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BY MIKE WASCOVICH, PHARMD, MBA, RPH
Turning the Corner on COVID-19

Happy Spring. As we head into March, the United States looks like it has turned a corner on the COVID-19 front. Hospitalizations and deaths are down nationwide and mask mandates are being lifted across many states, towns, and school districts.

Since the beginning of the pandemic in early 2020, pharmacists, pharmacy technicians, and other pharmacy employees have been on the front lines of this fight. Although it appears that COVID-19 may be moving into the endemic stage, it likely is not going away entirely anytime soon, nor is the role of pharmacy professionals in combating the disease.

For instance, during the State of the Union address on March 1, 2022, President Joseph R. Biden announced that a major part of the new National COVID-19 Preparedness Plan is a so-called Test to Treat, under which Americans would be able to get tested for COVID-19 at pharmacies and receive free antiviral pills “on the spot” if they test positive.

Count on Pharmacy Times® Health-System Edition™ to continue providing the latest news and actionable information on COVID-19 and on many other topics of interest to pharmacy professionals.

One such topic is integrating pharmacists into care teams, which is the subject of this month’s cover feature. Authors Rana Said, Eojin Lee, and Deepali Dixit, PharmD, BCPS, BCCCP, FCCM, discuss how pharmacists tapping their specific skill sets and training can help serve patients more effectively, although there are challenges that must be overcome.

Elsewhere in the issue, we look at how ignoring concussions can pose dangers, BRAF inhibition in previously treated colorectal cancer, and managing drug interactions HIV and tuberculosis coinfection.

Meanwhile, our Future of Pharmacy resource center is now live on the PharmacyTimes.com website. Pharmacists and pharmacy professionals can find video interviews, such as one with David Zgarrick, PhD, FAPhA, professor in the department of pharmacy and health systems sciences at Northeastern University, addressing what the profession could look like. There are also articles such as “The Future of Automation, Digital Health.” We will continue to populate this resource center with valuable content over the coming months, so check it out (https://www.pharmacytimes.com/clinical/future-of-pharmacy).

Be sure also to look at the robust content housed within PharmacyTimes.com’s many other resource centers, encompassing information on topics ranging from attention-deficit/hyperactivity disorder to herpes zoster. We also have content organized by clinical role, such as hospital, oncology, specialty pharmacy, students, and pharmacy technicians.

Thanks for reading.
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Rationing Health Care Is Uncomfortable, Unexpected, Unfortunate
It Is Imperative for Pharmacy Leadership to Work With Colleagues to Ensure the
Most Equitable and Ethical Approach Is in Place

BY CURTIS E. HAAS, PHARMD, FCCP, PHARMACY TIMES® HEALTH-SYSTEM EDITION™ EDITOR IN CHIEF

At the time of writing these comments, we are experiencing the worst of the COVID-19 Omicron variant surge in my region, and there is a widespread shortage of newly available therapeutic agents.

I am hopeful that by the time this is published, we will be in a better place and well on our way to referring to this as an endemic problem, but with this pandemic nothing has been predictable. The predominance of the Omicron variant has led to the suspension of clinical use of 2 monoclonal antibody (mAb) therapies, bamlanivimab/etesevimab and casirivimab/imdevimab (REGEN-COV), because of concerns about effectiveness, so sotrovimab (Xevudy) is the only mAb product available as an emergency use authorization for treatment of COVID-19–positive patients with mild to moderate symptoms who are at high risk of progressing to severe disease.

The recent introduction of the oral agents molnupiravir and nirmatrelvir/ritonavir (Paxlovid) offers additional therapeutic options for the prevention of severe disease in high-risk patients with mild to moderate COVID-19. Intravenous (IV) remdesivir (Veklury) is the only FDA-approved antiviral treatment for COVID-19, and the recently released PINETREE study (NCT04501952) provides evidence that a 3-day outpatient regimen may prevent progression to severe disease requiring hospitalization. In light of these developments, a National Institutes of Health (NIH) advisory panel released updated guidelines for the treatment of high-risk symptomatic outpatients. The guidelines recommend the following order of preference for treatment: a 5-day course of oral ritonavir-boosted nirmatrelvir, a single IV infusion of sotrovimab, a 3-day course of IV remdesivir, and a 5-day course of oral molnupiravir.

The Centers for Medicare & Medicaid Services recently released outpatient billing codes for remdesivir. In addition, cilgavimab/tixagevimab (Evusheld) was recently authorized as preexposure prophylaxis (PrEP) for moderately to severely immunocompromised patients 12 years and older and for patients who are unable to be vaccinated. This combination of mAbs is administered by intramuscular injection every 6 months, and the limited evidence available suggests that it can reduce the risk of severe COVID-19.

So the good news is that we are acquiring an ever-expanding armamentarium of treatment options against SARS-CoV-2. The bad news, however, is that we have a very limited supply of these agents, resulting in difficult decisions about health care rationing. An additional factor that limits treatment availability is that many health systems are compromised by severe
staffing shortages and therefore have a limited capacity to provide IV treatments (remdesivir and sotrovimab) for outpatients. In addition, home care agencies are equally overwhelmed by high demand and staffing shortages, limiting the ability to shift administration to the home. The logistical challenges of providing a 3-day infusion regimen of remdesivir in this environment will greatly limit the growth of this treatment option.

The first layer of rationing is occurring at the federal level by the US Department of Health & Human Services (HHS). The ethical framework is a utilitarian model based on the crisis standards of care. Essentially, the product available for distribution is allocated to states, territories, and other legal jurisdictions based on multiple variables, including current case, hospitalization, and utilization rates, as well as population. How each jurisdiction then further allocates its federal allocation is defined by each jurisdiction and, therefore, is not uniform. Once the drug product reaches the community providers, health systems, pharmacies, etc, the decisions concerning patient selection are primarily based on guidance provided by HHS, local and state departments of health, and the NIH but are really individualized by each provider.

The infusion center locations at our medical center are receiving 50 or more referrals daily for sotrovimab treatment, and there are likely many more patients eligible who are not being referred because of guidance to limit to the highest-risk patients. Based on our drug allocations and available infusion appointments, we can provide 30 or fewer infusions per week. Based on input from our medical ethics professionals, a process of ranking referrals by risk (data are limited to weight risk) and then randomizing high-risk patients has been implemented as the most ethical solution. By combing our electronic medical records, we have been able to identify just under 5000 patients who meet the highest-risk tier to be considered for PrEP treatment with cibivimab/tixagevimab. However, our allocation is just dozens of doses every 1 to 2 weeks. Again, with input from medical ethics, an allocation to specialty clinics with randomization of eligible patients within those specialties has been implemented. These can be heartbreaking decisions to make, especially when having to notify inquiring patients that they did not “win the lottery” this week. Maybe they will next week, but the odds are not good.

The decisions at the governmental level for distribution of the oral agents during this time of very limited supply have resulted in essentially a free-for-all, with very little ability to prioritize. Allocations are being sent to retail pharmacies, typically 1 to 3 per county in our state, and anyone with a license to prescribe can issue a prescription. Given the disconnected and independent nature of these pharmacies, there is no ability to target the highest-risk patients or to provide these treatments equitably and fairly. Patients with the luxury of resources and time can and will travel long distances to find available supplies, whereas the disadvantaged and underserved are unlikely to have that option. It is unfortunate that a more nuanced approach to distribution of these agents to our health systems that care for the highest-risk patients and are more likely to be able to prioritize based on ethical principles was not considered until more plentiful supplies were available. This approach of unlimited prescriptions being generated and very constrained supply is resulting in large numbers of disappointed and frustrated patients and further disillusionment with the handling of this pandemic by governmental agencies and health care professionals. This could have been better handled.

Rationing of health care in the United States, the land of plenty, is not something that most of us have dealt with prior to this pandemic or maybe ever expected to have to manage. It is unfortunate and often very uncomfortable. It is imperative that health-system pharmacy leadership be involved with colleagues to ensure that the most equitable and ethical approach possible for rationing these medical treatments is in place at the local level.

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Postvaccine Exercise Increases Antibodies

GETTING 90 MINUTES of mild- to moderate-intensity physical activity shortly after receiving the COVID-19 or influenza vaccine may offer an additional immune boost, according to findings from a study by Iowa State University.

The study authors found that individuals who exercised on a stationary bike or went for a 90-minute walk after immunization generated more antibodies in the subsequent 4 weeks compared with those who continued their daily routines or did not exercise after vaccination. The investigators noted similar results when they conducted an experiment with mice and treadmills.

Antibodies serve as the body’s “search and destroy” line of defense against viruses, bacteria, fungi, and parasites, and immunizations enable the immune system to identify specific antigens and respond to them by strengthening the body’s defenses.

—Jill Murphy

Link Is Likely Between Age-Related Cognitive Disorders and Mitochondrial Dysfunction

THE PROGRESSION OF Alzheimer disease (AD) is closely associated with oxidative brain damage, results of a study published in Biomedicines show.

Previously, the investigators had found that oxidation levels were substantially higher in older rats with vitamin E deficiency than in younger rats. Additionally, the reactive oxygen species (ROS) production via mitochondrial oxidation could damage brain cells, implying a strong link between AD and mitochondrial dysfunction.

The mitochondrial electron transport chain, which is required for generating energy during cellular processes, also produces ROS that attack tissues and cause oxidative damage. The damage can lead to mitochondrial dysfunction and even cell death.

Because the brain uses more oxygen than other organs, it is the most vulnerable to ROS damage.

According to other literature, ROS also causes the buildup of amyloid-β, which marks the onset of AD.

The investigators used 3 groups of mice with AD, aged 3, 6, and 20 months, along with healthy controls. To test their cognitive and coordination abilities, the mice were examined in 2 experiments: the Morris water maze and the rotarod test.

Investigators noticed that the mice with AD took longer to complete their maze goals but did not slow down. In the rotarod test, the 6- and 20-month-old mice with AD stayed on the rod for a longer time, whereas the age-matched control mice fell off more quickly.

Therefore, these results suggest that the mice with AD were cognitively impaired but did not have any coordination issues.—Ashley Gallagher

Data Show Elevated Risk of Blood Clots After COVID-19 Vaccine

THE RISK OF intracranial thrombosis increases slightly following vaccination with the ChAdOx1-S (AstraZeneca) COVID-19 vaccine, according to results of 2 studies published in PLOS Medicine.

In the first study, investigators from the University of Edinburgh and British Heart Foundation Data Science Centre, United Kingdom, analyzed the electronic health records (EHRs) of 46 million individuals in England. In a second study from the University of Edinburgh, investigators focused on a data set of approximately 11 million individuals in England, Scotland, and Wales.

Cases of thrombosis, which occurs when blood clots block an artery or vein, have been reported after individuals received the COVID-19 vaccine.

However, the rates of common arterial and venous events, including deep vein thrombosis, myocardial infarction, pulmonary embolism, and stroke, are typically hard to measure based on case reports alone.

In the first study, investigators analyzed the EHRs of individuals living in England. Approximately 21 million had received the vaccine at some point during the study time span of December 2020 and March 2021.

The investigators found that for individuals 70 years or older, the risk of arterial and venous thrombotic events was slightly lower in the 28 days following vaccination with either the Pfizer BNT162b2 or ChAdOx1-S vaccine. They adjusted for the range of demographic characteristics, as well as comorbidities. Additionally, in individuals under age 70 years, the risk of arterial and venous thrombotic events was comparable in the 28 days following vaccination. However, a small increased rate of intracranial venous thrombosis was observed after vaccination with ChAdOx1-S.

“In adults under 70 years, the small increased risks of intracranial venous thrombosis and hospitalization with thrombocytopenia after first vaccination with ChAdOx1-S are likely to be outweighed by the vaccines’ effect in reducing COVID-19 mortality and morbidity,” the investigators noted.

There was a corresponding excess risk of an estimated 0.9 to 3 per million, varying by age and sex. This was approximately twice the rate of those who were unvaccinated, even after adjusting for a range of demographic characteristics and comorbidities.—Ashley Gallagher
Integrating Pharmacists Into Care Teams Is Crucial
Tapping Their Specific Skill Sets and Training Can Help Serve Patients More Effectively, Although Challenges Exist
BY RANA SAID; EOJIN LEE; AND DEEPAI DIKIT, PHARMD, BCPS, BCCCP, FCCM

PHARMACISTS RECEIVE TRAINING in general health, medication use, patient and provider education, pharmacotherapy, preventive care, and wellness. However, it was not until the early 1960s that the healthcare model adapted to allow pharmacists a more clinical role.¹,²

Historically, a pharmacist’s core role was dispensing medications and ensuring their safe use. In the 1960s, government health care programs began enlisting pharmacists to aid in disease management and primary care.¹ By the 1970s, a core responsibility of pharmacists became drug regimen reviews, particularly in long-term care facilities—this practice has extended into all other settings in which pharmacists are employed.¹,² By the early 2000s, collaborative drug agreements were on the rise in government health care facilities, further expanding the scope of practice for pharmacists within direct patient care.¹ The role of pharmacists and their impact on patient care is still evolving and adapting to gaps in the health care system.
Within integrated care teams, a pharmacist’s primary responsibility is to optimize patient medication therapies through continuous coordinated medication management and review. Pharmacists accomplish this on their own and through multidisciplinary teams by doing the following:

- Communicating issues with physicians
- Ensuring therapies are not lost to transitions of care
- Evaluating patients and patient profiles for medication appropriateness
- Identifying and discontinuing duplicate or unnecessary therapies
- Identifying drug-related problems, such as allergies, dosing, drug interactions, and the potential for adverse events
- Identifying potential barriers to patient adherence
- Initiating or modifying medication therapy plans as patient needs change
- Monitoring outcomes of medication therapy, including effectiveness and safety
- Providing patient education

Although pharmacists are qualified to take on these responsibilities, allowing them a larger role on these teams has not been easy. Studies have shown that the rate of acceptance of pharmacist recommendations by physicians and their teams can vary from 11.4% to 94.2%. A successful team is built through respect and trust, which depend on the professional relationships among members. Consequently, varying team dynamics and relationships cause a wide range in the acceptance rate. Teams with experience in integrating other health care professionals or that had prior relationships with pharmacists allowed for easier collaboration. Additionally, orientation and role definition are common barriers to integration. Understanding the clinical roles and skills of pharmacists within the team fosters better relationships among health care professionals and less uncertainty about the benefits of integration. Finally, visibility and lack of resources are a major challenge to integrating pharmacists. Often, there is not dedicated space for clinical pharmacists on the floors, causing teams to sometimes forget about this resource and not consult them. This causes barriers in fostering the pharmacist-physician relationship because of lack of interaction.

However, the role of pharmacists is expanding continuously, causing a positive shift in the health care system. Although there are barriers to integrating pharmacists into primary care teams, more health care professionals and patients are recognizing the need for such integration. In a cross-sectional survey conducted in California, 90% of 69 physicians noted that integration of pharmacists in their team improved medication management, and 93% considered pharmacists’ recommendations clinically meaningful. Furthermore, patients benefit from pharmacist-provided education, having a better understanding of the medications they are taking and being more adherent. Patients are also at reduced risk of medication-related problems because pharmacists prevent many errors prior to dispensing the medications. The results of a study involving 969 patients in Ontario, Canada, showed that when a pharmacist was integrated into a primary care team, at least 1 drug-related problem was identified and prevented in 93% of patients.

The results of another study involving 237 patients showed that 16 pharmacists divided into different care teams found an average of 2.1 medication discrepancies and 3.6 drug-related problems per patient.

Pharmacist integration also benefits the health system. Regardless of practice setting, pharmacist-driven services have shown economic benefit: For $1 invested in pharmacist integration, more than a $4 benefit was seen. Evidence-based practice by pharmacists can further reduce downstream health care costs by doing the following:

- Providing medication reconciliation to detect and reduce drug discrepancies
- Providing behavioral and educational counseling to improve medication adherence
- Providing preventive care services such as immunizations
- Working in collaborative practice agreements to facilitate access to care and decrease the demand of physician-provided care

Pharmacists have been advancing their practices to deliver the most qualified care in specialized areas of medicine and to provide medication information to other health care professionals. The pharmacist’s role has expanded beyond medication dispensing and management to multiple therapeutic areas and settings. These include the following:

- In ambulatory settings, pharmacists play a behind-the-scenes role by reaching out to providers about alternate therapy because of cost issues, drug interactions, inappropriate prescriptions, and patient education prior to dispensing medications.
- In infectious disease, pharmacists are respected members of integrated teams, with involvement in developing algorithms and antibiograms, evaluating
Understanding the clinical roles and skills of pharmacists within the team fosters better relationships among health care professionals and less uncertainty about the benefits of integration.

- Oncology pharmacists work closely with nursing departments to administer anticancer medications effectively and follow up with chemotherapy management throughout a patient’s life, monitoring medication adherence and safety. Furthermore, oncology pharmacists in investigational drug studies are responsible for working with institutional and legal representatives to ensure that certain qualified patients have access to investigational drugs.

- In critical care, physicians often rely on pharmacist recommendations regarding antibiotics. Pharmacists are heavily involved in daily rounds, evaluating and monitoring efficacy of pharmacological treatments and providing relevant information to the team.

It is worth noting that during the COVID-19 pandemic, critical care and infectious disease pharmacists have played a vital role in developing and implementing protocols.

Conclusion
In general practice, care team members gain drug knowledge from pharmacists, increasing safety. Although there are challenges to integrating pharmacists into primary care teams, it is ultimately beneficial, clinically and economically.

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Pharmacies Should Review Automated Dispensing Cabinet Practices

How ADCs Are Used at an Institution Can Greatly Affect the Potential for a Drug Error to Occur Incident

BY CRAIG KIMBLE, PHARMD, MBA, MS, BCACP

MOST HEALTH SYSTEM pharmacies provide services to a mix of inpatient and outpatient care areas and use automated dispensing cabinets (ADCs). How ADCs are used varies slightly by facility, internal policies, and location. Many health systems use ADCs as their primary means of medication distribution and documentation throughout the campus.¹,² Several vendors manufacture these ADCs and offer a wide variety of hardware and software configurations, features, and workflows. All configurations and products are designed to address differing needs across a complex distribution process. Also, during the pandemic, many facilities have used temporary staffing with differing levels of experience in using ADCs. These variations make it difficult to standardize practices among facilities. In addition, diversion and improving medication safety remain issues that health system leaders must address. Looking at how ADCs are used is paramount to addressing these concerns.

The Institute for Safe Medication Practices (ISMP) recently issued updated guidelines for safe use of ADCs. The goal of this guidance is to help ensure that pharmacies adopt standard practices and processes that complement ADC design and functionality specifications.³ Pharmacy leaders are encouraged to review institution-specific practices to ensure adherence to ISMP recommendations. A full breakdown with case examples is available for pharmacy leaders on the ISMP website.

How ADCs are used at an institution can greatly affect the potential for a drug error. As access and volume increase, so does potential for an incident to occur. When reviewing or updating ADC policies, it is often smart to apply the ISMP best practices to existing policies to ensure that pharmacies are providing the safest possible environment for patients and staff members. It is also good internal practice to be proactive and periodically review in-house incidents and alerts issued through various notification systems as well as those involving nursing and pharmacy staff members. Educating staff members and taking preventive action where known hazards exist are good ways to improve overall safety and reduce risk in the pharmacy.

When reviewing internal policies and procedures, start with the core elements of the ISMP Targeted Medication Safety Best Practices for Hospitals.⁴ Following are recommendations from those practices.

**Engage nursing.** Pharmacy staff members should work with nursing to develop best practices, competencies, and procedures for safely conducting transfers and withdrawals from ADCs for bedside administration. The use of barcode technology throughout this process adds a layer of safety.

**Establish ADC system security.** Pharmacy staff members should ensure that there is adequate oversight where ADCs...
are located. Conducting frequent audits, keeping high-risk and high-theft products as secure as possible, and removing former employees’ access are all important steps.

- **The ISMP recommends using profiled ADCs and monitoring overrides for the system.** This helps ensure that there has been a pharmacy review and that problematic items are identified quickly. Limiting the number of medications that can be removed by override is considered a best practice. This helps prevent administration of medications that do not have active orders while keeping emergency medications available. Pharmacy staff members should also proactively audit overrides to ensure that safe practices are followed and appropriate documentation is completed.²⁴

- **Maintain optimal equipment and inventory configuration.** Inventory should be reviewed frequently so that modifications can be made to ensure that each ADC configuration maintains the optimal inventory for the space available.

- **Pharmacy leaders should ensure that environmental conditions for the safe use of ADCs are implemented.** The ISMP recommends placing ADCs where there is adequate lighting, enhancing existing lighting, and ensuring the area is clean and free of debris. There should also be adequate space to complete tasks performed by aides, nurses, and pharmacy technicians such as documentation or electronic charting.

- **Pharmacy staff members should ensure that all ADC areas are maintained in the appropriate configuration and functionality and updates are performed in a timely fashion.** This minimizes variation and the associated risk that can occur from out-of-date equipment or software.

- **Provide frequent education.** Pharmacies should provide frequent staff education on ADCs, including areas of concern, ways to get additional information from pharmacy services or the software, and what is different or new. This includes the use of pop-up warnings.²

- **Review internal ADC stocking and return processes.** This ensures that staff members follow best practices, including using barcode scanning when available.

- **Use safety alerts wisely.** Pharmacies should use the ADCs to display and flag important patient and drug information, such as allergies, high-risk medications, and interactions, when the technology is available.

Regardless of how health systems use ADCs, pharmacies should periodically conduct thoughtful reviews to ensure that staff members are using recommended best practices. A continual competency and education program can help ADC managers ensure that staff members are adequately trained and performing according to these specifications.

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Ignoring Concussions Can Pose Dangers
Patients May Not Admit or Recognize When They Have a Brain Injury, but Pharmacists Can Be a Valuable Resource

BY JOANNA LEWIS, PHARMD, MBA

TRAUMATIC BRAIN INJURY (TBI) is a leading cause of death and disability in the United States, affecting an estimated 2.5 million individuals each year.¹ The actual number likely is larger, because this statistic does not include TBIs that go untreated or that are treated in primary care, urgent care, or at the site of injury, such as a sports field. Mild TBIs, or concussions, account for more than 75% of TBI cases and are the result of a blow, bump, or jolt to the head or from a hit to the body that causes the brain and head to move rapidly back and forth.¹⁻³ For most individuals, a concussion and concussion symptoms resolve over time. However, in a small subset, postconcussive syndrome is present.

Epidemiology
The American Academy of Neurology defines concussion as a “clinical syndrome of biomechanically induced alteration of brain function typically affecting memory and orientation, which may involve loss of consciousness.”⁴ The sudden impact or movement that results in a concussion can alter the brain’s physiology, cause oxidative stress, and damage and stretch brain cells.⁵

In the United States, the highest rates of concussion are seen in individuals younger than 24 years and those older than 75 years.

Falls and motor vehicle accidents are the most common causes of concussion in those 75 years and older, with this age group having the highest number and rate of TBI-related deaths and hospitalizations.¹ Among those aged 15 to 24 years, motor vehicle accidents and sports are leading causes of concussions, and in children aged 0 to 4 years, falls are the primary cause.

Males are more likely to suffer head injuries, and it is postulated that this reflects their more frequent engagement in contact sports and high-risk activities.⁶ Other risk factors are a history of hospital admissions for intoxication and lower cognitive function or socioeconomic status.

Pediatric patients are more susceptible to the effects of concussions because of their developing nervous systems, increased chemical and metabolic changes that occur in the brain, and lack of musculature to absorb force.⁷ Pathophysiologic injury to the brain can affect a child’s ability to function cognitively, physically, and psychologically and has been the subject of much research.

Clinical Features
Concussion diagnosis involves a medical history, neurological examination, and sign and symptom evaluation. Symptoms vary among individuals and can change throughout recovery. A mild TBI has a Glasgow Coma Scale score of between 13 and 15 measured approximately 30 minutes after the injury.

Amnesia and confusion with or without a preceding loss of consciousness may be apparent immediately after the head injury or several minutes later.¹⁻²,⁷ Other early signs of concussion cover a spectrum of behavioral, cognitive, emotional, and physical symptoms. Dizziness and headaches are the most common symptoms, but patients can also experience acute nausea, lack of awareness of surroundings, and vomiting.²,⁵ Over the following days and hours, patients may complain about lethargy, mood and/or sleep disturbances, sensitivity to light or noise, and trouble concentrating.
Many concussions do not have observable findings, but signs may include incoordination, such as disorientation, emotions out of proportion to the circumstances, stumbling or inability to walk, incoherent or slurred speech, memory deficits, trouble focusing, and a vacant stare.2,3

**Acute Management**

Important considerations in the management of mild TBI include identification of immediate neurologic emergencies, prevention of cumulative chronic brain injury, and recognition and management of neurologic damage.9 Observation either at home or in an acute setting is recommended for at least 24 hours after a mild TBI because of the risk of intracranial complications.9 Imaging is suggested in a subset of patients with concussion to identify injuries that require immediate neurosurgical intervention or neurologic evaluation with medical management.

Posttraumatic seizures are those that happen within the first week after head injury, and these occur in less than 5% of mild or moderate TBI cases. Approximately half of patients who experience seizures will have the first occurrence within the first 24 hours. These seizures are considered acute events and not epilepsy.10 A patient may experience a variety of symptoms while recovering from a concussion. In most instances, sticking to cognitive and physical rest followed by gradual resumption of activities will improve symptoms. Medication may be prescribed for symptom management, such as headache relief. However, pharmaceutical therapies are not heavily relied upon and not used to speed recovery.

Once under observation, patients must understand when to seek additional medical help. Bowel or urinary incontinence, confusion, fever, inability to awaken a patient, numbness or weakness involving any part of the body, seizures, severe or worsening headaches, stiff neck, unsteadiness, vision problems, and vomiting are all symptoms warranting immediate medical attention.2,3

**Postconcussive Syndrome**

Most individuals who suffer concussion can recover safely at home after seeing a medical provider and will experience spontaneous resolution of symptoms. Most individuals recover from a mild TBI within 10 to 14 days, and symptoms are improved or resolved at 1 month. Postconcussive syndrome is present when symptoms last beyond the expected recovery period after the initial injury. Because a head injury in a child influences a growing brain, prolonged symptoms lasting more than 3 to 4 weeks in this age group may require a multidisciplinary approach.10 There is also research around second impact syndrome, especially among athletes. Premature return to play places an athlete at greater risk for recurring concussion or subsequent injury.4,8 Return to play for athletes should be done after an adequate recovery period, not until a patient is asymptomatic off medication, and under medical supervision.

**Pharmacist’s Role**

Individuals may not admit or recognize when they or someone in their care is having symptoms of a concussion. Pharmacists can help patients identify when they should get emergency help or see their health care providers for evaluation. Pharmacists can also be a valuable resource in symptom management and for multidisciplinary management of postconcussive syndrome.11

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COLORECTAL CANCER is the fourth most common cancer diagnosis in the United States and is associated with significant morbidity and mortality. Although incidence appears to be declining overall, there is a concerning trend of increasing prevalence among patients under age 50 years for reasons not entirely understood. Hypotheses include factors such as generational changes in diet, lifestyle, and environmental exposures. Most patients present with localized disease.

However, approximately 50% to 60% of patients will progress to metastatic colorectal cancer (mCRC) after locoregional therapy is unsuccessful. As such, much recent research has aimed to improve disease response and overall survival (OS) in patients with metastatic disease, particularly after traditional chemotherapy is unsuccessful and for patients with targetable mutations.

\textit{BRAF} mutations are present in approximately 5% to 15% of mCRC cases and represent an important therapeutic target. National Comprehensive Cancer Network (NCCN) guidelines recommend screening all patients upon diagnosis of mCRC for the presence of a \textit{BRAF} mutation. Unfortunately, \textit{BRAF} mutations are associated with poor prognostic factors, such as more invasive tumors, poor cellular differentiation, and right-sided heart failure. Patients with \textit{BRAF}-mutated colorectal cancers have demonstrated poorer OS and diminished responses to treatment, particularly the antivascular EGFR inhibitors cetuximab and panitumumab when given as monotherapy. \textit{BRAF} V600E is an activating mutation that perpetuates cellular growth and downstream signaling via MEK activation in the mitogen-activated protein kinase (MAPK) pathway. When \textit{BRAF} inhibitors are used alone, EGFR signaling is upregulated, resulting in continued cell proliferation and survival. This led investigators to study the combination of \textit{BRAF} inhibition, MEK inhibition, and an anti-EGFR monoclonal antibody (mAb) to synergistically block feedback signaling and cancer cell proliferation.

The BEACON trial (NCT02928224) was an open-label, phase 3 trial of patients with mCRC after not achieving success with at least 1 prior line of therapy and randomized patients 1:1:1 to receive triplet therapy (encorafenib, binimetinib, and cetuximab), doublet therapy (encorafenib and cetuximab), or control (cetuximab, with either FOLFIRI [folinic acid, fluorouracil, and irinotecan] or irinotecan). At the time of the prespecified interim analysis, the results showed improved OS of 9 months with triplet therapy vs 5.4 months with the control (HR, 0.52; 95% CI, 0.39-0.70; \(P < .001\)).

Grade 3 or greater adverse effects (AEs) were more common in patients receiving control compared with doublet or triplet therapy (61%, 50%, and 58%, respectively). The most common AEs in the triplet-therapy group included acneiform rash, diarrhea, and nausea.

In 2021, updated analyses of the BEACON
When BRAF inhibitors are used alone, EGFR signaling is upregulated, resulting in continued cell proliferation and survival.

Encorafenib is given as a once-daily dose of 300 mg in four 75-mg capsules and can be administered with or without food. There are important AEs associated with BRAF inhibitors that warrant careful monitoring and patient education, including an increased risk of new primary malignancies, such as basal cell and cutaneous squamous carcinomas. Of note, significant dermatologic toxicities are more likely when encorafenib is used without concomitant MEK inhibition. Patients should have comprehensive dermatologic evaluations every 2 months during treatment and for up to 6 months after completion. Prolongation of QTc is also possible. Baseline and periodic monitoring may be warranted in high-risk patients.

As demonstrated in the BEACON trial, BRAF inhibition in combination with an anti-EGFR mAb yielded clinically significant improvements in OS and ORR over standard therapy. The BEACON trial included binimetinib, a MEK inhibitor, along with encorafenib and cetuximab. However, there was no additional benefit in terms of OS and higher rates of toxicity. Although the BEACON trial used cetuximab for EGFR inhibition, panitumumab is considered therapeutically equivalent and may be substituted based on institutional or provider preferences. Given these findings, NCCN guidelines recommend doublet therapy with encorafenib and either cetuximab or panitumumab for patients with BRAF V600E-mutant mCRC who have progressed after at least 1 prior line of therapy.

References


When BRAF (B-A-F) inhibitors are used alone, EGFR signaling is upregulated, resulting in continued cell proliferation and survival. BRAF inhibitors include encorafenib and binimetinib. EGFR inhibitors include cetuximab and panitumumab. These agents are used in combination with BRAF inhibitors to enhance their therapeutic effects. The BEACON trial demonstrated improved outcomes in OS and response rates with the combination of encorafenib and cetuximab compared to standard therapy. The use of MEK inhibitors can further enhance these effects, as seen in the BEACON CRC trial, where the addition of binimetinib to encorafenib and cetuximab resulted in improved survival rates. However, the use of MEK inhibitors also increases the risk of dermatologic toxicities, particularly with the use of single-agent BRAF inhibitors. Therefore, careful monitoring and management of these toxicities is crucial to ensure patient safety and efficacy.
Managing Drug Interactions in HIV and TB Coinfection Is Complex

Best Practices Call for Referring to Resources, Such as Those From HHS and the University of Liverpool

BY MELISSA BADOWSKI, PHARMD, MPH, FCCP, FIDSA, BCIDP, BCPS, AAHIVP, AND RAJEEV SHAH, PHARMD, AAHIVP, BICDP

TUBERCULOSIS (TB) IS a serious health concern, especially when coupled with HIV. Individuals with HIV are more likely to become sick if they are coinfected with TB. Infections among individuals with TB include those in the following categories:

- **Active** (disease mainly affects the lungs and is spread individual to individual through airborne transmission)
- **Extensively drug resistant** (TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and a second-line injectable drug)
- **Latent** (the individual is infected with Mycobacterium tuberculosis but without symptoms and cannot spread it to others and may never develop active TB)
- **Multidrug resistant** (there is drug resistance to the 2 most potent TB medications, isoniazid and rifampin)\(^1\)\(^2\)

It is estimated that up to 13 million individuals in the United States have latent TB, but the incidence in individuals with HIV is not known. In 2020, of 6960 individuals in the United States who had diagnoses of active TB, 300—or 4.3%—had HIV.\(^3\)

Consequences of untreated TB, along with HIV, can lead to significant morbidity and mortality. Consequently, medication initiation for the management of HIV and TB tends to be complex, because concomitant drug interactions often affect treatment.

Rifamycin derivatives, such as rifabutin and rifampin, are core components of first-line TB treatment regimens. Unfortunately, they have the potential to cause drug-drug interactions through either enzymatic and/or transporter induction, not only with established first-line agents for the treatment of HIV but also those newly approved. This review will summarize rifamycin drug-drug interactions with novel agents and combinations, such as fostemsavir, tenofovir alafenamide (TAF), and 2-drug regimens (2DR).

Historically, TAF has been contraindicated with rifamycin, and tenofovir disoproxil fumarate (TDF) has been the preferred formulation. However, newer pharmacokinetic data suggest that concurrent therapy with TAF may be acceptable. This is particularly important, because TAF is often a key component of many first-line regimens for patients who have just received diagnoses of TB.

The results of one study show that coadministration of rifampin and TAF led to a decrease in plasma tenofovir area under the curve (AUC) and concentration at 24 hours by 54% and 55%, respectively.\(^4\) However, intracellular tenofovir diphosphate (TFV-DP) AUC remained 4-fold higher than those of TDF administered alone. Because the TFV-DP AUC at the site of action was higher, this shows promise for maintaining efficacy when rifampin and TAF are coadministered. Data regarding clinical outcomes are lacking, so coadministration of rifampin and TAF should only be considered when benefits outweigh risks.

Fostemsavir is a novel agent for the treatment of multidrug-resistant HIV.
Rifampin significantly reduces concentrations and exposure of the active metabolite temsavir, so coadministration is contraindicated. Rifabutin may be considered an alternative, because it only lowers temsavir AUC and minimum concentration by 30% and 41%, respectively. However, there are limited clinical data on efficacy with coadministration, and in the setting of multidrug-resistant HIV, these decreases may contribute to virologic failure of a fostemsavir-containing regimen.

Although there are pharmacokinetic data examining the effect of rifamycin on individual components of 2DR, there is a paucity of clinical data on the management of TB with 2DR. Dolutegravir, a cornerstone agent in oral 2DRs, continues to be evaluated for its role in HIV and TB coinfection. Dolutegravir/rilpivirine in oral 2DRs, can be complex. As new studies are published and recommendations may change, best practices call for referring to resources such as the US Department of Health & Human Services HIV guidelines or the University of Liverpool HIV drug interaction checker.

**Conclusion**

Managing drug-drug interactions in HIV/TB coinfection can be complex. As new studies are published and recommendations may change, best practices call for referring to resources such as the US Department of Health & Human Services HIV guidelines or the University of Liverpool HIV drug interaction checker.

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Health Systems Should Better Integrate Pharmacy Arrangements
Ideally, These Contracts Help Address Criticism of the 340B Program, Improve Patient Outcomes, and Increase Compliance

BY JUSTIN LINDHORST, MBA

INE IN 10 large hospitals operate a specialty pharmacy, and most of these pharmacies also participate in the federal 340B drug pricing program. Health system pharmacies participating in the program often use external contract arrangements to expand the reach of their offerings. Thirty-thousand pharmacy locations—nearly half the US pharmacy industry—participate as 340B contract pharmacies. Health systems often initiate these arrangements to expand access to payer contracts and increase the number of covered individuals who can participate in 340B programs. Focusing on contracts is an important consideration for health systems that expand the reach of some or all of their pharmacy services in this way. Nevertheless, focusing exclusively on payer contracts may cause health systems to miss opportunities for improving patient engagement and outcomes and for enhancing 340B compliance. Let’s review considerations beyond insurance contracts for 340B contract pharmacy partners and examine how health systems can better integrate their pharmacy arrangements to address criticism of the 340B program, improve patient outcomes, and increase 340B compliance.

Selecting a Program Partner
Organizational culture has long been understood to affect business failure or success. A toxic culture can affect turnover, hurt productivity, and reduce profitability. In health care, organizational culture has been shown to significantly affect patient experience and outcomes. To understand and promote a positive culture, health care leaders should examine areas where patients, service users, and staff members interface. In the case of buyer-supplier relationships in which a supplier acts as an extension of the organization, experts agree that cultural compatibility is an important component affecting the success of business relationships. Resources are available for organizations seeking to evaluate the cultural compatibility of their business partners. Jerry Ledlow, PhD, dean of the School of Community and Rural Health at The University of Texas at Tyler, and Karl Manrodt, PhD, a professor of logistics in the Department of Management at Georgia College & State University, developed a compatibility and trust assessment that examines cultural fit across 5 areas: communication, focus, innovation, team orientation, and trust.

Given the potential for regular interaction with employees and patients, the culture at a contract pharmacy is an important consideration for any health systems expanding their 340B programs or working to better integrate pharmacy services. The majority of 340B contract pharmacy arrangements are held by the nation’s largest retail pharmacies and the mail order/specialty pharmacies owned by large pharmacy benefit managers (PBMs). These organizations may hold contracts important to the health system, but their culture and patient-level experience may not always align with the goals and standards of mission-driven covered entities (CEs).

The nation’s largest retail pharmacies are increasingly dealing with a workplace culture dominated by fatigue and stress. Pharmacists and pharmacy technicians in the retail setting report high levels of burnout, with many indicating that they are fearful for patient safety. At the same time, patient sentiment toward the largest PBMs has reached a new low. Research from...
Consumer Affairs indicates that the number of patient complaints across the largest PBMs skyrocketed in 2021. These complaints included authorization, billing, customer service, and fulfillment issues. Market research also indicates that distrust often occurs between health systems and payers or PBMs. Payers view health systems as incentivized to keep revenue within their organizations, whereas health systems view payers as prioritizing market ownership over patient care. Big box pharmacies and PBMs have been accused of using their influence to increase profits at the expense of safety net providers participating in 340B programs.

“Insurance contracts are often top of mind for health systems expanding their 340B programs,” said Ted Traurig, vice president of specialty pharmacy operations for independently owned BioMatrix Specialty Pharmacy. “It is by far the No. 1 question that comes up, but contracts are not the only way a pharmacy can create value for a covered entity.”

Traurig notes that independent pharmacies often provide more engaged, high-touch services in line with the culture and values of mission-driven organizations. “In my experience, independents offer a more focused, customized level of service and are more open to negotiation than some of our counterparts,” he said.

Pharmacy Services
Health systems using contract pharmacy arrangements should identify opportunities to better integrate services with program partners to promote positive patient outcomes and strengthen 340B compliance. Integrating pharmacists as key members of the health care team has been shown to positively affect patient outcomes and satisfaction, particularly among those who take specialty medication for chronic, difficult-to-treat, or rare conditions. Health systems in the United States face ongoing staffing shortages. Integrating pharmacists can decrease the burden for health care providers without compromising clinical care. CEAs across the country are finding unique ways to integrate their 340B pharmacy teams and leverage cost savings from the program to enhance and improve patient care. A federally qualified health center in Pennsylvania assembled a multidisciplinary team, including a contract 340B pharmacy, to tackle a pervasive public health issue: hepatitis C. Working together, the team successfully designed a program that achieved an 87.2% treatment success rate in a high-risk population without an onsite gastroenterologist or hepatologist. The primary roles of the contracted 340B pharmacy were facilitating medication refills, identifying and mitigating drug-drug interactions, and obtaining prior authorization approvals.

Administrative and Support Services
CEs and contract pharmacies should work together to better integrate administrative and support services to promote patient engagement and program integrity. CEs maintain primary responsibility for their program’s compliance with Health Resources and Services Administration (HRSA) and Office of Pharmacy Affairs (OPA) 340B guidelines. A competent contract pharmacy partner will provide active and direct support for HRSA/OPA compliance, in addition to comprehensive intake, billing, and collection services. “Contract pharmacies also hold important dispense data that should be analyzed regularly to promote compliance, enhance cost savings, and identify areas of opportunity,” said Sabine Enright, director of 340B services at BioMatrix Specialty Pharmacy.

Apexus is the prime vendor for the 340B program. The organization has developed many resources, including self-auditing tools to evaluate program partners based on their ability to promote 340B program integrity. Using resources from Apexus, CEs and their pharmacy partners should actively develop systems and workflows demonstrating and promoting program integrity.

In addition to administrative and clinical services, many specialty pharmacies provide nonclinical patient-level support, including patient navigation designed to promote positive self-management and reduce barriers to care. This type of assistance can provide a strong value-add for CEs. Effective patient navigation has been shown to help individuals with chronic health conditions miss fewer doctor appointments, maintain insurance coverage, and obtain timely medication refills.

Addressing Critics, Creating Synergies, Improving Outcomes
Contract pharmacy arrangements are a hot-button issue in the 340B landscape. Critics posit that the 340B program needs more transparency and stronger government oversight while asserting that patients see little benefit from the program. Health systems should work with their contract and in-house pharmacy partners to increase visibility around measures taken to promote program integrity while tracking and communicating the outcomes and value of their 340B programs. For more successful business relationships, CEs should think beyond managed-care contracts and seek partnerships where culture, patient experience, and values align with strategic priorities. Working together, health systems and integrated 340B program partners can create synergies that address criticism, enhance program integrity, and improve outcomes.
It Is Time to Consider Alternatives to Discipline Programs
Professional Assistance Programs Provide Pathway for Health Care Professionals to Return to Practice Following Treatment for Substance Use Disorder

BY STEPHEN M. WEBSTER, PHARMD, MSBA

SUBSTANCE USE DISORDERS (SUDs) among health care professionals (HCPs) can potentially destroy careers and lives, hurt employers’ financial bottom line and reputation, and jeopardize patient safety. Unfortunately, HCPs who have developed SUDs may work under the influence or divert medications from their places of employment. The hope is that they are discovered or self-refer for treatment before harming a patient or themselves. If the HCP is caught, along with embarrassment and shame comes the real possibility of losing both job and license to practice, as well as criminal prosecution.

But state licensing boards increasingly have used an alternative to discipline in some cases of drug diversion, understanding that the behavior often is a symptom of an underlying SUD. Professional assistance programs (PAPs) exist in almost all states and can provide a pathway for licensed HCPs who have diverted to return to practice during or after SUD treatment. Furthermore, PAPs have shown success rates, measured by abstinence and retention to work through follow-up, varying from 60% to 90%.

Historically, HCPs discovered diverting would almost always have had their employment terminated. Some health care employers are planning or have instituted an alternative to discipline that would allow HCPs to maintain employment while receiving treatment for SUDs. Unfortunately, most employers have been slow to consider this approach. Opponents of this approach argue that keeping a known diverter on staff is unsafe and puts the employer and patients at risk, and that not having the strictest possible penalties may incite diversion. Proponents of the alternative-to-discipline approach, however, argue that data from state PAPs have shown that with the right elements, the option can prove highly successful and even improve patient safety. An alternative-to-discipline approach may encourage HCPs living with SUDs to self-report, and coworkers may also feel more comfortable reporting concerns if they know that it would not necessarily result in the employee being fired. It could also be argued that by terminating employment, employers pass on the problem to another institution, putting more patients at risk. Following a diversion complaint, state disciplinary processes can take 6 to 18 months before an HCP is removed from practice. Employers may also not learn as much as they could about the diversion, because HCPs are no doubt incentivized not to be forthright during an investiga-
tion if they know that termination would be the likely result. Termination also means that the employer is not addressing individuals’ problems and is passing up an opportunity to play a part in their recovery. In 2020, of the estimated 41 million Americans over age 12 years who had a SUD, only approximately 7% received treatment.7

The thought of creating an alternative to discipline can be overwhelming to some employers; such a program can be costly and labor intensive. However, the resources required to create and maintain a program can be minimal, assuming the organization resides within a state that has a robust PAP. One strategy is to require that the employee apply for, be accepted into, and maintain compliance with a state’s PAP to retain employment. By using this approach, employers can take advantage of the structure and monitoring resources already in place. Every state’s PAP is different, depending on the profession and state, but they generally have comparable structures. Initially, PAPs require cessation of practice for a period while the HCP begins treatment for the SUD. Following approval from a treatment provider, the HCP eventually returns to practice with certain workplace restrictions and a monitoring plan. Restrictions typically include no handling of controlled substances and possibly reduced hours for a period. These restrictions are eased as the HCP successfully progresses through the PAP. Monitoring requirements include the HCP being required to continue SUD treatment and submit to frequent random drug screens to ensure that they abstain from unauthorized use of alcohol or drugs for the duration of their participation in the PAP. The HCP will also have an assigned workplace monitor, often a supervisor, who is responsible for routine progress reports to the administrators of the PAP. This communication must be 2-way, because it is critical that the employer know whether the HCP has been noncompliant with other aspects of the PAP. The time required to successfully be discharged from a PAP varies based on the individual’s progress. However, the minimum required time is generally at least 2 years.1,2

Employers that institute an alternative-to-discipline approach must decide on eligibility criteria. Such an approach may not be deemed appropriate in all diversion cases. Instances in which HCP action caused or could have caused serious patient harm, such as drug substitution or tampering, may present such an egregious violation that an alternative-to-discipline approach may not be palatable. Diversion for trafficking purposes may be another reason not to use an alternative to discipline. Past job performance and the perceived level of cooperation with the diversion investigatory process may also be factors considered in deciding whether to offer a nonpunitive approach.

It is important to note that regardless of whether an employer uses an alternative-to-discipline approach, there remains an obligation to report controlled substances diversion to the US Drug Enforcement Administration and state regulatory agencies, including licensing boards.8 Regardless of the decision regarding continued employment, the employer also has a responsibility to provide information about SUD treatment to the employee.

SUDs continue to affect HCPs and their employers and patients. Effective alternative-to-discipline programs require long-term commitment by the employer and the HCP, but they can be successful in saving lives and livelihoods while having a positive impact on patient safety.

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503B Facilities Help Address Drug Shortages
Leveraging Automation Capabilities and Operational Capacity at Scale, They Bridge Gaps and Mitigate the Impact of Disruptions

BY MIKE WASCOVICH, PHARMD, MBA, RPH

A RECENT SURVEY OF health system pharmacy leaders and frontline staff showed that 94% of respondents have been affected by pharmaceutical supply interruptions over the past 18 months or longer. Severe production outages arising from natural disasters, manufacturing quality issues, raw materials sourcing, and now a global pandemic have served as a clarion call to address supply fragility and ensure sustainable access to high-quality medications.

In and out of a pandemic, a multifactorial approach is critical to combating drug shortages. Although no silver bullet exists, outsourced 503B compounding facilities can help to bridge gaps and to mitigate the impact of continuing drug supply disruptions.

Passed in 2013, the Drug Quality and Security Act allows 503B outsourcing facilities to compound certain products in anticipation of providers’ needs and based on meeting certain FDA requirements. 

503B outsourcing facilities differ from other compounders in that they:

• are inspected by the FDA according to a risk-based schedule;
• can source compounded drugs to clinics, hospitals, and specialists without a patient-specific prescription;
• must comply with the FDA’s Current Good Manufacturing Practice (CGMP) requirements; and
• must meet other conditions, such as reporting adverse events and providing the FDA with specific information about the products that are compounded.

With their automation capabilities and operational capacity, 503B outsourcing facilities streamline anticipatory batch compounding for large-volume sterile and nonsterile drug products and produce medications on the FDA’s drug shortage list. The facilities work with active pharmaceutical ingredients and raw materials meeting a CGMP standard so patients and providers have access to drugs that would otherwise be unavailable. In addition to producing in bulk, a 503B compounding facility can typically increase the manufacture of a drug within 5 to 6 weeks of its appearance on the FDA shortage list, helping reduce supply disruptions and price impacts.

As pharmacy leaders and teams are increasingly asked to do more with less, health system and hospital pharmacies with established 503B relationships can be vital. Throughout COVID-19, provider teams with limited resources and staff have turned to 503B facilities for help with production of laborious or infrequently used medications. This has provided an alternative supply option with high product certainty and quality. By committing to obtaining certain volumes of needed drugs from their 503B partners, pharmacies help to mitigate reflexive purchasing and to manage demand, which can reduce cost and waste.

The FDA has increasingly recognized the value of 503Bs, issuing a series of guidance documents in April 2020 for compounders to temporarily address shortages under certain circumstances. Overall, the FDA exercised regulatory flexibility 110 times in 2020 to address drug shortages for 78 products, but more must be done. Pharmaceutical suppliers agree; a recent Premier Inc survey of more than 50 drug manufacturers ranked expedited approvals as the single most effective...
strategy for alleviating drug shortages. Lessons learned throughout the pandemic show that many flexibilities could be implemented effectively and safely to mitigate drug shortages in more ordinary times. The FDA should allow 503Bs to continue producing certain drugs not on the shortage list, based on specific criteria such as regional or short-term shortages or demand surges for certain dosage strengths or packaging sizes. This waiver proved particularly helpful during the pandemic. It allowed 503B compounders to quickly and seamlessly fill capacity gaps and alleviate spot shortages before they became severe enough to spread nationwide and onto the FDA drug shortage list.

The FDA should permanently abandon the arbitrary geographical limitation known as the “1-mile radius” provision for hospital compounding. This waiver allows hospitals to consolidate pharmacy services into a single hub to preserve personal protective equipment, maximize use of available pharmacy staff, and avoid compounding at the patient bedside, which can lead to increased rates of medication errors.

Moving forward, the FDA should adopt a time-based standard rooted in scientific evidence for the stability and sterility of the compounded product.

Finally, the Coronavirus Aid, Relief, and Economic Security Act requires drug manufacturers to provide the FDA with additional information about supply disruptions, including the likely duration and severity of shortages. If the FDA adds such details to its drug shortage list, outsourcing facilities may decide to compound other vital products that they otherwise would not.

These policy levers are important tools in our arsenal against drug shortages, and they must be complemented by private-sector solutions that create the right economic incentives for new market entrants and healthy competition.

Compounding pharmacies are accredited, highly qualified institutions that are well positioned to respond effectively and swiftly to drug shortages. 503Bs can play an important role in enhancing pharmacy supply chain resiliency during COVID-19 and beyond.

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Venous Thromboembolism Prevention: What Pharmacists Need to Know

VENOUS THROMBOEMBOLISM (VTE) events, including deep vein thrombosis (DVT) and pulmonary embolism, represent a significant clinical and financial burden in the United States. Hospital-acquired VTEs are associated with serious health complications, reduced survival, and additional health care costs. Craig Beavers, PharmD, FACC, FAHA, FCCP, BCCP, BCPS AQ Cardiology, CACP, and Allison Burnett, PharmD, PhC, CACP, provided an eLearning session at ASHP Midyear on the prevention of VTE in patients who are medically ill.

Dr Beavers began his discussion by reviewing the clinical burden of VTE in medical patients who are acutely ill, including the mortality, clinical complications, and cost associated with VTE. He then discussed the risk factors for hospital-acquired VTE and emphasized that bleed risk must be considered when making decisions about VTE prophylaxis. Prophylaxis rates have increased to over 90%, but Dr Beavers highlighted that this has not impacted the incidence of VTE. He discussed the limitations of VTE prophylaxis and explained that a significant proportion of parenteral VTE prophylaxis doses are omitted due to patient refusal. Additionally, most hospital-related VTE events occur outside of the hospital in the first month after discharge, further limiting the utility of parenteral agents and representing a gap in care in VTE prophylaxis for patients who are medically ill.

To address this gap, Dr Burnett then reviewed the clinical trial data of direct oral anticoagulants for VTE prophylaxis using extended-duration therapy. In 2018, a de novo meta-analysis of 4 extended-duration therapy, randomized controlled trials showed a reduction in symptomatic proximal DVT at the cost of increased major bleeding. Dr Burnett described the American Society of Hematology Guideline recommendation against extended prophylaxis over shorter prophylaxis in medical patients who were acutely or critically ill post discharge. She then reviewed the data for extended-duration rivaroxaban for highly select patients at a low risk of bleeding, which resulted in the approval of rivaroxaban for this indication for 31 to 39 days. Dr Burnett stressed that appropriate patient selection is key in optimal use of extended-use prophylaxis.

Dr Beavers continued the discussion by reviewing the role of the pharmacist in VTE prevention. Pharmacists can target identification of the most appropriate patients for prophylaxis, optimizing inpatient prophylaxis and the duration of prophylaxis. Dr Beavers emphasized the use of risk assessment models to identify patients at high risk for VTE and those at high risk for bleeding in order to facilitate risk-balanced decisions during and after inpatient hospitalization.

Dr Burnett concluded the discussion by reviewing the role of the pharmacist in VTE prevention at a system level as part of anticoagulation stewardship. The use of standardized protocols, assessment tools, and clinical decision support tools can contribute to improved outcomes for VTE prophylaxis. Dr Burnett provided resources for pharmacists to assist with improving VTE prophylaxis and addressing questions regarding extended-duration prophylaxis.

Craig Beavers, PharmD, FACC, FAHA, FCCP, BCCP, BCPS AQ Cardiology, CACP, explained, “Patient refusal of injections is a common barrier for VTE prophylaxis in the inpatient setting. The availability of an oral option for VTE prophylaxis may help minimize gaps in care and reduce harmful events for patients.”

Allison Burnett, PharmD, PhC, CACP, stated, “Pharmacists can target identification of the most appropriate patients for prophylaxis, optimizing inpatient prophylaxis and the duration of prophylaxis.”
The Role of Biosimilars in Crohn Disease and Ulcerative Colitis: Clinical Strategies to Assist Pharmacists in Practice

INFLAMMATORY BOWEL DISEASE (IBD) affects more than 3 million adults in the United States. Patients with IBD face a large burden of disease and decreased quality of life associated with costly medications, invasive procedures, or radiographic studies required to monitor disease progress. Christopher Owens, PharmD, MPH, and Shubha Bhat, PharmD, MS, BCACP, presented at ASHP Midyear on the role of biosimilars in Crohn disease (CD) and ulcerative colitis (UC).

Dr Owens started the presentation by providing an overview of CD and UC and the pharmacologic management of IBD. He then introduced biologics and biosimilars and biosimilar approval and interchangeability requirements. Following the approval of the reference biologic, biosimilars may be approved after analytical studies showing the product is “highly similar” to the reference product, animal studies assessing toxicity, and a clinical study that demonstrates safety and efficacy for at least one condition for which the reference product is licensed. Dr Owens discussed that biosimilar indications might be extrapolated to include other reference product indications without specific studies of efficacy and safety of the biosimilar for a given condition. Dr Owens also highlighted clinical trial data supporting switching from the originator product to biosimilars in IBD for short- and long-term periods.

While biologics revolutionized IBD treatment, not all clinically eligible patients have access to these therapies due to their cost. Christopher Owens, PharmD, MPH, stated, “Integrating lower-cost biosimilars into managing inflammatory bowel disease can expand patient access to safe and effective therapeutic options.”

Dr Owens emphasized that biosimilars represent a less costly alternative that may improve patient access. Additionally, he reviewed biosimilars’ clinical and economic benefits for patients, providers, and the health care system beyond this direct cost savings.

Dr Bhat then began reviewing the clinical data for infliximab biosimilar use for IBD. She highlighted that most studies show that biosimilars are as safe and effective as reference infliximab for use in IBD. There are currently 10 FDA-approved biosimilars for IBD, including 4 biosimilars for infliximab and 6 biosimilars for adalimumab. Additionally, biosimilars for infliximab, adalimumab, and ustekinumab are currently under investigation in phase 1-3 studies. Despite this, Dr Bhat discussed that uptake of biosimilar use in practice remains low due to barriers during the biosimilar approval, marketing, ordering, and administration processes. She reviewed common concerns pharmacists, providers, and patients expressed regarding biosimilar use.

Dr Bhat ended the presentation by sharing the biosimilar adoption experience and lessons learned at Boston Medical Center. She discussed the timeline for implementation, noting that the infliximab biosimilar was not added to the medical center formulary until a year after FDA approval. Dr Bhat highlighted strategies to overcome barriers to biosimilar use by collaborating with the pharmacy team, providers, and patients. She emphasized best practices for biosimilar adoption, including engaging stakeholders in the adoption process, designating a pharmacy-based team to oversee the biosimilar adoption process, educating patients before making changes and utilizing shared decision making, addressing concerns in real-time, and monitoring outcomes post-biosimilar adoption.
Building Influenza Vaccination Rates in the Era of COVID-19: The Critical Need to Educate, Motivate, and Increase Access

Influenza is a vaccine-preventable illness that represents one of the top 10 leading causes of death in the United States. Despite this, the rate of influenza vaccination remains low among high-risk older adults, and vaccine rates fell in the 2019 to 2020 season with the advent of the COVID-19 pandemic. Rupal Mansukhani, PharmD, CTTS, FAPhA, and Liz Oler, PharmD, presented a session at ASHP Midyear on building influenza vaccinations rates in the era of COVID-19.

Dr Mansukhani began the presentation by providing an overview of influenza, including symptoms and epidemiology. Dr Oler then reviewed populations at an elevated risk of severe illness and complications of influenza, identifying older adults, pediatric patients, pregnant women, immunocompromised populations, and patients with comorbidities as those at the highest risk with influenza infections. These populations are also at high risk for severe illness and complications with COVID-19 infections. Dr Oler highlighted the challenges of influenza/COVID-19 coinfection and emphasized differentiating characteristics between the 2 viral infections.

Dr Mansukhani then discussed the influenza vaccines and recommendations for 2021 to 2022. She highlighted that all available influenza vaccines for this season are quadrivalent and noted that the composition of the vaccines has changed. In addition, the age requirements for the cell culture-based influenza vaccine have been reduced to a minimum of 6 months of age. Dr Mansukhani emphasized that this formulation represents an additional treatment option for pediatric patients at the highest risk.

Vaccine efficacy decreases around 6 months. Therefore, Dr Mansukhani spotlighted changes to the CDC guidance for timing of immunization, which recommends avoidance of early vaccination in July or August, except for women in the third trimester of pregnancy and for children who need 2 doses of influenza vaccine. Dr Mansukhani also emphasized that to provide protection from both influenza and COVID-19, these vaccines may be coadministered if an inactivated influenza vaccine is used.

Throughout the COVID-19 pandemic, vaccination rates, including influenza across all ages, have declined. Dr Mansukhani stressed the need to improve vaccination rates. Social media, education about myths, vaccine mandates, and improving health care access are all strategies for addressing declining vaccination rates. She continued the discussion by reviewing current trial data comparing the high-dose and adjuvanted vaccines in older populations.

Dr Oler ended the presentation by examining the pharmacist’s role in increasing influenza vaccination rates. The accessibility of pharmacists in the community and hospital settings was a major focus, with a significant percentage of adults and pediatric patients receiving influenza vaccines at the pharmacy. Dr Oler highlighted the opportunity during COVID-19 vaccination visits to screen patients for vaccine gaps and build a relationship as a trusted source for all vaccines. Vaccine hesitancy is a key barrier to immunizing at-risk populations. She concluded the discussion by emphasizing the pharmacist’s role in educating patients about influenza vaccination and shared recommendations for overcoming vaccine hesitancy.

Liz Oler, PharmD, emphasized, “Pharmacists are highly accessible to patients, providing an excellent opportunity for pharmacies to serve as centers for vaccination and improve influenza and COVID-19 vaccine rates.”
Opportunities for Pharmacists to Make Recommendations for the Treatment and Prevention of the Influenza Virus With COVID-19 Considerations

Influenza virus and COVID-19 are associated with serious health complications, especially in designated high-risk patient populations. In addition to the yearly fluctuations in severity and cases of influenza, the ongoing COVID-19 pandemic presents additional concerns for patients and providers, as the 2 viruses may coexist during the influenza season. Donald Klepser, PhD, MBA, and James S. Lewis II, PharmD, FIDSA, presented at ASHP Midyear on treatment and prevention of the influenza virus with COVID-19 considerations.

Dr Lewis started the discussion with an overview of influenza’s clinical burden, including the etiology and pathophysiology of influenza viral infections. He then compared symptoms of respiratory illnesses, including influenza, COVID-19, colds, and seasonal allergies. He emphasized that influenza and COVID-19 have marked overlap in symptoms, including fever, fatigue, cough, aches and pains, runny or stuffy nose, sore throat, and headache. Loss of taste or smell is only associated with COVID-19, and Dr Lewis highlighted that this might serve as a distinguishing feature of COVID-19 infections. Dr Lewis discussed overlapping patient populations at higher risk of serious complications from influenza and COVID-19, including pregnant women, long-term care residents, people who are obese, immunocompromised patients, older people, and people with chronic diseases such as pulmonary, renal, cardiovascular, or metabolic disease.

Dr Klepser then reviewed the epidemiologic burden of influenza in the 2020 to 2021 season. Due to widespread masking and social distancing, influenza activity last season was the lowest since current reporting began in 1997. Despite this, Dr Klepser described increasing influenza cases in recent weeks. In addition, Dr Klepser highlighted an expected seasonal overlap of influenza and COVID-19 mortality, complicating high-risk patients’ management.

Dr Lewis continued the presentation by reviewing influenza management strategies, including vaccination, treatment, and prophylaxis. Vaccination against influenza is the most studied and proven strategy for managing influenza infections. Dr Lewis emphasized that pharmacists should strongly recommend their patients get the influenza vaccine annually. Dr Lewis also highlighted that COVID-19 and influenza vaccines may be given together and discussed safe delivery of the influenza vaccine during the COVID-19 pandemic.

Early identification of the causative pathogen in high-risk individuals and hospitalized patients is key to initiating appropriate antiviral drug therapy. Dr Lewis explained that these patients should be screened for both influenza and COVID-19 viruses. Dr Lewis discussed how new COVID-19 therapies and treatment recommendations that emphasize anti-inflammatory agents might inform future treatment strategies for influenza. He then reviewed current influenza antiviral therapies oseltamivir and baloxavir and stressed that they should be started as soon as possible for hospitalized, severe, or high-risk patients.

Dr Klepser summed up the presentation by highlighting the pharmacist’s role in improving outcomes in influenza and COVID-19. Treatment with influenza antivirals carries benefits related to reduced duration of symptoms, improved outcomes, reduced disease burden, and decreased direct medical costs. Dr Klepser emphasized that pharmacists should use CDC recommendations to identify patients who would benefit from antiviral therapy. Additionally, Dr Klepser reviewed the impact pharmacists can make through patient education about vaccination and antiviral therapy.

James S. Lewis II, PharmD, FIDSA, stressed, “Starting antiviral therapies as soon as possible is key in treating influenza.”

Donald Klepser, PhD, MBA, said that “Pharmacists can play a crucial role in reducing the burden of influenza by identifying high-risk patients who would benefit from antiviral therapy.”
The Pharmacist’s Role in Optimizing Therapy for Heart Failure in an Evolving Treatment Landscape

Heart failure affects approximately 6 million adults in the United States, and this number is expected to increase to 8 million by 2030. Heart failure is associated with poor quality of life due to high hospitalization and mortality rates. Yasmin Grace, PharmD, and Tien M.H. Ng, PharmD, FHFS, FACC, FCCP, BCPS AQ Cardiology, provided a continuing education program at ASHP Midyear on the role of the pharmacist in optimizing heart failure therapy.

Dr. Grace began her discussion by providing an overview of heart failure, including epidemiology, classifications, and staging. She then reviewed the diagnostic criteria for heart failure and discussed the role of monitoring B-type natriuretic peptide (BNP) and NT-proBNP in patients at risk for heart failure and those with chronic ambulatory or acute hospitalized heart failure. She highlighted that natriuretic peptides might help evaluate a patient’s prognosis or disease severity and early recognition and prevention of heart failure onset by initiating prompt treatment.

Dr. Grace then discussed the current guideline-directed medical treatment (GDMT) for heart failure and highlighted the mortality benefits of GDMTs. Patients often face clinical or socioeconomic barriers in achieving target doses of GDMTs. Dr. Grace reviewed steps for addressing barriers to titrating GDMTs in clinical practice, including careful laboratory and clinical monitoring, patient education, and consideration of alternative or adjunctive agents. Dr. Grace emphasized for management of heart failure with reduced ejection fraction (HFrEF) that the addition of agents including loop diuretics, aldosterone antagonists, sodium-glucose co-transporter 2 (SGLT2) inhibitors, hydralazine plus isosorbide dinitrate, ivabradine, and digoxin must be individualized to patient characteristics.

Compared to HFrEF, there are fewer trials to guide the management of heart failure with preserved ejection fraction (HFpEF). Dr. Grace discussed the available therapies for HFpEF, which focus on symptom improvement and hemodynamic stabilization. In addition, she highlighted that angiotensin receptor-neprilysin inhibitor therapy may now be considered for patients across the range of ejection fractions.

Despite GDMT for HFrEF, mortality rates remain high. Dr. Ng reviewed the current trial data for emerging therapies for HFrEF targeting unique pharmacologic pathways of heart failure, including the soluble guanylate cyclase stimulator vericiguat and the myosin ATPase activator omecamtiv mecarbil. He emphasized that these agents may provide additional benefits in select patients with indicators of more severe disease. Dr. Ng also reviewed clinical trial data for emerging therapies for HFpEF, including sacubitril/valsartan and SGLT2 inhibitors, which appear to reduce morbidity in patients with HFpEF.

Dr. Ng finished the presentation by examining the pharmacist’s role in heart failure management. Education and counseling targeting lifestyle modifications and medication adherence were a major focus, and transitions of care were a key area for pharmacist intervention. Dr. Ng emphasized that pharmacist interventions for heart failure result in reduced medication errors and potential adverse effects, improved medication adherence, and in some instances, reduced mortality.

Yasmin Grace, PharmD, noted, “Natriuretic peptides might help evaluate a patient’s prognosis or disease severity and early recognition and prevention of heart failure onset by initiating prompt treatment.”

Tien M.H. Ng, PharmD, FHFS, FACC, FCCP, BCPS AQ Cardiology, said that “Emerging therapies for heart failure may help reduce residual risks of morbidity despite guideline-directed medical therapy.”
Advancements in Safe and Effective Treatment for Bipolar I Disorder

**EDUCATIONAL OBJECTIVES**

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

- Identify the types of bipolar disorder, pathophysiology, and prevalence as well as symptomology of patients
- Analyze evidence-based treatment for bipolar I disorder including efficacy, safety profiles, and treatment considerations for the use of newly approved and emerging treatment options
- Examine the role of pharmacists in counseling, monitoring, and providing education to help manage patients with bipolar I disorder

**TARGET AUDIENCE:** Pharmacists

**ACTIVITY TYPE:** Application

**RELEASE DATE:** January 31, 2022

**EXPIRATION DATE:** March 15, 2023

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

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

**Introduction**

Bipolar disorder is a chronic and often debilitating mental illness that affects approximately 4.4% of adults in the United States. Recent estimates place the economic burden of bipolar disorder at over $195 billion annually in the United States. Stigma associated with the condition can lead to shame, social withdrawal, and reduced quality of life for patients. Bipolar disorder is associated with an increased risk of several adverse patient outcomes including cognitive impairment, medical and psychiatric comorbidity, suicide, and mortality due to cardiovascular disease.

Long-term management with prescription medications is often necessary to prevent a relapse of mood symptoms; however, as many as half of patients will not be adequately adherent to maintenance therapy. It is important for pharmacists to be aware of the most evidence-based treatment recommendations and well-tolerated medications to best manage this complex disorder.

**Overview**

The 2 most common types of bipolar disorder are type I (BDI) and type II (BDII). Other less common types include cyclothymia or other specified or unspecified bipolar and related disorders. BDI is characterized by periods of elevated, expansive (demonstrating grandiosity), or irritable mood, typically alternating with periods of hypomania. Hypomania is a very similar presentation to mania, typically alternating with periods of depressed mood and normal mood (also known as euthymia). BDII is characterized by periods of depression alternating with periods of hypomania. Hypomania has a slightly higher prevalence in men, whereas BDII is estimated to affect 0.4% to 1.1% of individuals.
Table 1. Diagnostic Criteria for a Manic Episode

- Sustained period of abnormally elevated, expansive, or irritable mood AND increased energy or activity lasting at least 1 week or requiring hospitalization
- Three or more of the following symptoms (or four if the mood is irritable only):
  - Greatly elevated self-esteem
  - Feeling energetic despite sleeping less
  - Pressured speech or tautness
  - Racing thoughts or flight of ideas
  - Easily distracted
  - Psychomotor agitation or increased goal-directed activity
  - Impulsive behavior that may be dangerous or harmful
- There is significant impairment socially or occupationally, risk for harm to self or others requiring hospitalization, or psychotic symptoms
- The mood symptoms are not caused by a substance or other medical condition

Table 2. Diagnostic Criteria for a Major Depressive Episode

- At least five of the following symptoms present during a 2-week period (at least one of the symptoms must be depressed mood or loss of interest or pleasure):
  - Depressed mood
  - Decreased interest in activities
  - Appetite changes or significant unintended weight loss or gain
  - Decreased or increased sleep
  - Psychomotor changes (agitation or retardation) that are noticeable by others
  - Decreased energy or fatigue
  - Excessive guilt or feelings of worthlessness
  - Decreased ability to concentrate or make decisions
  - Persistent thoughts of death or suicidal thoughts or behaviors
- The symptoms are impairing socially, occupationally, or in other areas or cause significant distress.
- The mood symptoms are not caused by a substance or other medical condition.

Bipolar disorder is ranked as the 17th leading source of disability worldwide and the 6th leading cause of disability among people aged 10 to 24 years.5,9 While the onset of illness usually occurs in late adolescence to early adulthood, an earlier onset has been associated with poorer outcomes including more severe depressive episodes and higher rates of comorbid anxiety and substance use disorders.10 Additionally, 90% of individuals with bipolar disorder will have at least one psychiatric or medical comorbidity, with 50% having three or more comorbid conditions. The most common psychiatric comorbidities include anxiety disorders (present in 70%-90% of patients), substance use disorders (30%-50%), attention-deficit/hyperactivity disorder (25%-45%), and personality disorders (20%-40%).11 Other common comorbid medical conditions include metabolic syndrome, migraines, obesity, and type 2 diabetes.12 These comorbidities lead to significant morbidity and mortality. Individuals with bipolar disorder die an average of 10 to 20 years earlier than their peers, with cardiovascular disease being the most common cause of premature mortality.11 Individuals with bipolar disorder are also at an increased risk for suicide, with an estimated rate of suicide attempts 20 to 30 times the general population and approximately 6% to 7% of persons with bipolar disorder ultimately dying by suicide.13

Bipolar disorder is highly heritable, with a 10% to 15% risk of developing bipolar disorder in someone with a first-degree relative with the illness. Several genetic risk alleles have been identified; however, these variants account for only 25% of the overall heritability.14 While initial episodes of bipolar disorder may be linked to specific stressors in the patient’s life, after multiple mood episode recurrences, a “kindling” or episode sensitization effect is thought to occur, resulting in more frequent and spontaneous mood episodes occurring with minimal or no apparent stressors.4 This may be accompanied by progressive changes in brain structure such as reduced cortical thickness, particularly in the prefrontal cortex.15,16 A study of patients with BDI who were recently recovering from a manic or mixed episode found that during a 1-year follow-up period, patients who had a mood recurrence exhibited greater loss of gray matter volume in frontal, temporal, and left parietal lobes compared with those who maintained remission.17 An earlier study comparing progressive neurostructural changes in adolescent and adult patients with bipolar disorder found that changes in brain structure were more pronounced in older than younger patients.18 Abnormalities in the hypothalamic-pituitary-adrenal axis are also thought to contribute to the pathophysiology of bipolar disorder.19

Symptoms and Diagnostic Criteria

Symptoms of mania or hypomania include an increased level of goal-directed activity, decreased need for sleep, talkativeness, racing thoughts, and grandiose thinking. Manic episodes may or may not include psychotic features such as hallucinations or delusions; however, the estimated lifetime prevalence of manic episodes with psychosis is between 56% and 74% in BDI.20 The diagnostic criteria for a manic episode of bipolar disorder are listed in Table 1. An individual must have at least one manic episode in their lifetime to qualify for...
a diagnosis of BDI. Hypomania is characterized by the same symptoms and lasts at least 4 consecutive days but does not cause significant impairment socially or occupationally and does not require hospitalization. A diagnosis of BDII requires at least one hypomanic episode and at least one major depressive episode in a person’s lifetime. The diagnostic criteria for a major depressive episode of bipolar disorder are listed in Table 2. These criteria are exactly the same as what is required for a diagnosis of major depressive disorder (MDD), but in MDD there are no episodes of mania or hypomania present in the patient’s lifetime.

Patients with bipolar disorder may also display mixed features, which is defined as the presence of at least 3 mood symptoms that do not overlap with the current mood episode. For example, a patient with depression with mixed features will meet the full criteria for a depressive episode but will also have at least 3 symptoms of mania present concurrently. Another specifier that can be applied to the diagnosis of bipolar disorder is rapid cycling, which is defined as having at least 4 distinct mood episodes during the span of a year. Rapid cycling occurs in up to one-third of patients with BDI and places patients at an increased risk for mood recurrence, necessitating closer monitoring and often more complex treatment regimens.

Although mania and hypomania are known as the distinguishing features of bipolar disorder, depression is often the more predominant and debilitating feature for patients, with up to two-thirds of their life spent in a depressive episode. Patients are also more likely to present for treatment in a depressive episode but will also have at least 3 symptoms of mania present concurrently. Another specifier that can be applied to the diagnosis of bipolar disorder is rapid cycling, which is defined as having at least 4 distinct mood episodes during the span of a year. Rapid cycling occurs in up to one-third of patients with BDI and places patients at an increased risk for mood recurrence, necessitating closer monitoring and often more complex treatment regimens.

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Challenges in the Treatment of Bipolar Disorder

Pharmacotherapy is the cornerstone of treatment; however, on average, 40% to 50% of patients with bipolar disorder are at least partially nonadherent to their medication regimens and younger patients may be particularly vulnerable to nonadherence. Poor adherence is a key challenge in the treatment of bipolar disorder and associated with several negative outcomes including longer time to recovery, longer and more frequent hospitalizations, more frequent emergency department visits, greater risk for substance use disorders and suicide, and greater psychosocial impairment.

Another major challenge in the treatment of bipolar disorder is tolerability with long-term medication use. Antipsychotic medications may cause weight gain, metabolic adverse effects (AEs), sedation, prolactin elevation, and extrapyramidal symptoms (EPS) such as tardive dyskinesia. Mood stabilizers such as lithium and divalproex may also cause weight gain, sedation, and tremors, among other AEs. Tolerability concerns may further contribute to poor medication adherence. A study of patient preferences in treatment for bipolar depression found that weight gain, risk of sedation, and risk of becoming manic were the 3 most important attributes that patients considered in their treatment. In a national internet-based study in the United States, patients with bipolar disorder who had a greater AE burden were less likely to be adherent to their medication. Nonadherent patients had higher total AE burden ratings and scored higher on nearly all the subscale scores of the LUNSERS including EPS, autonomic AEs, psychic AEs (eg, difficulty concentrating, lack of emotions), and hormonal AEs (eg, swollen or tender chest, changes in sex drive). Therefore, it is important for pharmacists to ask patients about AEs when assessing for medication adherence concerns.

Current and Emerging Treatment Options

Overall, the main goals of treatment in bipolar disorder include achieving remission from the acute mood episode, minimizing residual mood symptoms, preventing relapse, reducing the risk of suicide, and improving functional outcomes such as quality of life. Psychosocial interventions and psychoeducation are important for the effective management of bipolar disorder, particularly in the treatment of acute depressive episodes and prevention of mood relapse during the maintenance treatment phase. Psychoeducation may also be helpful in promoting medication adherence. When selecting a
<table>
<thead>
<tr>
<th>Medication</th>
<th>Mania or mixed features</th>
<th>Depression</th>
<th>Maintenance</th>
<th>Clinical pearls/counseling points</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimanic agent</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lithium (Lithobid)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Anti-suicidal effects, blood level monitoring required, maintain adequate hydration, signs of toxicity include N/V/D, confusion, tremors</td>
<td>Hypothyroidism, renal toxicity, tremors, weight gain, polyuria, polydipsia, teratogenic effects</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Carbamazepine (Carbatrol, Epitol, Eque, Tegretol)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Significant drug interactions (CYP inducer) including oral contraceptives, blood level monitoring required</td>
<td>Rash (including SJS), hepatotoxicity, agranulocytosis, teratogenic effects</td>
</tr>
<tr>
<td>Divalproex (Depakote)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Helpful for mixed features and rapid cycling, blood level monitoring required, can use loading dose for mania</td>
<td>GI effects, sedation, weight gain, hepatotoxicity, thrombocytopenia, teratogenic effects</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>More effective for preventing and treating depression, drug interaction with oral contraceptives, titrate to avoid SJS, drug interaction with divalproex: increases lamotrigine blood levels and risk of SJS</td>
<td>Nausea, rash (including SJS)</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Long half-life</td>
<td>Lower metabolic risk, akathisia</td>
</tr>
<tr>
<td>Aripiprazole once-monthly injection (LAI) (Abilify Maintena)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Must overlap with oral medication for first 2 weeks</td>
<td>Lower metabolic risk, akathisia</td>
</tr>
<tr>
<td>Asenapine (Saphris)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Requires sublingual administration; do not eat or drink for 10 minutes after administration</td>
<td>Lower metabolic risk, dysgeusia</td>
</tr>
<tr>
<td>Cariprazine (Vraylar)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Long half-life</td>
<td>Lower metabolic risk, akathisia</td>
</tr>
<tr>
<td>Chlorpromazine (Thorazine)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>May induce depression</td>
<td>Sedation, orthostasis, anticholinergic, EPS</td>
</tr>
<tr>
<td>Lumateperone (Caplyta)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Avoid with CYP3A4 inducers or inhibitors</td>
<td>Lower metabolic risk, sedation, dizziness, nausea</td>
</tr>
<tr>
<td>Lurasidone (Latuda)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Should be ingested with at least 350 calories; avoid with strong CYP3A4 inducers or inhibitors</td>
<td>Lower metabolic risk, akathisia, sedation, dizziness, nausea</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>May work more rapidly; smoking may reduce blood levels due to CYP 1A2 induction</td>
<td>High risk for weight gain and metabolic effects, drowsiness</td>
</tr>
<tr>
<td>Olanzapine/fluoxetine (Symbyax)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Fluoxetine may induce mania</td>
<td>High risk for weight gain and metabolic effects, drowsiness</td>
</tr>
</tbody>
</table>
medication treatment, the clinician needs to consider not only the evidence base supporting its use, but also the patient’s preference, comorbid medical and psychiatric conditions, previous response to treatment, including a history of AEs, and tolerability or safety concerns. A summary of all Food and Drug Administration (FDA)-approved treatment options for BDI is provided in TABLE 3.

Several evidence-based guidelines are available to guide clinicians in the treatment of BDI. Recommendations from some of these guidelines are summarized in TABLE 4. The Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) guideline lists their recommendations in hierarchical order, with options listed in order of preference based on efficacy and safety/tolerability, while the International College of Neuro-Psychopharmacology (CINP) 2017 guideline lists their recommendations in alphabetical order. The British Association for Psychopharmacology also list their rankings in a hierarchy, although theirs is based strictly on evidence for effectiveness.

### Treatment Considerations

#### Current Treatment Options for Acute Management

While there is no true pharmacologic category of “mood stabilizers,” medications with known mood-stabilizing properties include lithium, second-generation antipsychotics (SGAs), and the anticonvulsants divalproex, lamotrigine, and carbamazepine. Medications with established efficacy in the treatment of acute mania include several of the SGAs, lithium, divalproex, and carbamazepine. There is some evidence that lithium or divalproex may be superior to SGAs in terms of reducing manic symptoms faster, and the combination of lithium or divalproex plus an SGA appears to be more effective than monotherapy with either medication. There are fewer evidence-based treatment options available for acute depressive episodes in bipolar disorder. Quetiapine, lurasidone, lithium, and lamotrigine are recommended as first-line options in most guidelines, with the combination medication olanzapine/fluoxetine relegated to second-line, mostly due to tolerability concerns. Cariprazine was also recently approved for the treatment of acute depressive episodes of BDI, and is included as a second-line treatment option in the CANMAT and ISBD guideline. Patients in acute depressive episodes may experience more tolerability issues with medication than they do during a manic episode; therefore, slow and careful titration of their medication is recommended.

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**TABLE 3. FDA-APPROVED TREATMENT OPTIONS FOR BIPOLAR I DISORDER**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Olanzapine/sumidorphan (Lybalvi)</th>
<th>Quetiapine (Seroquel)</th>
<th>Risperidone (Risperdal)</th>
<th>Risperidone microspheres (LAI) (Risperdal Consta)</th>
<th>Ziprasidone (Geodon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraindicated in patients taking opioids, may precipitate withdrawal</td>
<td>Somnolence, dry mouth, may have less risk of long-term weight gain than olanzapine monotherapy, unclear effect on glucose/lipids</td>
<td>Equally effective in preventing mania and depression; extended-release formulation available</td>
<td>Monitor for menstrual irregularities, gynecomastia</td>
<td>Administered every 2 weeks, must overlap with oral medications for first 3 weeks</td>
<td>Should be ingested with at least 500 calories</td>
</tr>
</tbody>
</table>

CYP, cytochrome P450; EPS, extrapyramidal symptoms; GI, gastrointestinal; LAI, long-acting injectable; N/V/D, nausea, vomiting, diarrhea; SJS, Stevens-Johnson syndrome.

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**STAR**

Which patients with BDI might be appropriate candidates for antidepressant therapy and what should be monitored in patients with BDI who are started on an antidepressant?
The use of adjunctive antidepressants is also a second-line option according to the CANMAT and ISBD. However, most guidelines recommend that they should only be used in combination with a medication that will reduce the risk of mania, such as lithium, divalproex, or an SGA. Antidepressants have shown only small benefit in clinical studies of bipolar depression and carry the risk of inducing mania, particularly in patients with BD1, depression with mixed features, or a history of rapid cycling. Tricyclic antidepressants and serotonin and norepinephrine reuptake inhibitors may have more risk for treatment-emergent affective switch than other antidepressants. Furthermore, patients treated with an antidepressant who experience an increase in agitation, dysphoria, restlessness, irritability, anger, insomnia, behavioral disinhibition, or mixed features may be at an increased risk for suicide.

Current Treatment Options for Maintenance

Most patients will require long-term, sometimes lifelong, therapy to prevent mood episode recurrence. Lithium, lamotrigine, valproate, and several of the SGAs have established efficacy for the maintenance treatment of BD1 although some may have more evidence for preventing recurrence of mania than depression and vice versa. Generally, whichever medication was found to be effective during the acute mood episode should be continued. Some medications, such as antidepressants or antipsychotics, may be tapered off after 6 to 12 months if there are tolerability concerns; however, the combination of an SGA plus a mood stabilizer has demonstrated reduced risk of mood recurrence compared with a mood stabilizer alone. Considerations when selecting a maintenance treatment include response to previous treatments, family history of treatment response, comorbid conditions, the polarity (mania or depression) of the most recent mood episode, and the predominant polarity of the patient (whether they tend to have more manic or more depressive episodes).

Lithium is often considered a “gold standard” for maintenance treatment of bipolar disorder due to its efficacy in preventing both manic and depressive episodes, and its well-established anti-suicide effect. Lithium used as monotherapy or in combination with valproate was also found to be superior to valproate monotherapy in preventing mood relapse for up to 2 years. However, lithium is associated with several potential long-term AEs, including hypothyroidism, hyperparathyroidism, kidney dysfunction, and tremors. Both lithium and valproate require frequent monitoring (every 3-6 months, or more often as clinically indicated) of serum levels. For lithium, the established target range is 0.8-1.2 mEq/L for acute mood episodes (or 0.4-0.8 mEq/L in older adults) and 0.6-1 mEq/L for maintenance treatment. The target serum level for valproate formulations is 50-100 mcg/mL, with some evidence that higher levels may be needed for acute antimanic efficacy. For valproate, a weight-based loading dose of 30 mg/kg/day may be used in acute mania. Lamotrigine is generally well tolerated by patients but is not recommended in those with frequent manic episodes, as it is mostly effective in preventing depressive episodes.

Antipsychotics have been increasingly studied for maintenance treatment of BD1, including long-acting injectable (LAI) antipsychotics. The use of LAI medications may be beneficial in optimizing patient adherence. In a nationwide cohort study of 18,018 patients with bipolar disorder who were followed for a mean of 7.2 years after hospitalization, patients treated with LAIs had significantly better outcomes when compared with the oral formulation of the same antipsychotics. These included a lower risk of psychiatric rehospitalization (HR, 0.70; 95% CI, 0.55-0.90) and a lower risk of all-cause hospitalization (HR, 0.70; 95% CI, 0.57-0.86). There are currently 2 FDA-approved LAI antipsychotics indicated for the maintenance treatment of bipolar I disorder: risperidone long-acting injection (RLAI) and aripiprazole once monthly (AOM) injection. RLAI is administered once every 2 weeks and can be given as monotherapy or adjunctively with lithium or valproate. It requires continued administration of oral antipsychotic medication for at least the first 3 weeks of therapy to achieve optimal blood levels. Aripiprazole is indicated as monotherapy and has the advantage of monthly administration. Oral antipsychotics should be continued for at least the first 14 days with AOM. While additional LAI formulations of risperidone and aripiprazole are commercially available, as well as formulations of other antipsychotics (eg, olanzapine, paliperidone), these have not been extensively studied in bipolar disorder.

A major concern with the use of antipsychotics is the risk for weight gain and metabolic AEs. Clozapine and olanzapine are associated with the highest risk of metabolic syndrome, hyperglycemia, type 2 diabetes, and dyslipidemia, followed by quetiapine and risperidone, and less often with aripiprazole, ziprasidone, asenapine, and lurasidone. Monitoring of weight is recommended monthly for the first 3 months and every 3 months thereafter while blood pressure, fasting glucose, and lipids should be evaluated at 3 and 6 months, then yearly thereafter. Lithium and divalproex have also been associated with...
significant weight gain while carbamazepine and lamotrigine appear to have less risk.6

**STAR**

What advantages do recently approved and emerging treatments offer patients with BDI?

### Novel and Emerging Treatment Options

#### Olanzapine/Samidorphan

Recently, a combination of olanzapine and the opioid antagonist samidorphan has been studied in an effort to minimize weight gain with olanzapine. In the 24-week randomized, double-blind ENLIGHTEN-2 study of 561 adult patients with schizophrenia who were randomized to treatment with either olanzapine/samidorphan or olanzapine alone, the percent weight change from baseline was lower in the olanzapine/samidorphan group than the olanzapine group (4.21% and 6.59%, respectively). Additionally, significantly fewer patients in the combination group had weight gain 10% or more of their baseline bodyweight (17.8% compared with 29.8%; odds ratio, 0.50) or 7% or more of their bodyweight (27.5% vs 42.7%; odds ratio, 0.50). Changes in waist circumference were also about half as much with the combination versus monotherapy (2.36 cm vs 4.47 cm). Efficacy of the combination was similar to olanzapine monotherapy with slightly more somnolence (21.2% vs 18.1%) and dry mouth (12.8% vs 8.0%). Interestingly, weight gain was similar between the 2 groups for the first 6 weeks of the trial, with a separation between the 2 groups occurring beyond that point.44 In this study and a previous phase 2 trial, weight gain with olanzapine/samidorphan occurred mostly during the first 4 to 6 weeks, but then stabilized.44,45

Based on the clinical trials in the schizophrenia population, olanzapine/samidorphan was granted FDA approval for the treatment of schizophrenia and BDI for the acute treatment of mixed or manic episodes either as monotherapy or in combination with lithium or valproate, or as maintenance monotherapy treatment.28 Additionally, results from the 52-week ENLIGHTEN-2 extension study were recently published. A total of 265 patients enrolled in the trial, with 63.0% completing the 52 weeks. The mean change in weight from enrollment in the open-label phase to study end point was −0.03 kg and the mean change in waist circumference was −0.35 cm, indicating a sustained response in mitigating weight gain with olanzapine/samidorphan. Changes in other metabolic parameters (eg, lipids, glucose) were generally minimal and transient; however, 11.0% of patients experienced a sustained shift in HbA1c from lower than 5.7% to greater than or equal to 5.7%.46

The prescribing information for olanzapine/samidorphan includes a warning regarding the possibility of precipitation of opioid withdrawal. It should only be initiated after an opioid-free period of at least 7 days for patients taking short-acting opioids or 14 days for longer acting opioids. Similarly, patients with a history of chronic opioid use should be counseled about the potential for decreased opioid tolerance if olanzapine/samidorphan is interrupted or discontinued, increasing the risk of opioid overdose if the use of opioids is resumed.28

#### Lumateperone

Another SGA, lumateperone, which was previously approved for schizophrenia, was recently approved by the FDA for the treatment of bipolar depression in BDI and BDII in adults (either as monotherapy or adjunctively with lithium or valproate).30 Similar to other SGAs, lumateperone is thought to work via antagonism at serotonin 5HT2A and partial agonism/antagonism at dopamine type 2 (D2) receptors. It has additional activity at D1 receptors, which plays a role in glutamate functioning, and acts as a serotonin reuptake inhibitor, but it is unclear how these effects contribute to its clinical efficacy and the FDA classifies it simply as an atypical antipsychotic.30,47

In a phase 3 randomized, double-blind, placebo-controlled study of 377 patients experiencing a major depressive episode of BDI or BDII, patients receiving lumateperone 42 mg/day for 6 weeks had a significantly greater reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) scores compared with placebo (least squares mean difference of −4.6 points; effect size, −0.56). Somnolence (8.5%) and nausea (6.4%) were the most common AEs occurring more frequently than placebo (1.1% and 2.1%, respectively).47 Results from a second phase 3 trial have not yet been published. Lumateperone could offer another well-tolerated option for bipolar depression.

#### Non-racemic amisulpride (SEP-4199)

Another investigational drug currently being studied for bipolar depression is SEP-4199, a derivative of the antipsychotic amisulpride with high affinity for 5-HT7 receptors relative to D2 receptors. In a 6-week randomized, double-blind, placebo-controlled phase 2 study of 344 patients experiencing a major depressive episode of BDI, the primary analysis of 289 patients enrolled in Europe or the United States...
failed to show a statistically significant effect compared with placebo. Patients in this cohort who were treated with 200 mg or 400 mg of SEP-4199 showed numerically, but not statistically significant, improvement in MADRS scores when compared with placebo (−19.5 in the 200-mg group, −19.3 in the 400-mg group, and −16.2 in the placebo group; \( P = .054 \) for both doses compared with placebo). A secondary analysis of the entire study population, including an additional 49 Japanese patients, was found to be significant, with a least squares mean difference of −3.7 points on the MADRS for the 200-mg dose (95% CI, −6.7, −0.7; \( P = .016 \)) and −3.4 points for the 400-mg dose (95% CI, −6.3, −0.5; \( P = .024 \)). The most commonly reported AEs were QT prolongation (in the 400-mg group), somnolence, constipation, galactorrhea, nausea, akathisia, dizziness, hypomania, and diarrhea.48

**Esketamine**

Other medications currently in development for the treatment of bipolar depression mainly target glutamate and gamma-aminobutyric acid (GABA), including N-methyl-D-aspartate (NMDA)-type glutamate receptor antagonists and GABA \(_A\) receptor modulators.36 Positive results were recently reported from a phase 2 study of esketamine dry powder for inhalation in patients with treatment-resistant bipolar depression. This trial was a randomized, double-blind, placebo-controlled study of 88 adult patients who had demonstrated inadequate response to at least 2 previous bipolar depression treatments. Patients who were randomized to receive adjunctive treatment with 24 mg, 36 mg, or 48 mg of esketamine twice weekly showed a significantly greater, dose-dependent reduction in the MADRS when compared with placebo after 2 weeks of

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**TABLE 4. BIPOLAR DISORDER TREATMENT GUIDELINES\(^{6,31,32}\)**

<table>
<thead>
<tr>
<th><strong>Acute mania</strong></th>
<th><strong>International College of Neuro-Psychopharmacology (CINP) 2017 guidelines</strong></th>
<th><strong>British Association for Psychopharmacology 2016 recommendations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1st-line monotherapy: lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone (&gt;6 mg), risperidone, cariprazine</td>
<td>1st line: aripiprazole, asenapine, cariprazine, paliperidone, quetiapine, risperidone, valproate</td>
<td>Antipsychotics, valproate, lithium</td>
</tr>
<tr>
<td>1st-line combination: SGA (quetiapine, aripiprazole, risperidone, asenapine) + lithium OR divalproex</td>
<td>2nd line: carbamazepine, haloperidol, lithium, olanzapine</td>
<td></td>
</tr>
<tr>
<td>2nd line: olanzapine(^<em>), carbamazepine(^</em>), olanzapine + lithium OR divalproex(^<em>), lithium + divalproex, ziprasidone(^</em>), haloperidol(^*), ECT</td>
<td></td>
<td></td>
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<table>
<thead>
<tr>
<th><strong>Acute depressive episodes</strong></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1st line: quetiapine, lurasidone + lithium OR divalproex, lithium, lamotrigine, lurasidone, lamotrigine (adjunctive)</td>
<td>1st line: quetiapine, lurasidone</td>
<td>Lurasidone, lamotrigine (adjunctive), quetiapine, olanzapine, olanzapine + fluoxetine, antidepressants</td>
</tr>
<tr>
<td>2nd line: divalproex, SSRIs/bupropion (adjunctive), ECT, cariprazine, olanzapine/fluoxetine</td>
<td>2nd line: fluoxetine, olanzapine, olanzapine/fluoxetine</td>
<td></td>
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<tr>
<th><strong>Maintenance</strong></th>
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</thead>
<tbody>
<tr>
<td>1st line: lithium, quetiapine, divalproex, lamotrigine, asenapine, quetiapine + lithium OR divalproex, aripiprazole + lithium OR divalproex, aripiprazole, aripiprazole monohydrate LAI</td>
<td>1st line: aripiprazole, risperidone LAI</td>
<td>Lithium (preventing mania, depression, suicide), antipsychotics, valproate (mainly preventing mania), lamotrigine (preventing depression)</td>
</tr>
<tr>
<td>2nd line: olanzapine(^*), risperidone LAI, risperidone LAI (adjunctive), carbamazepine, paliperidone (&gt;6 mg), lurasidone + lithium OR divalproex, ziprasidone + lithium OR divalproex</td>
<td>2nd line: index episode mania or depression: quetiapine, lithium, lamotrigine; index episode mania: olanzapine, paliperidone; index episode depression: fluoxetine</td>
<td></td>
</tr>
</tbody>
</table>

ECT, electroconvulsive therapy; LAI, long-acting injectable; SGA, second-generation antipsychotic; SSRI, selective serotonin reuptake inhibitor.

\(^*\)Considered 2nd line due to safety/tolerability concerns.
treatment (placebo-subtracted difference of −5.9, \( P = .009 \) in the 24-mg group; −6.7, \( P = .004 \) in the 36-mg group; −8.2, \( P < .001 \) in the 48-mg group). 49

Zuranolone
Preliminary results from a bipolar depression study of zuranolone, a positive allosteric modulator of GABA\(_A\) receptors, have been recently reported. In an open-label study, 35 adults experiencing a major depressive episode of BDI or BDII were treated with 30 mg of zuranolone daily for 2 weeks. Zuranolone demonstrated a mean decrease of 15.5 points in the MADRS at day 15 (\( P < .001 \)) and this response was maintained through day 42, with a mean decrease of 16.4 points compared with baseline at day 42. The most common AEs reported were somnolence, headache, diarrhea, and sedation. 50

NRX-101
An additional medication currently in development is NRX-101, a fixed-dose combination of the NMDA receptor modulator D-cycloserine and the SGA lurasidone, which received breakthrough therapy designation from the FDA for the management of severe depression and acute suicidality in bipolar disorder after initial stabilization with ketamine. Preliminary phase 2 data indicate that patients who were treated for 6 weeks with NRX-101 demonstrated lower levels of depression as measured by the MADRS compared with those who received lurasidone monotherapy, with no patients in the NRX-101 group demonstrating relapse (\( n = 12 \)), compared with 2 patients treated with lurasidone (\( n = 5 \)). 51,52

Role of the Pharmacist
Pharmacists can contribute to improved outcomes in bipolar disorder in a variety of ways, including counseling patients on the safe and effective use of medications and lifestyle modifications, comprehensively reviewing medication regimens to assess for potential efficacy and safety drug-related problems, and improving medication adherence. Furthermore, pharmacists can serve as providers or coordinators of care.

Counseling
Educating patients about how to properly take their medication, expected duration of treatment, and possible AEs are standard counseling points for any medication, but a key message in educating patients with bipolar disorder is that they should not stop taking medications once their acute depressive or manic symptoms have subsided. Many patients will consider stopping medications at this time, so education about the importance of continued medication to prevent mood episode recurrence is essential. Focusing on the benefits of the medication in treating their specific symptoms such as irritability or sleep difficulties, and potential benefits such as reducing the need for hospitalization or legal or financial consequences of behaviors seen during manic episodes (eg, excess spending or impulsivity) may better help patients understand the importance of medication adherence. The importance of blood level monitoring and signs and symptoms of toxicity with medications such as lithium, carbamazepine, and valproate should be discussed with the patients as well. 53 As many therapies for bipolar disorder can cause weight gain, providing counseling on lifestyle modifications such as diet and exercise or referring to a nutritionist may also be useful. Important patient counseling points for pharmacists are included in TABLE 36,12,28,30 and TABLE 56,53

Assessing Efficacy and Safety
When comprehensively reviewing a patient’s medication regimen for efficacy and safety, it is essential to have a complete and accurate list of medications. To evaluate the efficacy of the regimen, pharmacists should screen patients for signs and symptoms of mania or hypomania. This is particularly important for patients taking medications that may precipitate mania, such as antidepressants, psycho-stimulants, or dopamine agonists. 6 Depression and suicide screening is also important in this patient population and the use of screening tools such as the Patient Health Questionnaire-9 (PHQ-9) and PHQ-2 have been successfully implemented in the community pharmacy setting. 54 Additionally, when performing a medication review, pharmacists should ask if patients are experiencing somnolence, weight gain, tremors, EPS, or signs and symptoms of hyperprolactinemia (menstrual changes, sexual AEs, and gynecomastia) to identify medication-related AEs. With EPS in particular, patients with bipolar disorder (particularly in the acute depressive phase) may be more vulnerable than patients with schizophrenia. 35

It is important for pharmacists to identify when patients’ symptoms are not controlled or if they are experiencing AEs or drug interactions and recommend possible treatment alternatives. To promote evidence-based recommendations, pharmacists must keep up with new and emerging medication options that may offer distinct advantages over older treatments.
Adherence
Pharmacists are in an ideal position to monitor medication adherence and assess for factors that may impact adherence, such as AEs and negative attitudes toward medication. They can also identify patients who may be at risk for nonadherence, including patients who are younger in age, or who have substance use disorder, comorbid anxiety disorders, or a low level of education or socioeconomic status. To address nonadherence, pharmacists should explore the reasons and provide evidence-based interventions such as recommending changes to medications to reduce the complexity of regimens and minimize AEs as well as employing motivational interviewing and brief psychoeducational interventions.6,24,56

One way to improve medication adherence is through the use of LAIs. Administering LAIs in a community pharmacy setting may increase access to these medications, particularly in rural areas, and may help decrease stigma compared with administration in a mental health clinic.57 The American Pharmacists Association published a report on community pharmacists’ role in improving access to injectable medications in 2017.58 Since that time, they have published several resources for providing medication administration services in the pharmacy setting.59 At the time of this publication, all but 2 states (New York and Rhode Island) and Washington, DC, allow for pharmacist administration of LAIs.60

Pharmacists as Providers or Coordinators of Care
Pharmacists may also serve as a provider through collaborative practice agreements or independently through their scope of practice as in the Veterans Health Administration or as a link to specialty care and social services.61,62 This is particularly important in the context of the COVID-19 pandemic, when patients have been faced with decreased access to mental health clinics and difficulties such as disruptions in employment, loss of housing, and food insecurity.63 Disasters such as the COVID-19 pandemic dispor-
portionately affect patients with mental illness such as bipolar disorder. The disruption in mental health service delivery increased risk of patient disengagement, medication nonadherence, and distress, which resulted in increased risk for decompensation. With these changes, community pharmacists increasingly need to be prepared to act as the potential first point of contact for patients in mental health crises. Mental Health First Aid training is available through the National Council for Mental Wellbeing to help individuals identify risk factors and warning signs of mental health emergencies and how to respond.

Pharmacists have demonstrated positive outcomes for patients with bipolar disorder, including improved attitudes toward medication, medication adherence, quality of life, reduced anticholinergic medication burden, and decreased rates of hospitalization. In a study by Salazar-Ospina, et al, a specially trained pharmacist made weekly telephone calls to patients to assess for changes in symptoms, educate patients on the recognition and management of emerging symptoms, explain how to properly take medications, emphasize the need for continued adherence, and promote healthy lifestyle and eating habits. They then communicated with the medical team, patient, and family or caregiver to make any necessary interventions to promptly resolve medication-related problems identified during the counseling sessions. Over a 1-year period, patients in the usual care group had a 9-fold higher risk of hospital admission (HR, 9.03; 95% CI, 1.1-75.4) and were more than 3 times as likely to require emergency services (HR, 3.38; 95% CI, 1.1-10.5) than patients in the pharmaceutical care group.

Finally, it is important for pharmacists to keep up with new and emerging medication options that may offer distinct advantages over older treatments to be able to recommend them for patients with BDI. Several promising medications are in development, particularly for the treatment of bipolar depression, and recently approved medications such as olanzapine/samidorphan and lumateperone may offer distinct advantages in tolerability over other current treatment options.

**Conclusion**

Patients with BDI experience acute episodes of depression and mania, often requiring complex combinations of medication treatment to achieve remission from mood symptoms. Additionally, most patients will require lifelong maintenance treatment that may contribute to significant AEs such as somnolence, weight gain, metabolic syndrome, EPS, and liver or kidney dysfunction. These AEs can often lead to nonadherence with medications, resulting in poor treatment outcomes. New and emerging treatment options may offer advantages over current treatments, particularly in respect to efficacy for the treatment of depression and tolerability for long-term maintenance. Pharmacists are in an ideal position to monitor for AEs and adherence issues and recommend potential treatment alternatives that may best fit the needs of their patients.

**REFERENCES**


### ADDITIONAL RESOURCES

<table>
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<tr>
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<tr>
<td>National Institute of Mental Health</td>
<td><a href="www.nimh.nih.gov/health/topics/bipolar-disorder">www.nimh.nih.gov/health/topics/bipolar-disorder</a></td>
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<td>National Alliance on Mental Illness</td>
<td><a href="www.nami.org/About-Mental-Illness/Mental-Health-Conditions/Bipolar-Disorder">www.nami.org/About-Mental-Illness/Mental-Health-Conditions/Bipolar-Disorder</a></td>
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<td>Depression and Bipolar Support Alliance</td>
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<tr>
<td>Mental Health First Aid Training</td>
<td><a href="www.mentalhealthfirstaid.org">www.mentalhealthfirstaid.org</a></td>
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<td>American Pharmacists Association</td>
<td><a href="https://pharmacist.com/Practice/Patient-Care-Services/Medication-Safety-Access/Medication-Administration">https://pharmacist.com/Practice/Patient-Care-Services/Medication-Safety-Access/Medication-Administration</a></td>
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<tr>
<td>Medication Administration resources</td>
<td><a href="https://pharmacist.com/Practice/Patient-Care-Services/Medication-Safety-Access/Medication-Administration">https://pharmacist.com/Practice/Patient-Care-Services/Medication-Safety-Access/Medication-Administration</a></td>
</tr>
</tbody>
</table>


37. Kishi T, Sakuma K, Okuya M, et al. Effects of a conventional mood stabilizer alone or in combination with second-generation antipsychotics on recurrence rate and discontinuation rate in


POSTTEST QUESTIONS

1. Which of the following is required for a diagnosis of bipolar I disorder (BDI)?
   A. At least one lifetime episode of depression
   B. At least one lifetime episode of mania
   C. Presence of mixed features
   D. Presence of rapid cycling

2. Which of the following neuroendocrine systems is thought to be involved in the pathophysiology of bipolar disorder?
   A. Hypothalamic-pituitary-adrenal axis
   B. Hypothalamic-pituitary-thyroid axis
   C. Hypothalamic-pituitary-gonadal axis
   D. Hypothalamic-neurohypophysial system

3. Which of the following symptoms is required for a diagnosis of mania in bipolar disorder?
   A. Rapid or pressured speech
   B. Racing thoughts
   C. Increased energy or activity
   D. Hallucinations

4. Which of the following is considered a first-line option for the treatment of an acute depressive episode of BDI according to clinical practice guidelines?
   A. Divalproex
   B. Carbamazepine
   C. Lurasidone
   D. Cariprazine

5. A 23-year-old male patient with a diagnosis of BDI was started on a combination of lithium and quetiapine during his recent inpatient hospitalization. He has had several episodes of mania over the past 5 years but has never had an episode of depression in his lifetime. Since being discharged from the hospital 1 week ago, he complains of increased appetite and a 15-pound weight gain. He would like to change his medication to minimize the risk of further weight gain. Which treatment modification would be the most appropriate for this patient?
   A. Change the lithium to divalproex.
   B. Change the quetiapine to ziprasidone.
   C. Change the lithium to lamotrigine.
   D. Change the quetiapine to olanzapine.

6. Which of the following is a potential advantage to using lumateperone over other currently available treatment options for bipolar disorder?
   A. Greater efficacy for manic episodes
   B. Minimal drug interactions
   C. Efficacy in treatment-resistant patients
   D. Low risk for adverse effects

7. Which of the following outcomes has been demonstrated by pharmacist involvement in the care of patients with bipolar disorder?
   A. Improved medication adherence
   B. Reduced depressive symptoms
   C. Decreased risk for drug interactions
   D. Improved cognitive functioning

Use the following case to answer questions 8 and 9:
A 47-year-old patient comes into your pharmacy with a new prescription for olanzapine/samidorphan for the management of BDI. His current medications include lisinopril for hypertension, metformin for diabetes, albuterol inhaler as needed for exercise-induced asthma, and oxycodone/acetaminophen as needed for back pain related to a recent injury.

8. Which of this patient’s medications would you recommend changing to avoid a potential drug interaction with olanzapine/samidorphan?
   A. Lisinopril
   B. Metformin
   C. Albuterol
   D. Oxycodone/acetaminophen

9. The patient is concerned that the medication will cause him to gain weight and affect his blood glucose. How would you counsel this patient?
   A. Weight gain is possible, but it will not affect his blood glucose levels.
   B. Weight gain occurs mostly in the first 6 weeks of treatment, then stabilizes over time.
   C. Weight gain and blood glucose changes are unlikely to occur with this medication.
   D. Weight gain is unlikely, but blood glucose changes are common with this medication.
10. Which of the following patients with bipolar disorder would be most at risk for nonadherence to their medications?
   A. 23-year-old patient with alcohol use disorder
   B. 57-year-old patient on multiple medications
   C. 35-year-old patient with a college-level education
   D. 47-year-old patient with attention-deficit/hyperactivity disorder

INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.

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

Click “Proceed,” then complete the online pretest.

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

Complete the online posttest and activity evaluation form.

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

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

NOTE: Your CE credit will be automatically uploaded to CPE Monitor.

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SYSTEM REQUIREMENTS FOR COMPLETION:
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New Developments in the Treatment Approaches for Hepatorenal Syndrome Acute Kidney Injury (HRS AKI): Key Considerations for Pharmacists

**EDUCATIONAL OBJECTIVES**

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

- Differentiate the pathological characteristics, prevalence, risk factors, and burden associated with hepatorenal syndrome acute kidney injury (HRS AKI) and non-acute kidney injury (HRS NAKI)
- Explain the updated diagnostic criteria for HRS and the role of current and emerging treatment options, including their efficacy and safety profiles
- Determine the role of health-system pharmacists in the management of HRS AKI, including collaborating with the multidisciplinary team to ensure effective transitions of care and recommending evidence-based treatment protocols to optimize outcomes

**TARGET AUDIENCE:** Health-system pharmacists

**ACTIVITY TYPE:** Application

**RELEASE DATE:** January 20, 2022

**EXPIRATION DATE:** March 15, 2023

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

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

**Introduction**

Hepatorenal syndrome (HRS), a complication of advanced cirrhosis, is characterized by renal impairment secondary to hemodynamic alterations and inflammation leading to reduced renal perfusion.\(^1\) It is estimated that at least 633,000 adults in the United States have cirrhosis, with an annual estimate of 9000 to 35,000 of these cases progressing to HRS and requiring hospital admission.\(^2,3\) The prevalence of acute kidney injury (AKI), a precursor to HRS, is common among those hospitalized with decompensated cirrhosis, and incidence rates range from 27% to 53%.\(^4\) Despite available therapies, the rate of HRS reversal, defined as an improvement of serum creatinine (SCr) back to baseline values, is just 43% and in-hospital mortality rates approach 40%.\(^5,6\) Given the high mortality rate, there is an urgent need to increase identification of patients with renal impairment or AKI at risk for progression to HRS. Pharmacists on the care team must be involved in the rapid identification of these patients to support early intervention efforts and facilitate management or evaluate treatment decisions for these patients, including transplantation.

**Pathophysiology**

The pathophysiology of HRS is characterized by circulatory dysfunction and an elevation in inflammatory mediators (FIGURE 1).\(^7\) As cirrhosis advances, an increase in intrahepatic vascular resistance leads to portal hypertension. In response, endogenous vasodilators are released to address this portal hypertension, including nitric oxide, carbon monoxide, prostacyclins, and endocannabinoids. While these vasodilators produce splanchnic vasodilation, they also result in systemic vasodilation causing a reduction in effective arterial...
blood volume and overall systemic vascular resistance. As a compensatory mechanism to avoid systemic hypotension, the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), and arginine vasopressin (AVP) are all activated to produce sodium retention (to increase circulating volume) and systemic vasoconstriction, including vasoconstriction of renal blood vessels. These compensatory hormonal pathways are necessary to maintain systemic blood pressure but have the net detrimental effects of worsening fluid retention and ascites, causing dilutional hyponatremia, and reducing renal blood flow that can result in AKI and HRS.7

Newer data suggest that elevations in a variety of inflammatory mediators may play a role in the pathophysiology of HRS.7,8 Additionally, bacterial translocation from the gut, other bacterial infections, and even elevated blood levels of intracellular components from damaged hepatocytes may trigger a pro-inflammatory cytokine and chemokine response that results in arterial vasodilation and further circulatory dysfunction.8

**Diagnosis and Classification**

The definition of both AKI in cirrhosis and HRS has been updated several times, with the most recent update by the International Club of Ascites (ICA) in 2015.9 Historically, acute renal failure in cirrhosis was defined as a SCr increase of 50% or greater from baseline to a value above 1.5 mg/dL.10 Additionally, HRS was categorized as 2 phenotypes: HRS-1, an acute worsening of renal function, and HRS-2, a gradual worsening in renal function. In order to meet the criteria for HRS-1, SCr needed to double within 2 weeks to a level of 2.5 mg/dL or greater.

Since 2004, several new definitions of acute renal failure, now termed acute kidney injury (AKI), have been proposed.

---

**FIGURE 1. PATHOPHYSIOLOGY OF ACUTE KIDNEY INJURY AND HEPATORENAL SYNDROME**

AKI, acute kidney injury; AVP, arginine vasopressin; GI, gastrointestinal; HRS, hepatorenal syndrome; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

Adapted from Simonetto DA, et al. BMJ. 2020;370:m2687.
and validated in patients without cirrhosis, such as Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification; and Kidney Disease: Improving Global Outcomes (KDIGO) criteria for AKI. Unfortunately, patients with cirrhosis represent a unique patient group in which classifying AKI is problematic. For instance, muscle wasting and poor hepatic function seen in patients with cirrhosis lead to a reduced production of creatinine, thereby resulting in a falsely elevated creatinine clearance estimate. Additionally, urine output, a component of AKI definitions, is not a reliable metric of AKI in patients with cirrhosis. Due to substantial renal sodium retention, oliguria is common in patients with cirrhosis while often maintaining a normal glomerular filtration rate (GFR). Conversely, because the use of diuretics for ascites is common, urine output as a component of AKI definitions, is not a reliable marker. Additionally, the lack of a fixed SCr threshold for AKI criteria is important as some patients with very low baseline values would not meet the historical AKI criteria without having substantial impairment in renal function. This fact is particularly relevant because data in patients with cirrhosis have demonstrated that even small increases in SCr are associated with poor outcomes, and earlier treatment of AKI may be associated with a higher rate of renal recovery.

Because the definition of AKI in part requires a “baseline” SCr value for comparison (distinguishing AKI from chronic kidney disease), the ICA guidelines for AKI in cirrhosis also outline what value constitutes a baseline SCr value. A baseline value is defined as the most recent SCr value obtained within the previous 3 months. For hospitalized patients, if a pre-admission SCr value is not available, the SCr on admission should be considered a baseline.

In conjunction with the new ICA-AKI definition, the definition and classification of HRS was also updated. HRS-1 (rapid deterioration of renal function) has been renamed to HRS AKI. The primary change in HRS AKI compared with the previous HRS-1 criteria is the replacement of an absolute SCr value of 2.5 mg/dL or greater with the 2015 ICA-AKI criteria (Table 1). Renaming HRS-2 to HRS non-acute kidney injury (HRS NAKI) has also been proposed and is defined as meeting HRS criteria with an estimated GFR less than 60 mL/min/1.73m² but not meeting HRS AKI criteria. HRS NAKI can be further subdivided into HRS acute kidney disease (HRS AKD) and HRS chronic kidney disease (HRS CKD) based on the duration of renal impairment being less than 3 months or greater than 3 months, respectively.

A key component of the HRS AKI definition is to attempt to exclude renal structural or tubular damage (intrinsic AKI),

### Table 1. The 2015 ICA Diagnostic Criteria of AKI (ICA-AKI) and the Historical AKI Criteria in Cirrhosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>2015 ICA-AKI Definition</th>
<th>Historical AKI in Cirrhosis Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>SCr increase of ≥0.3 mg/dL OR ≥1.5- to 2-fold increase from baseline</td>
<td>SCr &gt;1.5 mg/dL and an increase of ≥50% from baseline</td>
</tr>
<tr>
<td>Stage 2</td>
<td>SCr increase of &gt;2- to 3-fold from baseline</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>SCr increase of &gt;3-fold from baseline OR SCr ≥4 mg/dL with an increase of ≥0.3 mg/dL from baseline OR initiation of renal replacement therapy</td>
<td></td>
</tr>
</tbody>
</table>


### Table 2. 2015 ICA Diagnostic Criteria of HRS AKI

- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI per ICA-AKI definition
- No improvement of SCr (≥0.3 mg/dL reduction) despite 2 consecutive days of diuretic withdrawal and albumin 1 g/kg/day (max 100 g/day)
- Absence of shock
- No current or recent use of nephrotoxic drugs
- No macroscopic signs of structural kidney disease, including no proteinuria (>500 mg/day), no microhematuria (>50 red blood cells per high power field), and normal renal ultrasound findings

which can include other etiologies of AKI, such as acute tubular necrosis (ATN). Differentiating HRS AKI from ATN is important as the treatment strategies are different. For example, albumin and vasoconstrictors are a hallmark component of HRS AKI therapy but have no role in ATN treatment. The fraction of excreted sodium (FENa) is commonly utilized in noncirrhotic patients to support the diagnosis of ATN; however, FENa is unreliable in patients with cirrhosis as it is virtually always low. Novel biomarkers of renal tubular injury, such as urinary neutrophil gelatinase-associated lipocalin (NGAL), may have a future role in distinguishing HRS AKI from ATN.

**Health Care Burden and Prognosis**

The health care burden, morbidity, and mortality of HRS is substantial. Among patients hospitalized with HRS in the United States, the average hospital stay cost exceeds $90,000, with a mean length of stay of about 30 days. Approximately 27% of patients will require hemodialysis during hospitalization. Recent observational data among tertiary care centers in the United States suggest that fewer than 20% of patients with HRS will have full recovery of renal function. In-hospital mortality rates are approximately 37%, with an additional 9% being discharged to hospice care. Furthermore, the 30-day readmission rate is 33%. Unfortunately, mortality rates in randomized controlled trials have remained consistent from 2002 to 2018, indicating that new treatment strategies during this time have not improved patient survival.

**Management of HRS AKI**

**Prevention of HRS AKI**

Prevention of HRS AKI is primarily focused on addressing precipitating factors that predispose patients to HRS AKI, including gastrointestinal bleeding, spontaneous bacterial peritonitis (SBP), and large-volume paracentesis (LVP).
In selected patients who are at high risk for variceal hemorrhage, nonselective β blockers (NSBBs), such as propranolol, may be considered. Controversy exists over whether the efficacy of NSBBs in preventing variceal hemorrhage may be offset by a detrimental effect on circulatory function, particularly in patients with ascites or advanced cirrhosis. Current guidelines suggest NSBBs be used with caution, dose reduced, or even temporarily discontinued in patients who have refractory ascites and a systolic blood pressure less than 90 mm Hg, SCr above 1.5 mg/dL, or hyponatremia (serum sodium <130 mEq/L). Among patients who develop SBP, defined as an ascitic fluid polymorphonuclear (PMN) count of 250 cells/mm³, the use of albumin reduces the risk of renal impairment and mortality.

In a landmark trial, 126 patients with cirrhosis and SBP were randomized to receive cefotaxime alone or cefotaxime plus 20% albumin (1.5 g/kg on day 1, then 1 g/kg on day 3). Despite nearly all patients having resolution of infection, in-hospital mortality was higher among those not receiving albumin (10% vs 29%; P = .01). Additionally, the development of renal impairment was more common in those who did not receive albumin (10% vs 33%; P = .002). An elevated baseline serum bilirubin (≥4 mg/dL) or SCr (≥1 mg/dL) was independently associated with the development of renal impairment. Arterial blood pressure was not different between the arms in the study; however, receipt of albumin was associated with lower plasma renin levels, a critical component of the pathophysiology of HRS AKI. Current guidelines support albumin 1.5 g/kg on day 1 then 1 g/kg on day 3 in patients with SBP and acknowledge that alternative dosing (such as 1 g/kg for 2 days) may also be appropriate.

In addition to albumin, antibiotics play an important role in SBP to prevent HRS AKI. In patients with confirmed SBP, a third-generation cephalosporin, such as ceftriaxone, is recommended as first-line empiric therapy for community-acquired SBP. In patients with recent health care exposure or sepsis and confirmed SBP, broad-spectrum antimicrobial coverage is warranted based on the prevalence of multidrug-resistant organisms and patient-specific factors. For primary or secondary SBP prophylaxis, norfloxacin or ciprofloxacin is recommended in selected patients.

LVP, defined as ascitic fluid removal exceeding 5 liters, is associated with post-paracentesis circulatory dysfunction (PPCD), a syndrome characterized by a decrease in effective blood volume leading to recurrent ascites, HRS, dilutional hyponatremia, and an increase in mortality. Albumin is recommended to decrease the risk of PPCD and its complications, including HRS, among patients receiving LVP. Although the optimal dose is not known, guidelines recommend 6 to 8 grams of 20% to 25% albumin for each liter of ascitic fluid removed. For example, if 6 liters of ascitic fluid are removed, an albumin dose of 36 to 48 grams is indicated. Although alternatives to albumin have been studied for LVP, such as dextran, gelatin, hydroxyethyl starch, and hypertonic saline, meta-analysis indicates that albumin is substantially more effective in reducing the risk of PPCD (OR, 0.39; 95% CI, 0.27-0.55), hyponatremia (OR, 0.58; 95% CI, 0.39-0.87), and death (OR, 0.64; 95% CI, 0.41-0.98).

**Treatment of AKI and HRS AKI**

The treatment of AKI in patients with cirrhosis can be divided into 3 steps: (1) clinical assessment, (2) risk factor management, and (3) response to albumin infusion (FIGURE 2). Clinical assessment involves identification of likely causes of AKI, such as dehydration, shock, or post-renal obstruction, based on patient presentation and diagnostic findings. Risk factor management includes discontinuation of nephrotoxic medications, withdrawal of diuretics, cessation of vasodilators (including NSBBs), identification and treatment of infection (if present), and volume replacement with 5% albumin or crystalloids if dehydration is suspected. In patients with stage 1A AKI with worsening renal function despite risk factor management or those with stage 1B, 2, or 3 AKI, volume expansion with 25% albumin for 2 days is recommended. If AKI does not resolve despite risk factor management and albumin, patients should be assessed for meeting the HRS AKI criteria. If HRS AKI criteria are met, vasoconstrictor therapy and albumin are indicated.

During the treatment of HRS AKI, the primary goal of therapy is to achieve a SCr less than 1.5 mg/dL or to return to within 0.3 mg/dL of baseline SCr. Treatment should continue for up to 14 days or until SCr returns to near-baseline values. In patients with no improvement (or an increase) in SCr by treatment day 4, vasoconstrictor and albumin therapy should be discontinued as continuing therapy is considered futile.

**Albumin**

A critical component of the pathophysiology of cirrhosis and HRS is that effective circulatory volume is diminished due to systemic vasodilation. In patients with decompenesated cirrhosis due to this vasodilation, administration of albumin can provide plasma expansion, improve systemic blood pressure, and blunt the deleterious compensatory increases of RAAS,
sympathetic tone, and antidiuretic hormone. In addition, albumin has other proposed mechanisms of benefit including being a common pathway for molecules, such as bilirubin, to be solubilized and transported to hepatocytes for elimination.16

In patients with cirrhosis who have AKI before the diagnosis of HRS AKI is made, diuretic withdrawal and 20% to 25% albumin (25% in the United States) is recommended at a dose of 1 g/kg/day (max 100 g) for 2 days.4 In patients with confirmed HRS AKI, albumin is recommended because in nearly all HRS AKI studies, patients were given supplemental albumin as background therapy; however, the majority of data do not support this practice, and data do not exist to confirm the optimal albumin dose for this indication.18 Just one small study of 21 patients (of which 16 had HRS-1) investigated the role of albumin in HRS-1; the use of albumin was associated with a higher likelihood of HRS response.17 Based primarily on historical precedence, albumin for HRS AKI treatment is typically dosed as 1 g/kg on day 1 (if not already received), then 20 to 40 g/day thereafter.8 It should be noted that the most recent American Association for the Study of Liver Diseases guidelines recommend a slightly higher dose of 40 to 50 g/day.4

**STAR***

What adverse effects of intravenous albumin would you expect to observe in clinical studies?

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

In a recent study of patients hospitalized for acute complications of decompensated cirrhosis with serum albumin levels less than 3 g/dL, the use of 20% albumin titrated to target serum albumin levels of 3.5 g/dL was not associated with any efficacy benefit, including reducing the risk of kidney dysfunction.18 In fact, the use of albumin was associated with severe pulmonary edema or fluid overload (6% vs 2%) prompting the authors to conclude that there is a need to reevaluate the use of albumin in patients with cirrhosis.18 Similar concerns regarding the aging evidence and small size of existing clinical trials investigating albumin in cirrhosis-related complications have been raised, indicating that more robust studies are necessary to understand the efficacy and safety profile of albumin.19

**Vasoconstrictors**

In patients with HRS AKI, vasoconstrictor therapy (in conjunction with albumin) is recommended.4 Vasoconstrictor is thought to address the systemic vasodilation and poor renal perfusion observed in HRS AKI, thereby reversing the underlying pathophysiology.20 Current guidelines prefer terlipressin as the vasoconstrictor of choice; however, terlipressin is neither FDA approved nor available in the United States.21 When terlipressin is unavailable, norepinephrine is preferred, although administration requires intensive care unit (ICU) admission and a central venous catheter (CVC). In patients who cannot receive or are not appropriate candidates for terlipressin or norepinephrine, midodrine with octreotide is the preferred vasoconstrictor therapy. Among tertiary care centers in the United States, midodrine with octreotide is selected in the vast majority of HRS AKI cases.31 Currently, no medication has FDA approval for the prevention or treatment of HRS AKI.2

**Terlipressin**

Terlipressin is an intravenous synthetic vasopressin analogue that acts as a vasoconstrictor primarily via the vasopressin V1 receptor on vascular smooth muscle, particularly within the splanchnic circulation.22 This vasoconstriction results in an increase in effective arterial blood volume and mean arterial pressure (MAP) and decreases the hormonal response associated with the pathophysiology of HRS, thereby improving renal blood flow.

Though terlipressin has been studied for HRS in several smaller studies, two phase 3 double-blind, placebo-controlled trials, REVERSE and CONFIRM, represent the largest studies to date. In the REVERSE trial, 196 patients with HRS-1 (defined as a SCr of ≥2.5 mg/dL and doubled from baseline) were randomized to terlipressin (1-2 mg intravenous [IV] push every 6 hours) or placebo for up to 14 days or until the primary end point of complete HRS reversal was achieved.22 Complete HRS reversal was defined as 2 SCr values less than 1.5 mg/dL drawn 40 hours apart. The study failed to demonstrate a difference in complete HRS reversal between terlipressin and placebo (19.6% vs 13.1%; P = .22). There were several potential confounders that could have resulted in the lack of benefit of terlipressin, including imbalanced baseline characteristics, patients being discharged before a second SCr value could be obtained, and possibly being underpowered given a potentially smaller effect size than anticipated.

In the CONFIRM trial, 300 patients with HRS-1 (defined as a SCr ≥2.25 mg/dL and doubled from baseline) were randomized to terlipressin (1-2 mg IV push every 6 hours) or placebo for up to 14 days or until complete HRS reversal, which was similarly defined to the REVERSE trial.23 In contrast to REVERSE, the CONFIRM trial demonstrated a higher rate of complete HRS reversal with terlipressin compared with placebo (32% vs 17%;
95% CI, 0.84-1.43, I^2 (46%).

Skin disorders, pulmonary edema, and respiratory failure.

Pain, nausea, diarrhea, intestinal ischemia, cyanosis, vascular

were gastrointestinal or ischemic in nature, including abdominal

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2.86, I^2 (38%) but does not improve 90-day survival (RR, 1.09; 95% CI, 0.84-1.43, I^2, 46%).

A recent meta-analysis, which included both REVERSE and CONFIRM among other studies, demonstrated that terlipressin

is superior to placebo for HRS reversal (RR, 2.08; 95% CI, 1.51-2.86, I^2, 38%) but does not improve 90-day survival (RR, 1.09; 95% CI, 0.84-1.43, I^2, 46%).

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Newer data have suggested that a lower SCr value at the time

of terlipressin initiation is associated with a higher probability

of HRS AKI reversal. A poster from the recent 2021 American

Association for the Study of Liver Diseases (AASLD) conference

highlighted data from a retrospective review of 203 patients

with HRS who received terlipressin at 26 sites in the United

Kingdom. Compared with those with a SCr of 5 or greater,

patients with a lower SCr (<5 mg/dL) at presentation

experienced significantly longer overall survival (P <.041), were more

likely to achieve a complete response to terlipressin (54.7% vs

13.6%; P <.001), and were less likely to experience AEs (fluid

overload or pulmonary edema [14.4% vs 27.3%]; multi-organ

failure [6.1% vs 31.8%]). This, in conjunction with the lower

SCr threshold for the 2015 ICA definition of HRS AKI, suggests

that future studies using the new HRS AKI definition as inclusion

criteria may demonstrate a more substantial benefit with

terlipressin than previous studies have shown.

In both the REVERSE and CONFIRM trials, drug discontinu-

ation due to AEs was more common with terlipressin than placebo

(20.4% vs 6.3% and 12% vs 5%, respectively). Most AEs

were gastrointestinal or ischemic in nature, including abdominal

pain, nausea, diarrhea, intestinal ischemia, cyanosis, vascular

skin disorders, pulmonary edema, and respiratory failure.

Respiratory-related AEs associated with terlipressin, most

notably observed in the CONFIRM trial, warrant further inves-

tigation. In the integrated analysis submitted to the FDA, which

pooled the results of three phase 3 studies of terlipressin versus

placebo, terlipressin was associated with higher rates of pulmo-

nary edema (8.3% vs 5.6%), respiratory failure (8.3% vs 3.6%),

and fluid overload (8% vs 3.6%). The same analysis demon-

strated a higher risk of dyspnea, wheezing, bronchospasm, and

pulmonary edema (34.8% vs 19.6%) as well as an increased risk

of death due to respiratory failure (4.9% vs 1.2%). The increased

risk of respiratory AEs with terlipressin may have been due to

pulmonary edema caused by an increase in preload (from terlipressin) and afterload (from albumin). Similar AEs have

not been observed with norepinephrine and albumin, leading

some to hypothesize that terlipressin may cause pulmonary

edema through pulmonary artery vasodilation, pulmonary vein

venoconstriction, increasing the alveolar capillary barrier, and

its lack of cardiac inotropy. Regardless of the mechanism of

harm, additional studies are needed to understand and mitigate

the AEs of terlipressin in this patient population.

In both the REVERSE and CONFIRM trials, terlipressin was
dosed as 1 mg IV push every 6 hours. If SCr did not improve by at least 30%, the dose was increased to 2 mg every 6 hours
(8 mg/day). Other studies have used a variety of terlipressin
dosing strategies for HRS AKI, such as titrating doses up to 12
mg/day and using continuous infusions as an alternative to IV
push. In a study comparing IV push terlipressin with IV infusion

terlipressin, a continuous IV infusion was associated with lower
daily dosing requirements (2.2 vs 3.5 mg/day; P <.05), similar
efficacy in improving renal function, and fewer AEs requiring
cessation of terlipressin (20.6% vs 43.2%; P <.05). Though
more data are needed, a continuous infusion strategy may repre-

sent a route of administration that reduces both AEs and drug

costs without reducing efficacy.

Terlipressin is not currently available in the United States. In July 2020, the FDA Cardiovascular and Renal Drug Advi-
sory Committee voted 8 to 7 in favor of approving terlipressin

for HRS-1 based on the CONFIRM trial. The FDA later issued

a Complete Response Letter indicating that more information

was necessary to support a positive risk-benefit profile, and the

agency required additional data to approve a terlipressin New

Drug Application potentially due to the respiratory-associated AEs

and lack of mortality benefit observed with terlipressin.

**Norepinephrine**

Norepinephrine is an IV catecholamine with both α- and
β-adrenergic properties that produces vasoconstriction as well as cardiac inotropy and chronotropy. Like terlipressin, the vasoconstrictive qualities of norepinephrine can result in systemic vasoconstriction, an increase in effective arterial blood volume and blood pressure, and an improvement in renal blood flow. In fact, both terlipressin and norepinephrine are associated with similar decreases in the hormonal response-associated HRS, such as plasma renin and aldosterone concentrations. Unlike terlipressin, norepinephrine is widely available in the United States.

For HRS AKI, norepinephrine initial dosing is 0.5 mg/hour (8.3 mcg/min) as a continuous IV infusion and titrated up to a maximum dose of 3 mg/hour (50 mcg/min). Unlike terlipressin, which is titrated based on SCr improvement, norepinephrine is titrated by 0.5 mg/hour every 4 hours to achieve a MAP increase greater than 10 mm Hg or a urine output increase greater than 200 mL over 4 hours. Furthermore, while terlipressin may be administered through a peripheral IV catheter on a medical floor, norepinephrine generally requires the use of a CVC and, typically, admission to an ICU. Although data exist supporting the safe short-term administration of norepinephrine through peripheral IV catheters, a CVC should be utilized when norepinephrine is required for an extended period of time (>24-72 hours), which is frequently necessary in HRS AKI treatment.

A meta-analysis comparing terlipressin with norepinephrine concluded that there is no difference in HRS reversal (53.5% terlipressin vs 52.9% norepinephrine; RR, 1.01; 95% CI, 0.65-1.57, F, 0%) but that terlipressin was associated with a higher incidence of AEs (25.4% vs 10.6%; RR, 2.72; 95% CI, 1.33-5.55, F, 4%). One study suggests that terlipressin may be more effective for HRS reversal in patients with acute-on-chronic liver failure (ACLF). In contrast to decompensated cirrhosis (DC), patients with ACLF may have more hemodynamic alternations and be more prone to AKI than patients with DC. In a single-center, randomized, open-label study of 120 patients with ACLF, patients randomized to terlipressin instead of norepinephrine were more likely to have HRS reversal at 14 days (40% vs 16.7%; P = .004), less likely to require dialysis (57% vs 80%; P = .006), and have higher survival rates (48.3% vs 20%; P = .001). Similar to other studies, AEs causing discontinuation were numerically more common with terlipressin (15% vs 8.3%; P = .39).

In most publications of HRS AKI, norepinephrine is well tolerated with few AEs; however, small sample sizes limit the ability to detect specific AEs. Its AE profile is well described in other patient populations, such as in septic shock, in which norepinephrine is associated with ischemic events, arrhythmias, and tachycardia.

Midodrine With Octreotide

Midodrine is an oral α-1 adrenergic agonist that causes peripheral vasoconstriction. Octreotide is a parenteral somatostatin analogue that inhibits glucagon-mediated splanchnic vasodilation, thereby enhancing splanchnic vasoconstriction. The combination of midodrine and octreotide for the treatment of HRS AKI has largely been supported in small, uncontrolled trials, suggesting an improvement in both SCr and mortality.

For the treatment of HRS AKI, midodrine is dosed 5 mg three times daily by mouth and octreotide 100 mcg three times daily subcutaneously. The dose of both medications should be increased as needed to achieve a goal MAP of about 10 to 15 mm Hg higher than baseline to a maximum midodrine dose of 15 mg three times daily and octreotide 200 mcg three times daily. Although not specifically studied in HRS AKI, octreotide may also be administered as a continuous infusion at a rate of 50 mcg/hour.

Midodrine and octreotide are not the preferred vasoconstrictor therapy by guidelines in large part due to a small randomized controlled trial of 49 patients comparing midodrine with octreotide versus terlipressin in patients with both HRS-1 and HRS-2. The study was stopped early due to a priori stopping rules owing to a substantially higher rate of HRS complete response with terlipressin (55.5% vs 4.8%; P < .001). Patients randomized to terlipressin demonstrated higher MAPs throughout the study; in fact, change in MAP from baseline was a predictor of HRS resolution.

Most HRS AKI publications investigating midodrine and octreotide have been very limited in sample size, therefore discerning the AE profile of these medications in patients with HRS AKI is difficult. In a large retrospective study of patients with septic shock receiving high-dose midodrine (mean dose 18.7 mg every 8 hours), bradycardia in 1 patient was the only complication associated with midodrine use. Midodrine could also exacerbate urinary retention via α-1 agonist activity of the bladder neck. Short-term octreotide use is associated with bradycardia, gastrointestinal complaints (such as diarrhea, nausea, and vomiting), and dysglycemia; however, these AEs have not been observed in HRS AKI studies and have generally been mild and infrequent when studied for other indications.
Other Vasopressin Analogues

Vasopressin (FDA approved as synthetic arginine vasopressin) is available in the United States for adults with vasodilatory shock who remain hypotensive despite administration of fluids and catecholamines. Although vasopressin, in combination with octreotide, has been studied in 1 small retrospective study, the optimal dose in HRS is not known. There is also a lack of randomized controlled trials supporting its use; therefore, it is not recommended in the treatment of HRS.

O nrnipressin, a V1 vasopressin receptor agonist that is not available in the United States, has limited data supporting its use in HRS; however, its utility was limited by a high incidence of ischemic AEs and is not specifically addressed in HRS treatment guidelines.

Transplant, Renal Replacement Therapy, and Goals of Care

Due to the high short-term mortality of HRS AKI, all patients should be evaluated for urgent liver transplant (LT). LT is the definitive treatment of choice for HRS AKI as it eliminates the underlying pathophysiology of HRS AKI. Up to 25% of patients with HRS AKI who receive LT will be dialysis-dependent, raising the question of a combination liver–kidney transplant in certain patients, especially those with more prolonged duration of AKI or a longer duration of pre-transplant dialysis.

Renal replacement therapy (RRT) does not improve survival in patients with HRS. Unfortunately, among patients receiving RRT who are not eligible for LT, mortality rates approach 90%, indicating the futility of RRT in this setting. Given this statistic, RRT should generally be considered as a bridge to LT when transplant is an option; for ineligible patients, a discussion of goals of care and possibly hospice may be more appropriate if indications for RRT are met. See the SIDEBAR for patient case examples.

Key Considerations for Health-System Pharmacists

As part of an interprofessional team, pharmacists can play an important role in developing and implementing evidence-based approaches for treatment, assessing cost-savings opportunities, improving transitions of care, and reducing the risk of medication errors in order to optimize outcomes of patients with HRS AKI.

The development of policies, procedures, guidelines, order sets, and pathways are foundational for pharmacists. This degree of involvement encourages evidence-based treatment decisions as part of routine practice within an institution, even when a pharmacist is not physically present. In a small single-center study, the application of an evidence-based protocol for HRS management was associated with a reduction in inappropriate terlipressin dosing and albumin utilization while actually reducing mortality rates.

SIDEBAR

**PATIENT CASE #1: PE**

PE is a 48-year-old woman presenting to the hospital with tense ascites, altered mental status, and an elevated SCr. Her past medical history is significant for non-alcoholic steatohepatitis (NASH) cirrhosis, ascites, and hypertension. Her home medications include furosemide 40 mg PO BID, spironolactone 100 mg PO BID, and lisinopril 20 mg PO daily. Two months ago, routine lab work indicated a SCr of 0.9 mg/dL; however, her SCr today is 1.7 mg/dL.

(1) Does this patient meet criteria for acute kidney injury (AKI) according to the 2015 ICA-AKI definition?

(2) What initial treatment strategy would you recommend to address this patient’s renal impairment?

**PATIENT CASE #2: RL**

RL is 69-year-old man admitted to the intensive care unit (ICU) for spontaneous bacterial peritonitis (SBP) and hepatic encephalopathy. His past medical history is significant for decompensated cirrhosis with ascites due to heavy alcohol use. Despite early identification of his SBP and treatment with appropriate antibiotics, the patient’s renal function has rapidly declined since admission. On hospital days 2 and 3, he was given 25% albumin 1 g/kg/day for 2 consecutive days, which did not improve his SCr. His blood pressure is 94/76 mm Hg (MAP 82 mm Hg), which is similar to his normal blood pressure. The ICU team has confirmed a diagnosis of HRS AKI for this patient and is contemplating the next step in treatment.

(1) Is RL indicated for additional albumin? If so, what concentration and dose would be most appropriate?

(2) Is RL indicated for a vasoconstrictor? If so, what therapy would be most appropriate and how would you titrate the vasoconstrictor dose?

*Please refer to the end of the article for an explanation of each case.*

**STAR**

What role can a pharmacist play in improving prescribing patterns of albumin in the hospital setting?
Numerous studies support the role of pharmacists in reducing drug costs, particularly with albumin. As previously discussed, albumin is commonly used in patients with cirrhosis and HRS. The concentration, dose, and indication for albumin are all important considerations. In fact, literature suggests that albumin is commonly prescribed inappropriately in patients when there is no indication; moreover, the dose or albumin concentration is also frequently incorrect.\textsuperscript{53} In 2 studies, pharmacist-led interventions to reduce inappropriate albumin use led to a more than 7-fold decrease in the frequency of albumin for inappropriate indications in both general ward and intensive care settings.\textsuperscript{54,55}

Patients with HRS in the ICU are medically complex and, as previously discussed, have a high incidence of morbidity and mortality. Given the complexity of patients with HRS AKI, pharmacists in the ICU play an important role in rounding as part of an interdisciplinary critical care team, providing drug therapy education, optimizing drug dosing (particularly in renal and hepatic impairment), engaging in antimicrobial stewardship, and, among other tasks, prospectively evaluating drug therapy for appropriateness, dosing, and monitoring for safety and efficacy.\textsuperscript{51} Recent data classifying and quantifying pharmacist interventions in the ICU demonstrated significant avoidance of health care costs, especially in individualizing patient care, preventing adverse drug events, and improving resource utilization with a cost savings-to-salary ratio between 3.3:1 and 9.6:1.\textsuperscript{56}

Medication errors are common during transitions of care, including hospital admission, from ICU to medical floor, and during hospital discharge. In a 2012 study, clinically important medication errors were identified in approximately 50\% of all patients discharged after a cardiac hospitalization.\textsuperscript{57} Literature suggests that pharmacist-led medication reconciliation during transitions of care, including admission and discharge, can reduce the rate of medication discrepancies, which are often associated with medication errors and adverse drug events.\textsuperscript{58} Additionally, pharmacist-driven intervention programs, which can include medication reconciliation, patient-centered education, evaluating access to care, and medication therapy management, have been shown to reduce 30-day unplanned readmission rates compared with usual care (20.4\% vs 9.8\%; \textit{P} < .001).\textsuperscript{59} Given the medical complexity and high readmission rate of patients with HRS AKI, the pharmacist’s role during transitions of care for patients with HRS AKI is particularly important.\textsuperscript{8}

As new HRS literature is published, pharmacists play an important role in interpreting and analyzing these data. As previously discussed, the role of albumin in patients with cirrhosis deserves further study, in particular regarding the use and dosing of albumin for HRS AKI. Furthermore, despite terlipressin being recommended as a first-line therapy, its safety profile in the CONFIRM trial supports the need for additional data to elucidate how to safely use the medication (eg, avoiding its use in at-risk patients or minimizing the use of albumin). Finally, although some comparative data exist between terlipressin and norepinephrine, larger-scale comparative studies with adjudicated safety end points of pulmonary edema or respiratory failure could be pivotal in optimizing vasoconstrictor therapy in HRS AKI.

ANSWERS TO PATIENT CASES

**PATIENT CASE #1: PE**

(1) Yes, this patient does have AKI based on the 2015 ICA-AKI definition. The patient’s SCr has increased 1.8x her baseline (1.7 divided by 0.9 = 1.8) and is more than 1.5 mg/dL. Because the SCr value is 1.5- to 2-fold higher than baseline and is more than 1.5 mg/dL, this patient has stage IB AKI according to the 2015 ICA-AKI definition. See Table 1 for more information.

(2) The initial management for stage IB AKI is to discontinue diuretics (spironolactone and furosemide) and medications that can worsen AKI (such as lisinopril). Given the patient’s presentation, an infectious work-up is important and empiric antibiotics could be considered. Lastly, the patient should be given 25% albumin 1 g/kg/day (max 100 grams) for 2 consecutive days to increase intravascular volume. See Figure 2 for more information.

**PATIENT CASE #2: RL**

(1) Yes, this patient has been diagnosed with HRS AKI and should receive a vasoconstrictor and albumin. For HRS AKI, albumin 25% should be given at a dose of 20 to 50 g/day. See “Albumin” section and Figure 24,8,12 for more information.

(2) Yes, vasoconstriction is a component of HRS AKI treatment. If available, terlipressin is the preferred vasoconstrictor, but it is not currently available in the United States. Because this patient is in the ICU, the first-line therapy is norepinephrine titrated to a goal MAP increase of +10 mm Hg from baseline (92 mm Hg for this particular patient). See “Norepinephrine” section and Figure 2 for more information.

**Conclusion**

HRS AKI is a late complication of cirrhosis resulting in AKI secondary to both hemodynamic alterations and inflamma-
tion. The development of HRS AKI carries a poor prognosis and is associated with prolonged lengths of hospitalization, frequent hospital readmission, and high mortality. The definitions and staging of AKI in cirrhosis as well as HRS AKI have been updated to incorporate many of the AKI staging criteria seen in the KDIGO AKI definition. Pharmacists can play an important role in the evidence-based approach to prevention and treatment of HRS AKI by selecting vasoconstrictor and albumin therapy, monitoring, dosing, and assisting in transitions of care for these patients.

**ADDITIONAL RESOURCES**

- American Association for the Study of Liver Diseases (AASLD) [aasld.org](http://aasld.org)
- European Association for the Study of the Liver (EASL) [easl.eu/](http://easl.eu/)

**REFERENCES**


INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.

Go to www.pharmacytimes.org/HRS-AKI to access the online version of this activity.

Click “Proceed,” then complete the online pretest.

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

Complete the online posttest and activity evaluation form.

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

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POSTTEST QUESTIONS

1. Which of the following conditions is associated with the highest risk of developing hepatorenal syndrome acute kidney injury (HRS AKI) in a patient with decompensated cirrhosis?
   A. Acute alcoholic hepatitis
   B. Hepatic encephalopathy
   C. Serum albumin less than 3 g/dL
   D. Spontaneous bacterial peritonitis (SBP)

2. A patient with cirrhosis is admitted to the hospital with AKI. Urinary neutrophil gelatinase-associated lipocalin (NGAL) concentrations are markedly elevated. On the basis of this patient's urinary NGAL concentration, what type of AKI do they most likely have?
   A. Acute interstitial nephritis (AIN)
   B. Acute tubular necrosis (ATN)
   C. HRS AKI
   D. Hepatorenal syndrome non-acute kidney injury (HRS NAKI)

3. Which statement best describes the underlying pathophysiology of HRS?
   A. Bacterial infection triggering an inflammatory cascade resulting in direct renal tubular cell damage
   B. Inappropriately low renin-angiotensin-aldosterone system (RAAS) serum levels leading to reduced renal blood flow
   C. Reduced renal blood flow due to low effective arterial blood volume from systemic vasodilation
   D. Renal venous congestion and blood stasis due to portal hypertension

4. A 50-year-old man is admitted to the hospital with worsening ascites and altered mental status. His past medical history is significant for cirrhosis and diabetes. His last serum creatinine (SCr), obtained 2 months ago, was 1.3 mg/dL; however, his SCr today is 2.1 mg/dL. Which AKI classification best describes this patient's renal impairment?
   A. ICA-AKI Stage 1A
   B. ICA-AKI Stage 1B
   C. ICA-AKI Stage 2
   D. ICA-AKI Stage 3

5. Based on the 2015 International Club of Ascites (ICA) definition, which of the following criteria must be met for a patient to be classified as having HRS AKI?
   A. Fraction of excreted sodium (FENa) greater than 2%
   B. Hypotension requiring vasopressors
   C. Lack of SCr improvement despite albumin administration over 2 days
   D. SCr greater than 2.5 mg/dL or 2-fold increase from baseline

6. A 48-year-old woman is admitted to the hospital with decompensated cirrhosis and tense ascites. She undergoes a large-volume paracentesis (LVP) with the removal of 8 liters of ascitic fluid. Following LVP, which albumin regimen is most appropriate for this patient?
   A. 20 grams of 5% albumin
   B. 20 grams of 25% albumin
   C. 50 grams of 5% albumin
   D. 50 grams of 25% albumin

7. A 52-year-old man with advanced cirrhosis was admitted to the hospital with COVID-19 pneumonia and respiratory failure requiring mechanical ventilation. Three days into his ICU stay, he was diagnosed with HRS AKI and was given 40 g/day of 25% albumin and intravenous (IV) norepinephrine titrated to a MAP increase of +10 mm Hg from baseline. After 4 days of his HRS AKI treatment, his SCr has continued to worsen despite achieving MAP goals of 95 mm Hg. Which of the following treatments is most appropriate at this time?
   A. Change norepinephrine to midodrine with octreotide
   B. Discontinue norepinephrine; continue albumin
   C. Discontinue albumin; continue norepinephrine
   D. Discontinue both norepinephrine and albumin

8. A patient is currently receiving albumin and terlipressin 1 mg IV push every 6 hours for HRS AKI treatment and has started to demonstrate improvement in renal function. She is complaining of abdominal pain and diarrhea, which started when terlipressin therapy was initiated. Which of the following therapeutic recommendations is most appropriate to address this patient’s abdominal complaints?
   A. Continue terlipressin IV push; add loperamide
   B. Continue terlipressin IV push; add propranolol
   C. Change terlipressin to a continuous infusion
   D. Discontinue terlipressin; initiate midodrine with octreotide

9. Based on phase 3 trial data, which of the following adverse effects should be monitored in patients receiving terlipressin in combination with albumin?
   A. Atrial fibrillation
   B. Digital ischemia
   C. Respiratory failure
   D. Tachycardia

10. Which of the following outcomes have been demonstrated by the use of a pharmacist as part of a multidisciplinary team among hospitalized patients?
    A. Increase in the number of dialysis-free days in patients with HRS AKI
    B. Increase in 28-day survival rates in patients with HRS AKI
    C. Reduction in inappropriate albumin usage
    D. Reduction in terlipressin drug costs
Optimizing the Management of Atypical Hemolytic Uremic Syndrome: The Important Role of the Pharmacist

EDUCATIONAL OBJECTIVES

At the completion of this activity, the participant will be able to:
• Explain the pathophysiology, diagnosis criteria, and burden of disease for atypical hemolytic uremic syndrome (aHUS)
• Examine the current treatment landscape and the efficacy and safety data of new treatment options for aHUS
• Identify the role of novel biologics on clinical outcomes in those with aHUS and how specialty and infusion pharmacists can improve the care of patients through interventions related to medication use and education of patients and health care providers

TARGET AUDIENCE: Pharmacists

ACTIVITY TYPE: Application

RELEASE DATE: March 17, 2022

EXPIRATION DATE: September 17, 2022

ESTIMATED TIME TO COMPLETE ACTIVITY: 2.5 hours

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

Introduction

Thrombotic microangiopathies (TMAs) are a heterogeneous group of life-threatening disorders that result in microvascular injury, tissue ischemia, and end-organ damage. TMA is an umbrella term that describes multiple distinct clinical syndromes, as shown in FIGURE 1. The distinct TMA subtypes differ in both pathophysiology and treatment but share common clinical features. Hemolysis occurs in these conditions due to the presence of thrombosis in the microvasculature, which is accompanied by laboratory findings suggestive of hemolysis, such as elevated lactate dehydrogenase and reduced plasma haptoglobin. Schistocytes, which are fragmented red blood cells, are present on the peripheral blood smear in patients with TMAs due to the destruction of red cells as they travel past microthrombi and platelet aggregates. Thrombocytopenia is also present due to platelet consumption in the setting of microthrombosis. End-organ dysfunction also frequently occurs, and may include renal dysfunction and neurologic symptoms, among others, with the specific end-organ dysfunction being somewhat dependent on which TMA subtype is present.

Atypical hemolytic uremic syndrome (aHUS) is a rare form of TMA that is associated with an incidence in the United States of 2 cases per million patients and affects patients of all ages. Although aHUS can occur at any age, two-thirds of patients with genetic mutations associated with aHUS are diagnosed with aHUS during childhood. Despite the higher incidence of aHUS in pediatric patients compared with adults, adult cases are typically more severe and are associated with a higher rate of progression to end-stage renal disease (ESRD). Overall, aHUS is associated with a poor prognosis, with progression to ESRD occurring in half of affected patients and death in up to 25%.

This portion of the activity is unique and interactive, as it simulates real patient cases and highlights the role of the pharmacist in educating patients about atypical hemolytic uremic syndrome. Access the simulation at www.pharmacytimes.org/aHUS.
aHUS Differential Diagnosis, Presenting Symptoms, and Pathophysiology

The 2 main subgroups of TMAs are thrombotic thrombocytopenic purpura (TTP) and HUS, as indicated in Figure 1.1,2 HUS is further categorized into 1 of 4 categories: typical HUS, aHUS, idiopathic HUS, and secondary HUS.1-3,6 Typical HUS occurs in patients with Shiga toxin-producing *Escherichia coli* infections, and these patients often present after or concurrent with symptoms of gastrointestinal (GI) illness; first-line treatment for typical HUS is generally supportive care.1-3,6 aHUS results from overactivity and dysregulation of the complement system in patients with genetic mutations in the complement pathway as described further below. aHUS is treated with medications that inhibit the complement protein C5.1-3,6 HUS is considered idiopathic when there is laboratory and clinical evidence of HUS but the cause is unclear and is categorized separately from aHUS because of the absence of genetic mutations known to be associated with aHUS.1-3,6 However, idiopathic HUS is generally treated the same way as complement-driven HUS, using anti-complement therapies for 2 reasons. First, genetic sequencing results are not available for several weeks after obtaining samples, so it is unknown at the time of treatment initiation whether patients have aHUS with associated genetic mutation or if the case is indeed considered idiopathic. Secondly, it is likely that all genetic mutations associated with aHUS have not yet been identified because there is still much to be explored with genetic sequencing within the complement pathway. Therefore, anti-complement treatment is typically continued in patients with idiopathic HUS if there is an initial clinical response. Secondary HUS occurs due to a bone marrow transplant, pregnancy, medications, or malignancy, among other things, and, in these cases, general management of the underlying disorder is the first-line treatment.1,3,6

Although the clinical manifestations of TTP and HUS can have significant overlap, the pathophysiology of these diseases differs notably, and treatment approaches are also very different for that reason, as shown in Table 1.9 Because of the negative consequences of delayed initiation of appropriate treatment for both TTP and aHUS, it is important to know how to differen-
To differentiate these 2 conditions. TTP is caused by a deficiency in the enzyme responsible for cleavage of ultra-large von Willebrand factor multimers, ADAMTS13, whereas aHUS is driven by complement dysregulation; therefore, initial treatment for TTP involves plasma exchange, whereas initial treatment for aHUS involves initiation of complement protein C5 inhibitors. In order to differentiate TTP and aHUS, an ADAMTS13 activity assay should be obtained; a value less than 10% confirms TTP, while a value above this suggests HUS is more likely. Both conditions can be triggered by pregnancy and have microangiopathic hemolytic anemia and neurologic symptoms as part of typical presentations. However, the degree of thrombocytopenia and renal impairment can help to differentiate the two. In TTP, thrombocytopenia is typically more severe, with nadir less than 30,000 x 10^9/L, whereas platelet count nadir in aHUS is typically higher than this threshold. Renal impairment, especially with serum creatinine above 2.25 mg/dL, is often a distinguishing feature of aHUS, and is less prominent with TTP. However, renal failure alone cannot distinguish the two conditions, as TTP may rarely present with acute kidney injury, and for this reason the entire clinical picture must be considered to differentiate the two conditions. Other symptoms of aHUS can impact nearly every organ system, with extra-renal involvement occurring in up to 20% of patients. Central nervous system symptoms can range from altered mental status to seizures or stroke. Cardiovascular manifestations include myocardial infarction and peripheral ischemia. Although GI symptoms are common in typical HUS due to Shiga toxin-producing E. coli infections being the underlying driver, patients with aHUS can also present with GI symptoms; therefore, the presence of diarrhea or GI upset does not rule out an atypical form of the condition.

As previously noted, dysregulation of the complement system underlies aHUS. Complement is involved in innate immunity and serves to differentiate self from non-self, leading to destruction of invading substances, such as bacteria. Once activated, the complement system consists of an amplification cascade that ultimately causes profound inflammation and cell lysis. The complement system is always active at a low level, and for this reason the negative feedback loops (inhibitors) in this cascade are critical to keep the system in check and prevent complement overactivation and damage to...
healthy tissues. When complement overactivation does occur, it leads to recruitment of inflammatory cells, target opsonization (where pathogens are marked for destruction), and ultimately cell lysis.10

The complement pathway is a very complex system of checks and balances, as shown in Figure 2.3,11 There are 3 pathways involved in activating the complement: classical, lectin, and alternative. All 3 of these pathways converge on the C3 convertase enzyme, which cleaves C3 into C3a and, more importantly, C3b, which is used with other complement proteins by C5 convertase to cleave C5 into C5a and C5b-9 (also known as the membrane attack complex).1,3,10 The membrane attack complex (C5b-9) is the terminal product of complement activation, and results in endothelial injury as well as increased production of tissue factor, leukocytes, and increased platelet activation, the end result of which is ultimately thrombosis. This process is amplified by proteins that promote complement activation and amplification, such as factor B and factor D. As mentioned previously, the complement system is always active at a low level, and in order to prevent overactivity of this system and damage to normal host cells, a series of inhibitors is also present, including factor H, membrane cofactor protein (MCP), factor I, and others.1,3,10 Genetic mutations resulting in inadequate production of complement pathway inhibitors or increased production of activators put patients at risk for aHUS.1-3 There are two FDA-approved medications, eculizumab and ravulizumab, that are the backbone of aHUS treatment and work as inhibitors of the complement system to shut down complement dysregulation in aHUS.5,12 Both medications work as C5 inhibitors and bind to complement protein C5 to prevent the conversion of C5 to the membrane attack complex, thus reducing the negative sequelae of complement activation, such as microthrombosis risk.5,12

The pathogenesis of aHUS involves incomplete penetrance, meaning this is a two-hit disease where genetic predisposition is accompanied by a trigger, and presence of the genetic mutation alone does not cause disease activity in the majority of patients.2 Under normal conditions, there is a balance between complement activators and inhibitors that prevents the negative sequelae of overactivity of the complement system. Patients with genetic mutations affecting production of complement system activators (gain of function mutations in factor B, factor D, and others) or inhibitors (loss of function mutations in factor H, MCP, and others) are at risk for fulminant aHUS development once exposed to a trigger.2,3,5 Potential triggers include pregnancy, infection, surgery, or flare of an autoimmune condition.2,3,5

There are several genetic mutations that have been identified as risk factors for aHUS, which can be inherited (<20% of cases) or occur spontaneously.3,5 Factor H loss of function mutations occur most frequently, with up to 20% to 30% of patients affected, followed by loss of function mutations in MCP (10%-15%), factor I (4%-10%), and gain of function mutations in C3 (5%-10%).5 The specific genetic mutation present is correlated with clinical manifestations and prognosis.4 Of note, up to 40% of patients with aHUS do not have identifiable mutations, and half of patients with identified mutations do not go on to develop aHUS, likely because of absence of exposure to an aHUS trigger to push the complement system into full dysregulation.3,5 While it is common practice to send genetic sequencing for patients with suspected aHUS undergoing treatment, aHUS treatment should not be delayed until genetic sequencing results are available, as results are typically not available for several weeks after sample collection. For this reason, genetic sequencing results are not required to make the initial aHUS diagnosis, but genetic sequencing results can support the diagnosis and enlighten future decisions regarding the duration of aHUS treatment and may be helpful in predicting relapse risk if aHUS treatment is discontinued.13

aHUS Treatment Approach

Treatment Approach Prior to C5 Inhibitor Availability

Before the availability of C5 inhibitors, aHUS treatment options were limited to plasma infusion, which provides functional complement proteins, with or without plasma exchange to remove antibodies to complement proteins (such as anti-factor H antibodies).6 During this era, significant morbidity and mortality remained, as up to 75% of patients with aHUS progressed to ESRD or ultimately died of the condition.6 Complement protein C5 inhibitor therapy is now considered the gold standard first-line treatment for aHUS, and with these therapies renal function recovery has been reported to occur in up to 80% of patients.6,14 Importantly, earlier initiation of C5 inhibitors is associated with a greater improvement in renal function; therefore, prompt initiation of appropriate therapy once TTP is ruled out and aHUS is suspected is critical in order to improve long-term outcomes for patients.6 aHUS is a complex disease and involvement of a multidisciplinary team of physicians from various specialties (renal, hematology, and transfusion medicine) and pharmacists is essential to ensure patients receive optimal care.
The therapeutic effects of plasma infusion in aHUS are thought to occur as a result of providing a source of normal levels of complement system inhibitors, such as factor I, factor H, and factor B. The addition of plasmapheresis before administration of plasma replacement, also known as plasma exchange, offers a potential added benefit in aHUS by removing antibodies against factor H, which are present in approximately 10% of patients with aHUS.† There are very limited data to support both of these treatment options in aHUS, but the data that are available suggest the efficacy of these therapies depends on the patient’s genotype.‡ Some patients may experience hematologic improvement with plasma infusion and/or plasma exchange, but many still progress to ESRD, and relapses occur in many patients without the use of long-term maintenance therapy.¶ The benefit of plasma infusion or exchange depends on the specific mutation, with MCP mutations being particularly responsive with a 97% rate of remission. However, complete response rates for non-MCP or THBD mutations are much lower (5%-43%) and significant morbidity remains.†† Reported rates of progression to ESRD or death with plasma infusion or plasma exchange treatment during the initial aHUS episode range from 13% to 75% during the acute episode.†‡ Plasma therapies are associated with adverse effects (AEs) including allergic reactions, and catheter-related complications such as thrombosis and infection.§ C5 inhibitors are more effective than plasma therapies and have more data supporting their use. For these reasons the use of plasma infusion and/or plasma exchange is no longer recommended once aHUS is considered the most likely diagnosis and TTP is ruled out unless C5 inhibitors are unavailable.‡‡

**Current aHUS Treatment Therapies**

There are currently two FDA-approved C5 inhibitors for aHUS treatment. Eculizumab (Soliris) was FDA approved for aHUS treatment in September 2011, and ravulizumab (Ultomiris) was subsequently approved for this indication in October 2019.†§†§ Notably, neither agent is approved for treatment of typical HUS. Both eculizumab and ravulizumab are also approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), and eculizumab has additional FDA approvals for the treatment of generalized refractory myasthenia gravis and neuromyelitis optical spectrum disorder.†³§†³ Both agents exert their effects by inhibiting terminal complement activation by binding to C5 and thereby inhibiting the conversion of C5 to the membrane attack complex (C5b-9).†³§†³

**Eculizumab**

Eculizumab dosing for aHUS is shown in **Table 2**.†³ All adult patients receive the same induction dose, maintenance dose, and dosing interval, but pediatric dosing depends on patient weight. Per the FDA labeling, eculizumab doses may be administered within 2 days of the target administration date. Supplemental eculizumab doses are required for patients undergoing plasma exchange or receiving plasma infusion because plasma infusion provides a source of uninhibited C5 proteins, and eculizumab is also significantly removed by plasmapheresis.†³ For plasmapheresis or plasma exchange, if the most recent dose was 600 mg or more, an additional 600-mg supplemental dose should be administered within 60 minutes after each session. If the most recent dose was 300 mg, an additional 300-mg dose should be administered within 60 minutes of each session. For patients receiving plasma infusions, if the most recent eculizumab dose was 300 mg or more, a supplemental eculizumab 300-mg dose should be administered within 60 minutes before each plasma infusion.†³ Additionally, recent intravenous (IV) immunoglobulin administration has been shown to reduce eculizumab exposure because it interferes with neonatal Fc receptor recycling of

**Table 2: Eculizumab Dosing**

<table>
<thead>
<tr>
<th>Patient age and weight</th>
<th>Induction dosing</th>
<th>Maintenance dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adults: ≥40 kg pediatric patients*</td>
<td>900 mg weekly x 4 doses</td>
<td>1200 mg at week 5, then 1200 mg every 2 weeks</td>
</tr>
<tr>
<td>30-39.9 kg³</td>
<td>600 mg weekly x 2 doses</td>
<td>900 mg at week 3, then 900 mg every 2 weeks</td>
</tr>
<tr>
<td>20-29.9 kg³</td>
<td>600 mg weekly x 2 doses</td>
<td>600 mg at week 3, then 600 mg every 2 weeks</td>
</tr>
<tr>
<td>10-19.9 kg³</td>
<td>600 mg weekly x 1 dose</td>
<td>300 mg at week 2, then 300 mg every 2 weeks</td>
</tr>
<tr>
<td>5-9.9 kg³</td>
<td>300 mg weekly x 1 dose</td>
<td>300 mg at week 2, then 300 mg every 3 weeks</td>
</tr>
</tbody>
</table>

*Pediatrics = patients <18 years.
monoclonal antibodies, thereby reducing eculizumab serum concentrations, although clinical data on management of this phenomenon are limited. Eculizumab possesses linear pharmacokinetics and has a small volume of distribution which approximates blood volume. The half-life of eculizumab is 11 to 17 days, but is reduced to approximately 1.26 hours in dosing considerations exist. According to the FDA labeling, eculizumab is not excreted in the urine, and therefore no renal dysfunction is apparent. Eculizumab is not associated with changes in renal function. 

Patients receiving eculizumab include headache, diarrhea, hypertension, upper respiratory infection, abdominal pain, vomiting, nasopharyngitis, anemia, cough, peripheral edema, nausea, urinary tract infection, and pyrexia. Of note, these AEs are largely reported from single-arm studies for both agents, and therefore it is difficult to know if these are related to the disease or the medication due to lack of availability of baseline AE rates from a control group. Eculizumab carries a black box warning for risk of meningococcal infection and additional recommendations for precaution against other encapsulated organisms, both of which are discussed in more detail below.

Several studies have reported the safety and efficacy of eculizumab use for aHUS. Two separate phase 2, single-arm studies of eculizumab enrolled patients 12 years or older with aHUS to receive eculizumab 900 mg induction dosing weekly for 4 weeks, then 1200 mg every 2 weeks starting 1 week after the last loading dose. Both trials required patients to have evidence of hemolysis and impaired renal function for study inclusion. In addition, active TMA despite plasma therapy was a requirement for enrollment in trial 1. For enrollment in trial 2, a stable platelet count for a minimum of 8 weeks after plasma exchange or plasma infusion treatment was required. The co-primary efficacy end points were inhibition of complement-mediated TMA and normalization of hematologic values. Inhibition of complement-mediated TMA was defined as a change in platelet count for trial 1 and TMA event-free status for at least 12 weeks for trial 2, which was further defined as the absence of a greater than 25% decrease in the platelet count, plasma exchange or plasma infusion, and dialysis initiation. A total of 17 patients were treated for 64 weeks in trial 1 and 20 patients were treated for 62 weeks in trial 2. Eculizumab administration was associated with significant inhibition of complement-mediated TMA in trial 1 at 26 and 64 weeks follow-up. Similarly, eculizumab administration resulted in a significant increase in TMA event-free status in trial 2, with 80% of patients meeting the primary end point by week 26 and 85% by week 62. At 62 weeks follow-up, normalization of hematologic values occurred in 88% and 90% of patients in trial 1 and trial 2, respectively, with a significant improvement in platelet count noted as early as day 7 after treatment initiation. Renal function was significantly improved with eculizumab use with 65% of patients in trial 1 experiencing a 25% or greater improvement in serum creatinine from baseline to week 26, which was maintained through the 64-week follow-up period. Additionally, 59% of patients in trial 1 experienced an improvement in chronic kidney disease stage I by ≥1 stage. Importantly, dialysis discontinuation occurred in 80% (4/5) of patients who were dialysis dependent at the time of study enrollment. These findings in the trial 1 cohort, which included patients who inadequately responded to plasma therapy, suggest eculizumab results in a greater improvement in renal function than plasma therapy. The effect of eculizumab on renal function recovery was greater if started soon after aHUS diagnosis. Eculizumab was also associated with improvement in health-related quality of life. No serious infection-related AEs were observed throughout the trials or extension period.

The long-term benefits and risks of eculizumab use have been evaluated in real-world studies. One study used data from the global aHUS registry and evaluated patients treated with eculizumab in the first 5 years of the registry compared with those who never received eculizumab with the objective of assessing the long-term safety of eculizumab use. A total of 1321 adult and pediatric patients were included in this study, with 865 treated with eculizumab and 456 never treated with eculizumab. Patients who received at least one dose of eculizumab (“ever treated” group) had more severe disease as evidenced by a higher rate of renal and extra-renal symptoms, and a greater proportion of patients requiring dialysis, transfusions, and kidney transplantation. There were no differences in AEs between those who were treated with eculizumab compared with those who were not, with the exception of serious infections in pediatric patients which were more common in eculizumab-treated patients (5.15 vs 1.12 events/100 patient-years). Most infection-related AEs were unspecified or viral in cause and resolved with appropriate management. Because the eculizumab cohort included any patient who had received at least one dose of eculizumab during the study timeframe, the events did not necessarily occur while patients were actively on therapy with eculizumab. Three (0.4%) meningococcal infections were reported in patients who had received eculizumab, one of which was fatal. Of these 3 patients, two did not receive prophylactic antibiotics. Overall, this observational
study found no new safety concerns with eculizumab use, confirming a positive benefit-risk profile in the real-world setting.

A prospective, observational, multicenter study of patients with aHUS treated with eculizumab was also conducted to investigate long-term safety and efficacy outcomes over a 6-year period. Patients with aHUS who participated in any of 5 parent trials and received at least one dose of eculizumab were eligible for inclusion. The primary end point was rate of TMA manifestations while on versus off of eculizumab therapy. Secondary end points looked at renal outcomes and treatment-emergent AEs. A total of 93 patients were included, with 51 patients remaining on eculizumab therapy, 42 discontinuing eculizumab therapy, and 21 of those 42 patients reinitiating therapy at a later time. During the study, 3 TMA manifestations occurred in 2 patients (2%) during treatment with eculizumab and 14 manifestations occurred in 10 patients (24%) during off-treatment periods. All TMA manifestations during off-treatment periods occurred during the first 30 months following therapy discontinuation. Eculizumab led to a rapid improvement in estimated glomerular filtration rate, which remained above or near 60 mL/min/1.73m² during the follow-up period. Eculizumab was well tolerated. Three definite and 1 possible meningo-coccal infections occurred while on eculizumab, but all patients continued eculizumab and recovered from the infection. Three deaths occurred but none were considered related to eculizumab therapy. This trial confirmed the long-term efficacy and safety of eculizumab in aHUS, particularly in regard to renal function and TMA events.

Although eculizumab has been shown to be safe and effective for aHUS treatment, it requires a standard treatment regimen of IV infusions every 2 weeks for the majority of patients. In response to this limitation, ravulizumab was developed as a re-engineered version of eculizumab with a longer half-life to allow for reduced administration frequency. This re-engineered version is ravulizumab. TABLE 3 shows the results from trial 1, which supports the efficacy of both eculizumab and ravulizumab.

### TABLE 3. ECULIZUMAB AND RAVULIZUMAB SUPPORTING DATA FROM CLINICAL TRIALS AT 26-WEEK FOLLOW-UP14,21

<table>
<thead>
<tr>
<th>End point</th>
<th>Rondeau et al: ravulizumab, n/n total (%) (n = 56)</th>
<th>Legendre et al: eculizumab, n/n total (%) (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete TMA response</td>
<td>30/56 (54)</td>
<td>13/17 (76)</td>
</tr>
<tr>
<td>Platelet count normalization</td>
<td>47/56 (84)</td>
<td>14/17 (82)</td>
</tr>
<tr>
<td>LDH normalization</td>
<td>43/56 (77)</td>
<td>14/17 (82)</td>
</tr>
<tr>
<td>&gt;25% improvement in SCR from baseline</td>
<td>33/56 (59)</td>
<td>11/17 (65)</td>
</tr>
<tr>
<td>CKD stage improvement by ≥1 stage from baseline</td>
<td>38/56 (68)</td>
<td>10/17 (59)</td>
</tr>
<tr>
<td>Dialysis discontinuation</td>
<td>17/29 (59)</td>
<td>4/5 (80)</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; LDH, lactate dehydrogenase; SCR, serum creatinine; TMA, thrombotic microangiopathy. *Data shown are from trial 1 of 2 (progressive disease despite plasma therapy) in Legendre et al 2013 publication.

### TABLE 4. RAVULIZUMAB DOSING16

<table>
<thead>
<tr>
<th>Patient weight</th>
<th>Loading dose (mg)</th>
<th>Maintenance dosing (mg) and interval</th>
<th>Repeat every weeks starting 2 weeks after loading dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥100 kg</td>
<td>3000</td>
<td>3600</td>
<td>Repeat every 8 weeks</td>
</tr>
<tr>
<td>60-99.9 kg</td>
<td>2700</td>
<td>3300</td>
<td>2 weeks after loading dose</td>
</tr>
<tr>
<td>40-59.9 kg</td>
<td>2400</td>
<td>3000</td>
<td></td>
</tr>
<tr>
<td>30-39.9 kg</td>
<td>1200</td>
<td>2700</td>
<td></td>
</tr>
<tr>
<td>20-29.9 kg</td>
<td>900</td>
<td>2100</td>
<td></td>
</tr>
<tr>
<td>10-19.9 kg</td>
<td>600</td>
<td>600</td>
<td>Repeat every 4 weeks</td>
</tr>
<tr>
<td>5-9.9 kg</td>
<td>600</td>
<td>300</td>
<td>2 weeks after loading dose</td>
</tr>
</tbody>
</table>

Ravulizumab

The mechanism by which the half-life of ravulizumab was extended was by increasing the affinity of ravulizumab for the neonatal Fc receptor, which is responsible for recycling monoclonal antibodies, resulting in a half-life 3 to 4 times that of eculizumab at 51 days. Like eculizumab, ravulizumab has linear pharmacokinetics and a small volume of distribution similar to that of blood volume. Ravulizumab dosing recommendations are shown in TABLE 4. Unlike eculizumab, where all adult patients receive the same dose regardless of weight, ravulizumab dosing for aHUS differs according to patient weight. Additionally, in contrast to eculizumab, where up to 4 loading doses are administered once weekly, only 1 loading dose is required with ravulizumab use upon initiation of therapy. Maintenance ravulizumab dosing is administered once every 8 weeks for adults, starting 2 weeks after the initial loading dose. Maintenance doses of ravulizumab may be administered within 7 days of the target administration date, with the exception of the first maintenance dose that should be administered 14 days...
exactly after the loading dose. Similar considerations to eculizumab exist regarding the effect of plasma infusion or exchange on ravulizumab efficacy, although no supplemental dosing recommendations are available for ravulizumab, and thus, this should be avoided. Ravulizumab AEs reported to occur in at least 20% of patients include headache and upper respiratory infection. As noted previously, these AE rates are difficult to interpret due to their origination from largely single-arm studies. Similar to eculizumab, the ravulizumab FDA labeling includes a black box warning regarding increased risk of meningococcal infection and precautionary statements regarding heightened risk for infection with other encapsulated organisms, both of which are discussed in more detail below.

The efficacy and safety of ravulizumab in adults have been reported in a single-arm, phase 3 study of 56 patients with acute aHUS. Ravulizumab dosing in this trial was consistent with the dosing in the current FDA labeling described in Table 4, and the end points from this study were very similar to the aforementioned eculizumab phase 2 trial. As shown in Table 3, results from the 2 landmark trials evaluating the available C5 inhibitors were highly similar. For the primary end point of complete TMA response, ravulizumab use successfully resolved the acute TMA episode in 54% of patients at the end of the follow-up period (183 days after enrollment). Lactate dehydrogenase and platelet count normalized in 77% and 84%, respectively. Consistent with the findings from the eculizumab phase 2 trial, platelet count normalization was seen 1 week after treatment initiation and maintained through the remainder of the follow-up period. Ravulizumab administration was also associated with a significant improvement in renal function. Dialysis discontinuation occurred in 59% of patients who were dialysis dependent at the time of study enrollment. This rate is numerically lower than with eculizumab, but the 2 trials differed in their definitions of baseline dialysis dependence, which likely explains this discrepancy.

Due to the more recent FDA approval of ravulizumab, long-term efficacy and safety data are limited, but an ongoing 4.5-year extension phase of the phase 3 trial recently reported interim results. Of the 58 patients in the initiation phase, 49 patients elected to continue in the extension phase. Results at a median of 76.7 weeks demonstrated that 4 additional patients achieved complete TMA response, and other secondary end point findings in the initial phase were sustained. Importantly, many AEs decreased during the extension phase.
necessary precautions continued until 3 months after the last dose of eculizumab and 8 months after the last dose of ravulizumab. Patients receiving C5 inhibitors are at increased risk for infection with other encapsulated organisms in addition to meningococcus, including Streptococcus pneumoniae and Haemophilus influenzae, and, although these infections are not included in the REMS program, patients receiving C5 inhibitors should be immunized against these organisms to reduce the risk of infection, according to ACIP guidelines.15,16

For protection against meningococcus, the ACIP guidelines recommend immunization against both meningococcal groups, MenACWY and MenB.25 For meningococcal groups ACWY, 2 quadrivalent vaccines exist (Menactra and Menveo). For adults, both products are administered as two 0.5-mL intramuscular injections given at least 2 months apart, with booster doses administered every 5 years. For meningococcal group B prophylaxis, 2 vaccines are available (Bexsero and Trumenba). Bexsero dosing for adults requires two 0.5-mL intramuscular injections be administered at least 1 month apart, with booster dosing given 1 year after the first series and then every 2 to 3 years thereafter while still at increased risk of infection. Trumenba dosing involves 3 injections given at months 0, 1 to 2, and 6, followed by booster dosing 1 year after the first series and then every 2 to 3 years thereafter while still at increased risk of infection. ACIP also recommends pneumococcal immunization for patients receiving C5 inhibitors.29 Two pneumococcal vaccines exist, one of which is a 13-valent vaccine (PCV13), and the other is a 23-valent polysaccharide
vaccine (PPSV23). For PCV13 (Prevnar 13), 1 dose should be administered before PPSV23. For PPSV23 (Pneumovax 23), the first dose should be given 8 weeks after PCV13, and a booster dose should be administered 5 years later. Immunization against H influenzae is also recommended per ACIP for patients receiving C5 inhibitor treatment, with 1 dose of any of the 3 available H influenzae vaccines (ActHIB, Hiberix, or PedvaxHIB) rendering patients fully vaccinated. With similar efficacy and safety profiles, the choice between eculizumab and ravulizumab is often dependent on patient preferences and medication costs. Ravulizumab is more costly during the first year of therapy due to the large first loading dose but is significantly less costly than eculizumab after the first year of therapy. Ravulizumab also offers much less frequent administration compared with eculizumab, which is a very attractive feature of this product to improve patient quality of life. To transition patients currently receiving eculizumab to ravulizumab, the ravulizumab loading dose should be administered 2 weeks after the last eculizumab dose, with ravulizumab maintenance dosing initiated 2 weeks after the ravulizumab loading dose. Conversely, the optimal approach to switching from ravulizumab to eculizumab is not clear at this time.

STAR
What is the initial approach to treatment for a patient with undifferentiated TMA, and what laboratory assays and clinical symptoms should be obtained to further tailor treatment? If aHUS is ultimately diagnosed, how would the treatment approach be altered?

Treatment Algorithm
An approach to initial and definitive treatment for TMAs is shown in FIGURE 3. In patients presenting with evidence of TMA, an ADAMTS13 activity should be obtained to rule out TTP, stool studies should be sent to identify Shiga toxin-producing E coli, as well as other laboratory assays that could identify potential causes of HUS including obtaining of a S pneumoniae urine antigen and anti-complement factor H antibodies. Of note, plasma exchange is the first-line therapy for TTP, which is considered to be more rapidly fatal than aHUS. Because TTP cannot be ruled out until the ADAMTS13 activity result is available, which can take 24 hours or longer, plasma exchange should generally be initiated first to provide optimal TTP treatment, which would also provide some benefit for aHUS (though not considered optimal therapy). An exception to this approach is made in patients with prior known aHUS experiencing a relapse, in which case aHUS treatment should be initiated upfront with C5 inhibitors rather than plasmapheresis.

Treatment should be adjusted once the ADAMTS13 antibody and stool Shiga toxin results are received. If the ADAMTS13 activity is less than 10%, aHUS is ruled out, the patient is diagnosed with TTP, and plasmapheresis is continued for TTP treatment with additional therapies added. If the stool sample is positive for Shiga toxin, typical HUS is diagnosed and plasmapheresis is discontinued, in favor of implementation of supportive care measures alone. If TTP and typical HUS are ruled out, aHUS should be considered, which warrants plasmapheresis discontinuation and initiation of C5 inhibitor therapy. While not yet standard of care, if aHUS is suspected and there is no response to C5 inhibitor therapy after 4 to 6 weeks, a CH50 assay can be obtained, which is a functional assay of the complement system. A CH50 value above or below 10% can be used to assess treatment response and the need for C5 inhibitor discontinuation or dose adjustment. If the CH50 result is below 10%, the patient is unlikely to have aHUS, and C5 inhibitor therapy should be discontinued and alternative etiologies of the patient’s presenting symptoms should be considered. If the CH50 is above 10% in the setting of suboptimal response, the C5 inhibitor dose may be increased or dosing interval reduced.

Treatment Duration
Historically, aHUS treatment with C5 inhibitors was considered a lifelong therapy. However, recent data suggest early discontinuation may be considered in patients with complete remission, stable and recovered renal function, a clearly identified and resolved aHUS trigger, and patient agreement and compliance with frequent follow-up and laboratory monitoring. In general, early treatment discontinuation is not considered applicable to patients who have undergone renal transplantation or for patients with certain genotypes who are at high relapse risk. If relapse does occur, prompt reinitiation of C5 inhibitor treatment is vital. Patients with successful C5 inhibitor discontinuation should have therapy reinitiated if undergoing a high-risk exposure, such as pregnancy or surgery.

Future Directions in aHUS Treatment
There are many exciting developments underway to increase treatment options for aHUS, many of which address limitations of current treatment options, such as the IV route of
administration of eculizumab and ravulizumab. Ravulizumab is currently being investigated for subcutaneous (SC) administration in a phase 3, randomized, open-label, parallel-group, multicenter study of patients with PNH.32,33 This study aims to evaluate SC versus IV administration of ravulizumab. The ongoing study met its primary objective of pharmacokinetic-based noninferiority of SC ravulizumab administration compared with IV administration at day 71 (P <.0001 for noninferiority). Additionally, serum-free C5 concentrations remained below the target threshold, and safety outcomes through the follow-up period were consistent with previous trials and did not reveal any unexpected findings. All but one of the 135 patients in this trial are also participating in the extension study that will follow patients for an additional 182 weeks. Based on these findings, Alexion planned to file for FDA approval for ravulizumab administration via the SC route in the third quarter of 2021. If approved, ravulizumab via SC injection will give patients with PNH an additional treatment option that would allow for self-administration of this medication.

Other complement inhibitors with novel mechanisms of action are currently under investigation in preclinical and clinical trials for the management of aHUS. One such agent is narsoplimab (OMS721), a human monoclonal antibody targeting mannann-binding lectin-associated serine protease-2, the effector enzyme of the lectin pathway of the complement system.34 This novel drug is designed to prevent complement-mediated inflammation and endothelial damage while leaving other functions of the innate immune system intact. Narsoplimab has received FDA Fast Track designation for the treatment of aHUS. The safety and efficacy of narsoplimab in adults and adolescents with aHUS is currently being studied in a phase 3, uncontrolled, open-label, multicenter study.35 This study will evaluate narsoplimab use in patients with plasma therapy-resistant aHUS and plasma therapy-responsive aHUS. The primary outcome is the effect of narsoplimab platelet count recovery. Recruitment is currently underway with an anticipated approximate enrollment of 80 subjects. Interim results are expected to be performed on 40 subjects after 25 weeks of treatment are completed.

Nomacopan (formerly known as Coversin) is a C5 complement inhibitor that also binds the pro-inflammatory eicosanoid leukotriene B4.36,37 This agent is currently being studied for several conditions involving complement pathway overactivity, including aHUS and PNH, among others. A phase 3 clinical trial is currently recruiting to assess the long-term safety and efficacy of this agent in patients with either aHUS or PNH.38 The study population will consist of patients who have completed participation in other nomacopan clinical trials and wish to continue to receive nomacopan for up to 4 years. The estimated study completion date is June 2025.

Importance of Pharmacist Involvement in aHUS Treatment

The use of C5 inhibitors is complex and involvement of pharmacists with experience and expertise regarding the use of these medications is critical. As previously mentioned, both eculizumab and ravulizumab are costly medications that often require prior authorization or other requests for insurance coverage, which pharmacists can assist with. Navigating the REMS program for both eculizumab and ravulizumab can be overwhelming for patients and providers, and pharmacists can serve as a resource to help ensure the necessary steps required of all involved parties for REMS program compliance occur. To optimize patient safety and ensure compliance with the REMS program, patients must be prescribed antimicrobial prophylaxis against meningococcal infection until they are fully immunized; pharmacists can assist in ensuring this occurs and assist providers with agent selection and dosing. Similarly, it is vital that patients be immunized against encapsulated organisms while receiving C5 inhibitor therapy, and pharmacists serve as important resources to navigate immunization schedules including not only the initial series but also booster doses as indicated. Pharmacists working at facilities where C5 inhibitors are infused can assist in dose preparation and procedures outlining monitoring parameters during and after administration and assist with AE management. Lastly, pharmacists in all areas of practice can engage with patients receiving C5 inhibitors to provide extensive counseling to empower patients with knowledge about these therapies.

Conclusion

aHUS results from dysregulation of the complement system resulting in hemolysis, thrombocytopenia, and renal failure.1 aHUS frequently occurs in patients with a genetic predisposition who experience a triggering event.2 Once diagnosed, C5 inhibitors such as eculizumab or ravulizumab are first-line treatment options.1,3 Notable AEs associated with C5 inhibitors include infusion reactions and an increased risk of infection with encapsulated organisms, most notably N meningitidis but also S pneumoniae and H influenzae.15,16 Immunization against encapsulated organisms and initiation of antimicrobial
prophylaxis against *N meningitidis* until at least 2 weeks after immunization are critical to reduce the risk of infection.15,16 Both eculizumab and ravulizumab are associated with REMS programs aiming to reduce *N meningitidis* infection risk, and require prescriber enrollment and patient counseling.27,28

According to the REMS program, patients should be provided with the patient safety brochure and patient identification card upon C5 inhibitor treatment initiation. Discontinuation of C5 inhibitors may be considered in select patients under close monitoring. Pharmacist involvement in the treatment of patients with aHUS involves many different aspects of care and can help to optimize patient outcomes.

**ADDITIONAL RESOURCES**


**REFERENCES**


POSTTEST QUESTIONS

1. Which of the following findings are characteristic of atypical hemolytic uremic syndrome (aHUS)?
   A. Normal lactate dehydrogenase
   B. Positive stool culture for Shiga toxin-producing Escherichia coli
   C. ADAMTS13 greater than 10%
   D. Preserved platelet count

2. RG is a 55-year-old patient receiving a C5 inhibitor for aHUS who has not been previously immunized against meningococcal infection. Which of the following is recommended for this patient in addition to antibiotic prophylaxis?
   A. No vaccination is needed based on the patient’s age.
   B. Vaccination against meningococcal groups ACWY only
   C. Vaccination against meningococcal group B only
   D. Vaccination against meningococcal groups ACWY and group B

3. Which statement is true regarding intravenous (IV) dosing considerations of C5 inhibitors for the treatment of aHUS in adult patients?
   A. Eculizumab maintenance doses are administered once weekly.
   B. Eculizumab dosing is based on patient weight.
   C. Ravulizumab requires administration of 4 weekly doses before initiation of maintenance dosing.
   D. Ravulizumab maintenance doses are administered once every 8 weeks.

4. Which statement is true for adult patients with aHUS when transitioning from eculizumab maintenance therapy to ravulizumab IV infusions?
   A. The first dose of ravulizumab should be given the same day as the last maintenance dose of eculizumab.
   B. Administer 1 ravulizumab loading dose 2 weeks after the last eculizumab maintenance dose.
   C. Initiate ravulizumab maintenance dosing 1 week after the ravulizumab loading dose.
   D. Maintenance doses of ravulizumab can only vary within 3 days of scheduled administration.