result, increases tissue factor-initiated thrombin generation. Andexanet alfa is dosed as either a high-dose or low-dose regimen, depending on the baseline anticoagulant therapy, last administered dose, and time from last administration. Immediately after administration of the andexanet alfa initial bolus, a rapid reduction in apixaban and rivaroxaban anti-FXa activity occurs. 58 Major adverse effects reported include thromboembolic events, infusion reactions, urinary tract infections, and pneumonia.

The efficacy and safety of andexanet alfa for oral FXa inhibitor reversal were evaluated in the ANNEXA-A, ANNEXA-R, and ANNEXA-4 clinical trials. 57,58 The ANNEXA-A and ANNEXA-R trials enrolled 145 healthy volunteers randomized to receive an andexanet alfa IV bolus, andexanet alfa IV bolus followed by 120-minute infusion, or placebo while on apixaban (ANNEXA-A) or rivaroxaban (ANNEXA-R). 37 The apixaban group was administered low-dose andexanet alfa 3 hours after the last apixaban administration as a 400-mg IV bolus, 400-mg IV bolus followed by 4-mg/min infusion for 120 minutes, or placebo. The rivaroxaban group was administered high-dose andexanet alfa 4 hours after the last rivaroxaban administration as an 800-mg IV bolus, 800-mg IV bolus followed by 8-mg/min infusion for 120 minutes, or placebo. The primary end point evaluated was the percent change in anti-FXa activity at the completion of bolus and at the end of the continuous infusion. Compared with placebo, mean reduction of anti-FXa activity at completion of the bolus was significantly higher in patients who received andexanet alfa bolus while on apixaban (94 ± 2% vs 21 ± 9%; P < .001) and rivaroxaban (92 ± 11% vs 18 ± 15%; P < .001). Mean reduction of anti-FXa activity at completion of the continuous infusion was also significantly higher in patients who received andexanet alfa IV bolus followed by infusion while on apixaban (92 ± 3% vs 33 ± 6%; P < .001) and rivaroxaban (97 ± 2% vs 45 ± 12%; P < .001). All patients had at least 80% reversal of anti-FXa activity after administration of andexanet alfa. A significant decrease in the pharmacologically active unbound apixaban and rivaroxaban levels was observed within 2 to 5 minutes after administration with andexanet alfa. Notably, unbound apixaban and rivaroxaban levels returned to therapeutic levels similar to those observed in the placebo group within 1 to 3 hours after completion of bolus monotherapy or the continuous infusion. No thromboembolic events were reported.

The ANNEXA-4 trial enrolled 352 patients with major bleeding within 18 hours of last known administration of an oral FXa inhibitor (rivaroxaban, n = 128; apixaban, n = 194; edoxaban, n = 10). 56 Andexanet alfa was administered as a bolus
followed by continuous infusion for 120 minutes in alignment with current FDA-approved dosing recommendations. Major hemorrhage subtypes included intracranial (64%: 227/352) followed by gastrointestinal (26%; 90/352). Safety analysis was performed in the entire enrolled population while the efficacy analysis was restricted to 254 patients with baseline anti-FXa activity 75 ng/mL and higher. For the primary outcome measure, a 92% reduction in anti-FXa activity was observed in patients receiving apixaban and rivaroxaban therapy at baseline. Similar to ANNEXA-A and ANNEXA-R, rebound anticoagulation was observed to occur after cessation of the continuous infusion. In the efficacy analysis, 85% of patients with gastrointestinal hemorrhages and 80% of patients with ICH were determined to have good or excellent hemostatic effectiveness. A reduction in anti-FXa activity was not found to be associated with hemostatic effectiveness. The 30-day mortality was reported in 14% (49/352) patients, and thromboembolic events occurred in 10% (34/352) within 30 days. A subgroup analysis of 90 patients with GIB reported a hemostatic effectiveness of 85%, 30-day thromboembolic rates of 6%, and 30-day mortality rate of 13%.59

The ANNEXA-4 trial excluded patients with severe ICH (Glasgow Coma Scale [GCS] score <7; hematoma volume >60 mL), expected survival less than 1 month, thromboembolic events within previous 2 weeks, or planned surgery within 12 hours.58 As a result, the mortality rates of patients in the ANNEXA-4 trial may have been biased towards lower complications compared with clinical practice. The magnitude of the effectiveness of this exclusion on the mortality rates observed in the ANNEXA-4 trial is unknown.

Post-Clinical Trial Real-World Experience With Andexanet alfa
Since approval of andexanet alfa for apixaban- and rivaroxaban-associated major hemorrhages in 2018, significant interest has been brought forth by the clinical and scientific community to determine whether the low mortality rates and high hemostatic effectiveness rates would persist in clinical practice in the absence of strict exclusion criteria.60-70 In patients who received andexanet alfa across 9 observational cohort studies, pooled mortality rates are approximately 11.5% (92/799), similar to the 14% mortality rate reported in the ANNEXA-4 trial.58,60-68,70 Anti-FXa–associated ICH mortality rates are notably higher than patients without anti-FXa–associated ICH, with pooled mortality rates of 17.9% (29/162) when reported independently.60,62,64,67,70 Recent preliminary reports suggest treatment with andexanet alfa may be associated with lower total and ICH-related mortality in patients with anti-FXa–associated hemorrhages.63,64 However, further information is required on baseline characteristics and disease severity as well as concurrent treatments prior to making an accurate assessment of the strength of these data. Overall, hemostatic effectiveness was achieved in 50% to 90.9% of patients across 7 observational cohort studies evaluating this end point.50,62,65-68,70 Those with poor hemostasis, when reported, often had higher mortality rates compared with those considered to have good hemostasis. A significant mortality rate was present even in those with good hemostasis, suggesting the risk of mortality through withdrawal of care or hospital complications may not be reduced even with administration of anti-FXa–specific reversal agents in select patient populations. Pooled thromboembolic events occurred in 11.7% (20/171) of patients across 8 observational cohort studies, similar to the 10% thromboembolic rate observed in the ANNEXA-4 trial.58,60,62,65-70

Patients represented in observational real-world experience often include those who would have been excluded from ANNEXA-4 for receiving additional blood products, are hemodynamically stable, have baseline intracranial hematoma volume above 60 mL, or with last known administration more than 18 hours or unknown; therefore, these observational studies provide insight into the efficacy and safety of andexanet alfa outside rigorous clinical trials. The median time from hospital presentation to andexanet alfa administration was reported to range from 1.5 to 3.6 hours, underscoring the potential window of opportunity for urgent control of hemorrhage prior to expansion to optimize patient outcomes.50,66,70 In patients with ICH, the risk for hematoma expansion is greater than 30% within the first 3 hours of symptom onset and a significant predictor of poor outcomes.60,71-73 Although patients with anti-FXa–associated ICH are at highest risk of morbidity and mortality compared with those without ICH, urgent evaluation is needed for subpopulations in which specific reversal agents offer undeniable benefit over supportive care alone or factor replacement therapy to provide cost-effective therapy.

Andexanet alfa Comparison With Off-Label Factor Replacement Therapy for Oral FXa Reversal
Based on observational data with VKAs, the ability to perform a randomized controlled trial of agent-specific reversal agents compared with placebo has been considered unethical.21 Prior to approval of andexanet alfa, available guidelines provided weak recommendations for the use of PCCs for reversal of oral FXa inhibitor-associated major bleeding.55,73,74 These recommendations were largely derived based on low-quality evidence in animal and healthy human volunteers showing normalization of laboratory parameters. To date, no randomized controlled trials have been conducted to compare andexanet alfa with PCCs.
In vivo data have suggested that complete and partial reversal of coagulation parameters in healthy patients on rivaroxaban is possible after administration of 4F-PCC 50 IU/kg and 25 to 37.5 IU/kg, respectively. After a single dose of edoxaban 60 mg, partial to full reversal were observed after 3-factor PCC (3F-PCC) or 4F-PCC 10 to 50 IU/kg in a dose-dependent manner. Subsequent studies have shown mixed results. In the setting of high costs associated with DOAC-specific reversal agents, a number of observational and prospective studies have been published highlighting outcomes of patients with anti-FXa–associated major bleeding receiving factor replacement therapy with aPCC or 4F-PCC.

Similar to criticisms surrounding the use of andexanet alfa, studies evaluating PCC effectiveness and safety in patients with major hemorrhage have been completed without a comparator arm or in a randomized fashion, risking significant bias and challenge comparing the benefits of one therapy with another. Lack of standardization in treatment protocols for PCCs and patient selection for reversal further complicates the comparison of outcomes associated with PCCs and andexanet alfa treatment in patients with major hemorrhage. The 14% mortality rate in patients with major hemorrhage treated with andexanet alfa in ANNEXA-4 is similar to the 30-day mortality rate of 13.5% in an observational cohort study of 732 patients with DOAC-associated hemorrhages requiring hospitalization, of which 38% of patients were treated with PCCs. In this cohort, 74% of patients were adjudicated to have major bleeding. Mortality among those with spontaneous ICH was 28%, traumatic ICH 17%, and gastrointestinal hemorrhage 12%. In patients with DOAC-associated ICH where PCC therapy was provided in 82.2% of patients, a significant increase in 30-day mortality was observed in those who did not receive reversal versus those who did (48.8% vs 30.1%, respectively). The mortality rates reported in this registry study remain concerningly high and are similar to those reported in early clinical trials during the absence of any reversal therapy. A recent meta-analysis found a crude mortality rate of 16% in patients who received PCC for anti-FXa reversal, far lower than reported by other study groups. Whether andexanet alfa offers increased benefit for ICH-related mortality is unknown, as a subgroup analysis on the population of patients with ICH has not yet been published. The approximately 80% hemostatic efficacy rate observed in patients with ICH enrolled in the ANNEXA-4 trial is similar to the rates of hemostatic effectiveness observed (69% to 77%) in patients with anti-FXa–associated bleeding managed with PCCs. Notably, lower rates of thromboembolic events (estimated at 4%) have been observed with PCC in this setting compared with andexanet alfa (10%).

The optimal PCC dose required to effectively overwhelm the anticoagulant effect of FXa inhibitors is currently unknown. In patients with major bleeding or those requiring urgent surgery, a low-dose PCC strategy of 35 IU/kg or less offered similar rates of hemostatic success (using ANNEXA-4 criteria) compared with high-dose PCC of 35 to 50 IU/kg (75.4% vs 78.6%; P=.715) as well as similar rates of in-hospital mortality (19.3% vs 35.7%; P=.067) and thromboembolic events (5.3% vs 2.4%; P=.635), respectively. In patients with ICH, hemostatic success was achieved in 77.4% and 74.1% of patients in each cohort. Patients with in-hospital mortality and those who received high-dose therapy were more likely to have lower baseline GCS, a known predictor for in-hospital mortality. Low-dose PCC strategies have established similar success in other small observational cohort settings.

Due to the heterogeneity of studies evaluating PCCs and andexanet alfa, no definitive conclusions can be drawn comparing outcomes such as hemostatic effectiveness or mortality between these 2 agents. In real-world settings, utilization of 4F-PCC for DOAC reversal has been observed to be reserved for use in patients with worse baseline clinical status and larger hematoma volumes due to the paucity of data to support its use. It is difficult to directly compare outcomes data between 4F-PCC and andexanet alfa for DOAC reversal, as patient populations and severity have varied across studies. A head-to-head trial is underway comparing andexanet alfa with usual care; the estimated completion date is 2023 (Clinical-Trials.gov Identifier: NCT03661528).

**Emerging Therapy**

**Ciraparantag**

Ciraparantag is a universal anticoagulation reversal agent currently under development for reversal of DOAC (dabigatran, apixaban, rivaroxaban) and heparinoid (enoxaparin, heparin) therapy. It is a small, synthetic, water-soluble molecule that exerts its anticoagulant reversal effect through binding of heparin, FXa inhibitors, and dabigatran by charge interaction. Preliminary results of 2 randomized, placebo-controlled, dose-ranging studies found ciraparantag restored whole blood clotting time in 83% and 100% of patients on baseline apixaban after 60-mg and 120-mg IV doses, respectively, compared with 0% after placebo. In patients on baseline rivaroxaban, normalization of whole blood clotting time occurred in 92%, 92%, 100%, and 0% of patients after administration of ciraparantag 60 mg, 120 mg, 180 mg, and placebo, respectively. Similar results were reported with edoxaban, with complete reversal observed after administra-
tion of ciraparantag 100 mg to 300 mg. The reversal effects of ciraparantag occurred within 10 minutes of administration and lasted for the duration of the 24-hour monitoring period.

The Role of the Pharmacist in Improving Clinical Outcomes

Institutions encounter several challenges when considering addition of specific reversal agents to hospital formulary, including (1) high cost of therapy; (2) unclear benefit of andexanet alfa in safety, efficacy, and mortality in comparison with existing therapies; (3) compounding complexity; (4) appropriate timing of procedures after administration; (5) whether circumstances may allow redosing; (6) utilization in patients already treated with PCCs; and (7) off-label requests for use or use in patients with no expectation of survival and non–life-threatening hemorrhages. 65,96,97

Economic Considerations

DOAC reversal agents are associated with significant costs, regardless of the strategy utilized. The American Society of Hematology suggests that the cost and risk of thromboembolic complications of reversal therapy likely outweigh any potential benefit in the setting of non–life-threatening bleeding; therefore, consideration for reversal should be reserved for patients presenting with life-threatening or uncontrollable bleeding. 21 In a survey conducted by the Anticoagulation Forum, 66% of hospitals reported cost as the primary reason for which andexanet alfa was not added to formulary. 9 The projected cost of andexanet alone is expected to exceed hospital reimbursement in up to 75% of patients by over $7500/hospitalization. 98 The Centers for Medicare & Medicaid Services approved an add-on payment for patients receiving andexanet alfa therapy, effective October 1, 2018. 99 This add-on payment provides up to $18,281.25 additional reimbursement per qualifying cases to acute care hospitals participating in the Inpatient Prospective Payment System for fiscal year 2021 and is incremental to the Medicare Severity Diagnostic Related Group reimbursement. 100

Health systems considering adding idarucizumab and andexanet alfa to formulary should estimate the budget impact based on predicted case load. The majority of patients in the ANNEXA-4 and observational cohort studies require low-dose rather than high-dose andexanet alfa therapy, with roughly 84% of patients receiving low-dose therapy when reported. 58,60,62,65-68,70 At one health system, the estimated cost to replace 4F-PCC with andexanet alfa in 48 oral FXa inhibitor-related bleeds over a 1-year span was estimated to increase by 5-fold, from $276,161 to $1,365,900. 101 Although uncommon, centers have reported use of idarucizumab in patients not on dabigatran or andexanet alfa in patients with unknown or last documented dose more than 18 hours prior to anti-FXa reversal administration. 29,30,58,60,62,65,66,70 In an observational cohort study, 62% of patients with DOAC-associated bleeding had plasma concentrations assessed at presentation, and 9.2% of these patients were found to have plasma concentrations below 50 ng/mL, a threshold cutoff suggested for treatment by the International Society on Thrombosis and Haemostasis. 15,80 This raises the question of whether the availability of rapid turnaround times of laboratory analyses of DOAC concentrations presents an opportunity for significant cost-savings.

Due to the high cost of specific reversal agents, regional hospitals and rural health care facilities may be required to assess the cost-benefit of drug acquisition compared with rapid transfer of patients to institutions with the ability to treat with specific reversal agents. The minimum necessary doses required to keep on hand to meet patient needs should be considered to alleviate cost on health care systems.

Underutilization of Specific Reversal Agents

Appropriate patient selection is instrumental for health systems aiming to ensure optimal patient outcomes while balancing the costs for specific reversal agent therapy. Access to anticoagulation reversal should be available around-the-clock, with a focus on the ED setting where patients are mostly likely to require treatment on an urgent basis. Despite the availability of agent-specific or nonspecific reversal agents, utilization of these strategies for management of major hemorrhage remains low. It has been reported that nearly 50% of patients with DOAC-associated major hemorrhage received either no treatment or only symptomatic support with fluid replacement and blood transfusions, with more than 30% of patients not treated in accordance with guideline recommendations. 102 While the Anticoagulation Forum recommends health systems develop and implement strategies to promote multidisciplinary and shared stewardship of reversal agent utilization in order to optimize care, 9 no formal guidelines were in place at many institutions for the reversal of anti–FXa-associated life-threatening hemorrhages, according to 20.3% critical care and emergency medicine pharmacist survey respondents. 103 In this survey, the primary anticoagulation reversal agent was 4F-PCC for anti-FXa reversal (73.3%), followed by andexanet alfa (12.8%), aPCC (9.6%), 3F-PCC (1.4%), and other nonspecified agents (2.8%). Teaching hospitals reported a significantly higher proportion of andexanet alfa usage (17.2%) compared with nonteaching hospitals (5%). Idarucizumab was the agent-of-choice for dabigatran-associated life-threatening hemorrhage in 96.4% of respondents. Further-
more, EDs with dedicated ED pharmacists had a higher proportion of andexanet alfa usage (27.1%) compared with those that did not have ED pharmacists (9%).

Health systems should carefully evaluate available reversal agents on formulary, and institutional guidelines should be developed through multidisciplinary collaborative groups of physicians, pharmacists, and nurses from various specialties, such as neurology, cardiology, emergency medicine, and hematology, to guide clinical decision making. Ongoing continuing education should be provided to all health care practitioners regarding safe and efficacious use of DOACs and their reversal agents, as limited knowledge of available therapeutic options for reversal agents has been cited as a reason for delayed access and administration in the ED. Implementation of standardized electronic order sets with clinical decision support tools can aid clinicians in appropriate therapy selection during time-critical, high-stress events.

Storage and Handling
Pharmacy departments should identify the best storage locations to meet the needs of their patients, taking into consideration inventory control procedures and ease-of-access for emergency situations. Idarucizumab was reported to be stored within the primary centralized pharmacy at 67.2% and in the ED at 29.5% of centers, with a median dose on hand of 2.0 (IQR, 1.0-3.0). The ED was the most common setting for idarucizumab administration. Opening of idarucizumab boxes at the patient bedside may reduce waste and provide cost-savings if dabigatran reversal is no longer required, as opened packages are only stable at room temperature for up to 6 hours once contents are exposed to light. Due to compounding complexity and high cost, andexanet alfa is likely best stored within the primary centralized pharmacy. As of January 2019, a 200-mg package size was commercially available and is likely to ease some of the compounding challenges associated with slow reconstitution and dissolution of numerous 100-mg vials. Time from order entry to andexanet alfa administration has ranged from a median of 46 minutes to 1.1 hour in observational studies. Significant delays in procurement in the treatment of high-risk conditions, such as ICH, must be considered, and systems must be in place to ensure expedited review for indication, pharmacist verification, and efficient delivery and administration during high-risk treatment windows. Reconstituted vials are stable at room temperature for up to 8 hours, and IV bags are stable at refrigerated temperature for up to 24 hours.

Joint Commission Considerations
In 2019, the Joint Commission revised its National Patient Safety Goals to improve safe prescribing of anticoagulant therapy. Clinicians can employ this resource to help ensure the safe and efficacious management of DOAC reversal. Critical access hospitals are encouraged to use approved protocols and evidence-based practice guidelines for reversal of anticoagulation. Details should be provided on which reversal agents and doses should be used for specific anticoagulation-associated hemorrhages, outlining conservative measures for management. Additionally, the Joint Commission also sets mandatory standards for hospitals designated as Comprehensive Stroke Centers to meet performance requirements, and documentation of procoagulant reversal agent administration in patients presenting with an ICH is one of the core measures. Explicit documentation must be provided in the medical record by the health care provider for reasons as to why a procoagulant reversal agent was not administered. Factor replacement therapy and idarucizumab are currently listed as therapeutic options, though inclusion of andexanet alfa is expected to occur with future reiterations. Institutions should review and update guidance documents cyclically as new information emerges.

The Pharmacist’s Role in Optimizing Outcomes
Pharmacists can play integral roles in the developing guidelines and order-sets, monitoring for efficacy and adverse effects, educating providers, medication order entry, consulting on anticoagulation restart, as well as conducting medication-use evaluation activities. The electronic health record and pharmacy order, processing, compounding, and delivery strategies should be evaluated for maximal efficiency to provide timely reversal, reduce waste, and decrease inappropriate utilization. Patients initiated on DOAC therapy should be counseled to obtain a medical alert bracelet or necklace or carry a wallet card indicating the anticoagulant they are taking, the dose, and usual time of day taken to facilitate timely and accurate access to DOAC reversal agents if the unfortunate circumstance arises.

Site-specific protocols to ensure appropriate use and access within a timely manner without the need to convene a team of expert consensus during a time-critical situation is imperative. Protocols should be developed by incorporating input from key stakeholders including clinical pharmacists, cardiologists, neurologists, hematologists, emergency medicine, and allied health care providers. Hemorrhagic complications are heterogeneous in real-world settings; therefore, management will need to be individualized based on location and severity of hemorrhage. Every effort should be made to identify the baseline anticoagulation upon presentation as well as the last known ingestion time to avoid increased risk of patient harm and unnecessary drug expenditures. Institutions have grappled with the best approach towards ensuring safe and effective use of andexanet alfa in
patients with major or life-threatening hemorrhages undergoing procedures due to the short duration of action.60,68,97

Due to the complexity of manufacturing associated with DOAC-specific reversal agents, significant manufacturing delays were present upon initial FDA approval that resulted in limited access to andexanet alfalfa therapy. This has since resolved; however, institutions should prepare for alternative therapy recommendations if therapy becomes unavailable due to anticipated or unanticipated manufacturing delays.7 In the presence of drug shortages or limited availability, consideration should be given to patients who are most likely to benefit from therapy and directed by institutional anticoagulation reversal guidelines.96 As idarucizumab and andexanet alfa are currently the only FDA-approved reversal agents for DOAC-associated major hemmorhages, and current guidance preferentially recommends treatment with these agents over alternative therapies, these agents have been integrated as the standard of care for patients requiring reversal for oral FXa-associated major hemorrhages.96

Conclusion
While DOACs have an improved safety and ease-of-use profile compared with traditional VKA therapy, the risk of major and life-threatening hemorrhagic complications remains. Available agent-specific reversal agents for patients with life-threatening or uncontrolled major hemorrhages include idarucizumab for dabigatran reversal and andexanet alfa for apixaban and rivaroxaban reversal. Currently available guidelines recommend utilization of a specific reversal agent over nonspecific reversal agents when available. Pharmacy departments can participate in multidisciplinary coordination efforts to guide anticoagulation reversal selection and supportive care to optimize patient outcomes.

REFERENCES


64. Coleman CI, Dobesh PP, Danese S, Ulloa J, Lovelace B. Real-world management of oral factor Xa inhibitor-related bleeds with reversal or replacement agents including andexanet alfa and four-factor prothrombin complex concentrate: a multicenter study. Future Cardiol. Published online July 3, 2020. doi:10.2217/fca-2020-0073


73. Panos NG, Cook AM, John S, Jones GM; Neurocritical Care Society (NCS) Pharmacy Study Group. Factor Xa inhibitor-related intracranial hemorrhage: results from a multicenter, observational cohort receiving prothrombin complex concentrates. Circulation. 2020;141(21):1681-1689. doi:10.1161/CIRCULATIONAHA.120.045769


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POSTTEST QUESTIONS

Please use the following case to answer questions 1-3.
LP, a 72-year-old man, presents to the emergency department (ED) at 13:08 after being found unresponsive at the foot of his bed. According to his health care proxy, his past medical history is notable for atrial fibrillation, coronary artery disease (not on aspirin), and diabetes. He takes apixaban 5 mg twice daily, with last known administration with his breakfast that morning. A stat head CT shows the patient has left temporal intracerebral hemorrhage with midline shift. His blood pressure is 110/75 mm Hg, heart rate 72 beats per minute, respiratory rate 13 breaths per minute. His stat coagulation labs result with a hemoglobin of 9.5 g/dL, hematocrit of 30%, INR 1.4, and partial thromboplastin time (PTT) 37.6 seconds.

1. The emergency medicine physician consults you, the pharmacist, to inquire whether this patient is eligible for anticoagulation reversal. Which statement best describes LP's indication for anticoagulation reversal?
   A. He is hemodynamically unstable with active hemorrhage, and he should be reversed.
   B. He has a critical organ site hemorrhage, and he should be reversed.
   C. He is hemodynamically stable, and reversal can be deferred while supportive care is provided.
   D. His coagulation parameters are within acceptable range, and reversal can be deferred while supportive care is provided.

2. The emergency department team determines that LP is eligible for anticoagulation reversal. Which specific reversal agent is available and approved by the Food and Drug Administration for his management?
   A. Activated prothrombin complex concentrate (aPCC)
   B. 4-factor prothrombin complex concentrate (4F-PCC)
   C. Idarucizumab
   D. Andexanet alfa

3. As the clinical pharmacist on service, you place the medication order on behalf of the responding clinician per the pharmacist-driven anticoagulation reversal protocol. What order do you place?
   A. Andexanet alfa 400 mg intravenous (IV) bolus followed by 4 mg/min for up to 120 minutes
   B. Andexanet alfa 800 mg IV bolus followed by 8 mg/min for up to 120 minutes
   C. Andexanet alfa 2.5 grams IV x 2 consecutive doses
   D. Andexanet alfa 2.5 grams IV

Please use the following case to answer questions 4-6.
KC is an 82-year-old woman who presented to the ED following significant black tarry stools for the past 2 days. Her past medical history is notable for pulmonary embolism (on dabigatran 150 mg twice daily), coronary artery disease, and hypertension. Stat coagulation labs are sent and result in a hemoglobin of 5.5 g/dL, hematocrit 20%, INR 2.1, and activated PTT 45 seconds. Despite treatment according to institution protocol, including administration of fluids and norepinephrine, she remains hypotensive and continues to decline.

4. The emergency medicine physician consults you, the pharmacist, to inquire how to best manage this patient’s major gastrointestinal bleed. Which of the following best describes KC’s indication for anticoagulation reversal?
   A. She is hemodynamically unstable with active hemorrhage, and she should be reversed.
   B. She has a critical organ site hemorrhage, and she should be reversed.
   C. She is hemodynamically stable, and reversal should be deferred while supportive care is provided.
   D. Her coagulation parameters are within acceptable range, and reversal should be deferred while supportive care is provided.

5. The medical team determines that KC is eligible for anticoagulation reversal. Which anticoagulation reversal therapy has the strongest evidence to support beneficial therapeutic effects for reversal of anticoagulation in patients on baseline dabigatran?
   A. aPCC
   B. 4F-PCC
   C. Idarucizumab
   D. Andexanet alfa

6. What operational strategy can be employed by pharmacy departments to reduce inadvertent waste of idarucizumab?
   A. Compounding the idarucizumab 5-gram total dose in an empty PVC bag in the centralized Sterile Products Room prior to delivery
   B. Opening the idarucizumab boxes at the bedside immediately prior to administration
   C. Maintaining supply at the off-site specialty pharmacy center for distribution to all instructions within a health care system
   D. Batching precompounded 5-gram total dose IV bags for storage in the ED automated dispensing cabinet
7. Which of the following contributions can pharmacy administrators and clinical pharmacists make in the management of DOAC reversal at their institution to optimize patient outcomes and decrease mortality?
   A. Establish anticoagulation reversal protocols in collaboration with multidisciplinary teams
   B. Create electronic health record medication order-sets to provide clinical decision support on DOAC reversal
   C. Conduct medication-use evaluations to ensure appropriate use and adherence to institutional guidelines
   D. All of the above

8. Which strategy can pharmacy departments employ to reduce costs associated with anticoagulation reversal in the setting of DOAC-associated hemorrhage?
   A. Purchase idarucizumab and andexanet alfa in bulk for reduced pricing
   B. Restrict use to patients with confirmed life-threatening or uncontrolled hemorrhages
   C. Give anticoagulation reversal empirically while awaiting confirmation of home DOAC use to avoid delays in care
   D. Do not add anticoagulation reversal therapy to formulary

9. Which reason has been cited for delayed time to anticoagulation reversal in patients presenting with major bleeding?
   A. Lack of provider knowledge of available reversal agents at their institution
   B. Storage of idarucizumab in the ED automated dispensing cabinet for immediate use when needed
   C. Use of andexanet alfa 200-mg vials in place of 100-mg vials
   D. Use of clinical decision support tools for DOAC reversal management

10. What is the recommended anticoagulation reversal strategy for the management of life-threatening hemorrhage associated with apixaban and rivaroxaban anticoagulation when specific reversal agents are not available?
    A. Idarucizumab
    B. Recombinant factor VIIa
    C. 4F-PCC
    D. Supportive care only
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