Pharmacy Today
An official publication of the American Pharmacists Association
MARCH 2023

CONTINUING PHARMACY EDUCATION
CPE
New therapeutic agents marketed in 2022: Part 1

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BENEFITING PATIENTS AND THE PHARMACY

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OUD guidance needed

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Off-label demand and depletion

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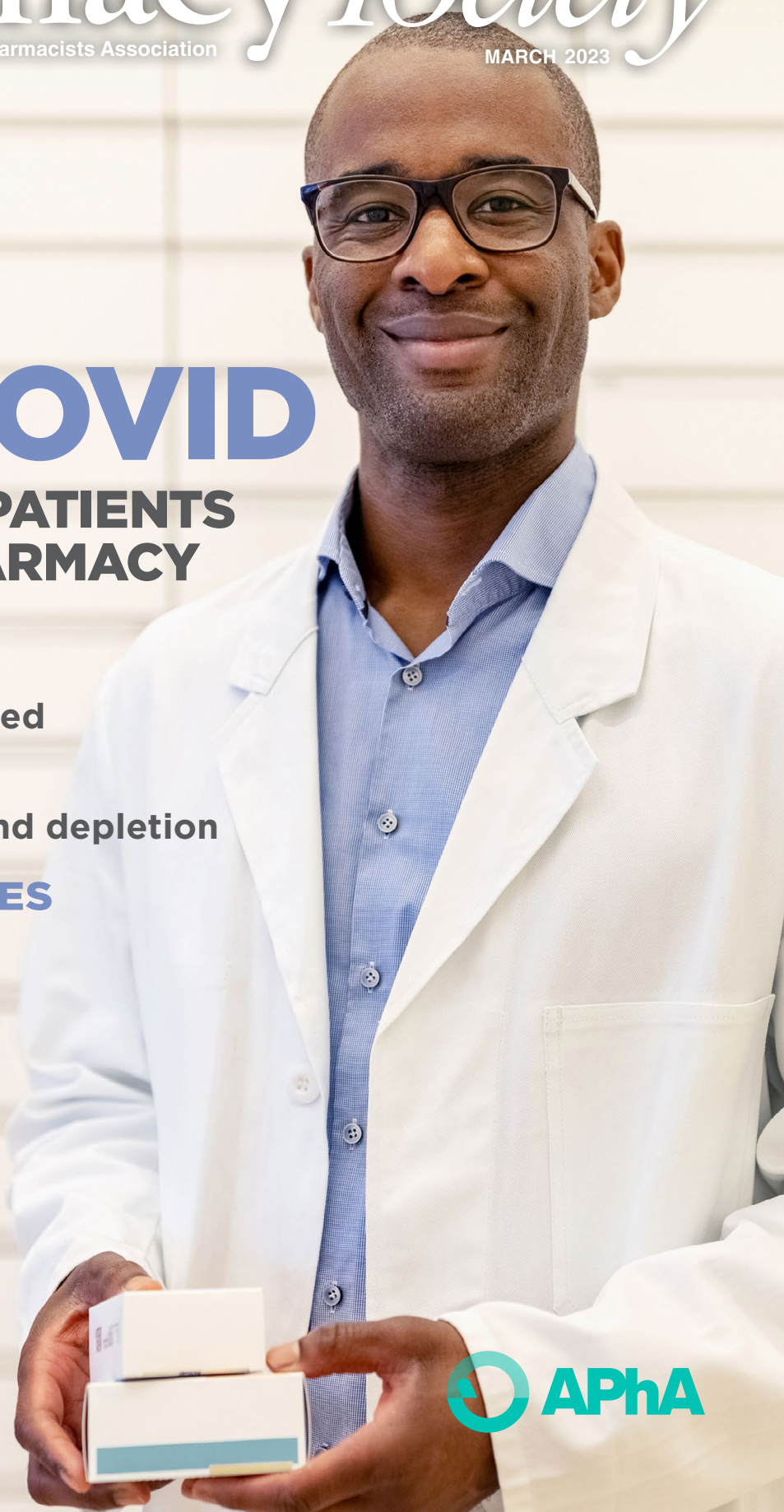
FDA explains



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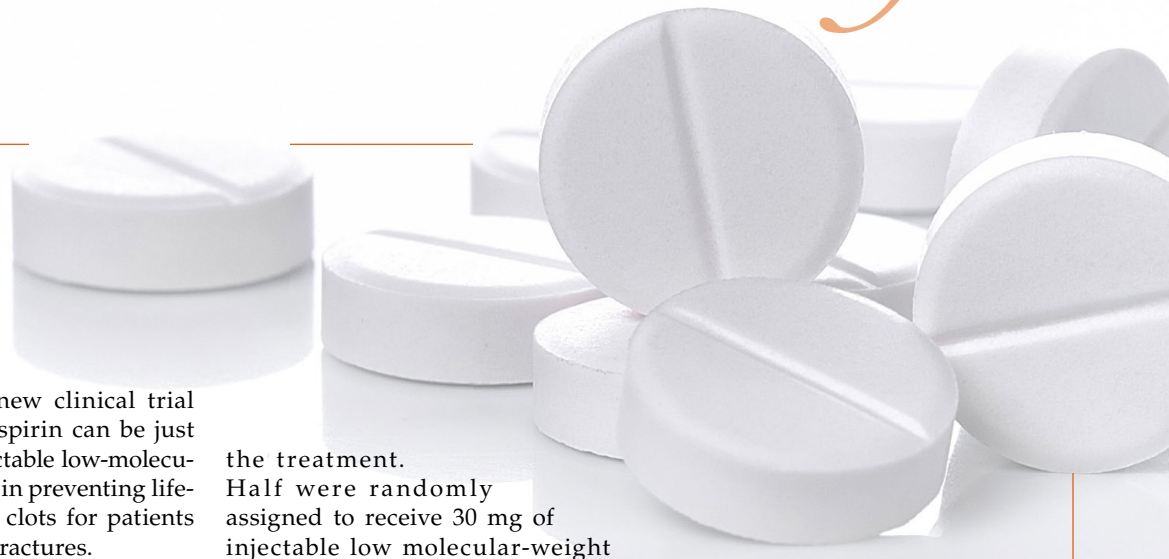


Aspirin may be just as good as blood thinner injections for patients hospitalized with fractures

Findings from a new clinical trial found that OTC aspirin can be just as effective as injectable low-molecular-weight heparin in preventing life-threatening blood clots for patients hospitalized with fractures.

The findings, published January 13, 2023, in *NEJM*, could even lead surgeons to change their practice and administer aspirin to these patients.

"Many patients with fractures will likely strongly prefer to take a daily aspirin over receiving injections after we found that both give them similar outcomes for prevention of the most serious outcomes from blood clots," said the study's lead investigator Robert V. O'Toole, MD, chief of orthopaedics at the R Adams Cowley Shock Trauma Center at the University of Maryland Medical Center (UMMC), in a news release. "We expect our findings from this large-scale trial to have an important impact on clinical practice that may even alter the standard of care."

The study enrolled 12,211 patients with leg or arm fractures at 21 trauma centers in the United States and Canada. Patients had experienced a fracture of an extremity that required surgery or a pelvic fracture regardless of the treatment. Half were randomly assigned to receive 30 mg of injectable low molecular-weight heparin twice daily. The other half received 81 mg of aspirin twice daily. Patients were followed for 90 days to measure health outcomes from the two treatments.

The main finding of the study was that aspirin was noninferior, or no worse than low molecular-weight heparin in preventing death from any cause—47 patients in the aspirin group died, compared with 45 patients in the heparin group. The researchers also found no differences between the two groups in pulmonary embolisms. The incidence of bleeding complications, infection, wound problems, and other adverse events from the treatments was also similar in both groups.

Of all the outcomes studied, the only potential difference noted was in deep vein thrombosis. This condition was relatively uncommon in both groups as it occurred in 2.51% of patients in the aspirin group, and in 1.71% of patients in the heparin group.

"This relatively small difference was driven by clots lower in the leg, which are thought to be of less clinical significance and often do not require treatment," said study author Deborah Stein, MD, MPH, director of Adult Critical Care Services at UMMC, in the news release.

An estimated 1 million American are hospitalized each year with extremity fractures. According to Mark Gladwin, MD, from the University of Maryland School of Medicine, findings from this new study could help prevent potentially fatal blood clots in these patients using a medication that is cheaper and much easier to administer.

"Given these important results, we can expect the guidelines for the prevention of blood clots to be revised to include the option of aspirin for patients with traumatic bone fractures," he said in the news release. ■

CDC reports new drop in child vaccination rates

CDC said that disruptions in health care access during the COVID-19 pandemic contributed to declining rates of routine immunizations among young children. In a new report, the agency found that uptake of state-mandated vaccines dropped in 2021–2022 for kindergarteners.

People may still be trying to get back on schedule, and vaccine hesitancy is likely playing a role as well—even as COVID-19 lockdowns have ceased, CDC noted.

The CDC study examined data from federally funded immunization programs that work with education departments and schools nationwide to estimate vaccination rates among kindergarteners. Overall, vaccination rates were 93% in the 2021–2022 school year, down from 94% in the previous school year and 95% in the year before that.

The researchers noted that coverage for the measles, mumps, and rubella vaccine was 93.5%, below the approximately 95% rate needed for a community to avoid being prone to a measles outbreak. A recent measles outbreak in Ohio infected more than 80 children, all of whom were unvaccinated or only partially vaccinated.

CDC found in a separate study that national vaccine coverage by age 2 years continued to be strong and rose for some vaccines; however, routine vaccination dropped by several percentage points for children living below the federal poverty line or in rural areas who were born in 2018 and 2019.

Also, according to the study, the percentage of uninsured children who were not vaccinated by age 2 years was 8 times higher than that of children who were covered by private insurance. ■

FDA calls for authority to regulate CBD products

Citing safety risks, FDA said that products containing cannabidiol (CBD) call for greater supervision than the agency can now offer, and FDA will request new regulating authorities from Congress.

FDA also said products derived from legal cannabis should not be regulated as they currently are (i.e., as dietary supplements or food additives) in light of the products' risk to humans—particularly to children and pregnant people—and to animal health.

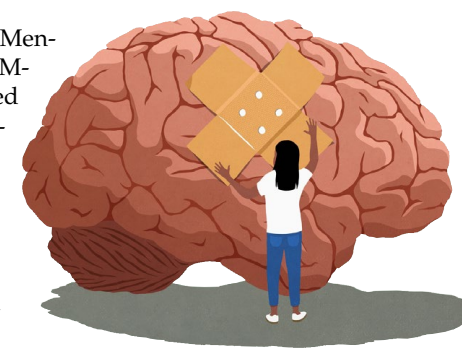
FDA's expanded authority could include mandating clear labels, prohibiting contaminants, restricting doses, and establishing a minimum purchase age, according to the agency.

"Given the available evidence, it is not apparent how CBD products could meet safety standards for dietary supplement or food additives," said FDA Principal Deputy Commissioner Janet Woodcock in a press statement.

She also said studies suggest that long-term use of CBD products could have safety issues, such as drug interactions, potential damage to an individual's liver, and possible harm to the male reproductive system.

When Congress legalized hemp and related products in 2018, it left their regulation to FDA. As a result, makers of CBD products have operated in the absence of specific federal rules over their marketing or manufacturing. Some states have established their own sets of rules. A report from FDA in 2021 estimated that the $4.6 billion market would quadruple by 2026. ■

New SAMHSA data reveals mental illness and substance use levels



New data from the Substance Abuse and Mental Health Services Administration (SAMHSA) reveal how people living in the United States reported their experiences with mental health conditions, substance use, and the pursuit of treatment in 2021.

Among individuals ages 12 years and older, 61.2 million people used illicit drugs in 2021, most often marijuana, according to key findings from the National Survey on Drug Use and Health.

Additionally, 9.2 million people 12 years or older misused opioids in the past year, and 94% of people in that age group with a substance use disorder did not receive any treatment.

The survey also found that about 20% of adolescents in 2021 had a major depressive episode in the past year, with almost 75% reporting symptoms consistent with severe impairment. Nearly 25% of adults age 18 years and older had a mental illness in the past year in 2021, and that figure jumped to about 33% among adults aged 18 to 25 years. Roughly 13.5% individuals 18 to 25 years old reported both substance use disorder and any mental illness in 2021.

The report also found that 12.3 million adults had serious thoughts of suicide in 2021, while 3.5 million made suicide plans and 1.7 million attempted suicide. ■

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48 **New therapeutic agents marketed in 2022: Part 1**

Daniel A. Hussar

Take the Crossword Challenge

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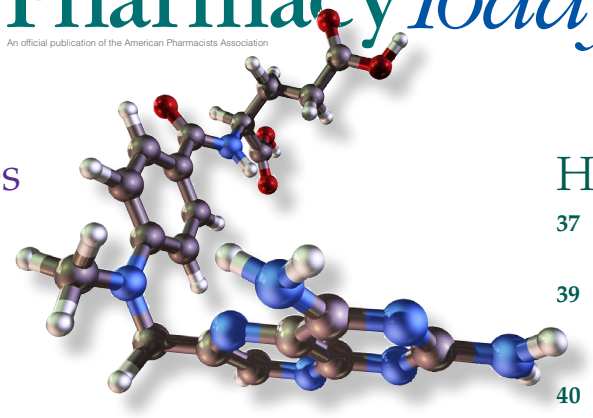

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Pharmacists have opportunities, challenges when prescribing Paxlovid

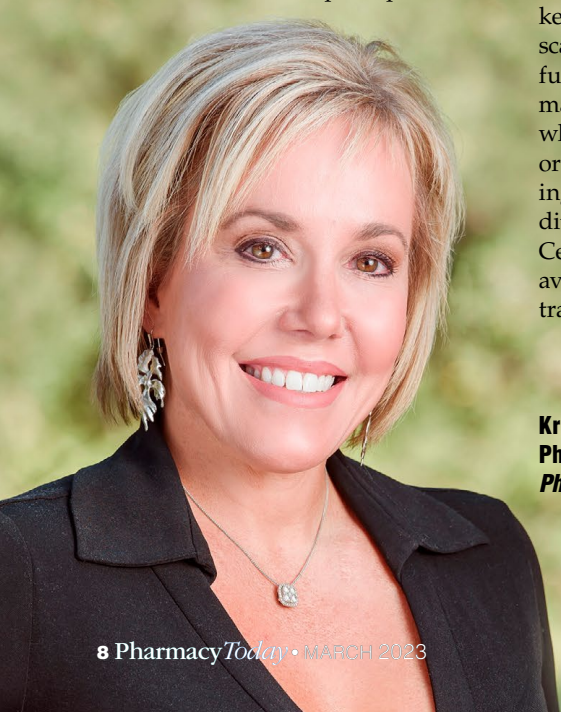
Since the onset of the COVID-19 pandemic, pharmacists' scope of practice has expanded exponentially, with pharmacists on the front lines administering COVID-19 vaccines and offering COVID-19 testing services. As of February 2023, CDC reports more than 300 million COVID-19 doses have been given in pharmacies. In July 2022, FDA revised the EUA for Paxlovid to authorize pharmacists to prescribe Paxlovid to eligible patients, with certain limitations.

This issue of *Pharmacy Today* reviews the guidelines for testing to treat COVID-19 and prescribing Paxlovid in the pharmacy, overviews practice models, and sheds light on hurdles that pharmacists must overcome in order to administer Paxlovid. According to Patrizia Cavazzoni, MD, director for FDA's Center for Drug Evaluation and Research, "FDA recognizes the important role pharmacists have played and continue to play in combatting this pandemic." She also emphasizes the role of the pharmacist in expanding early access to Paxlovid, which must be taken within 5 days after symptoms begin. This is an exciting development that increases the scope of practice for pharmacists, but it comes with challenges stemming from the time needed to assess patients' symptoms, medications, and laboratory values as well as a changing reimbursement landscape. While the federal government has provided Paxlovid to pharmacies at no cost to date, this won't be the case forever, with government funding expected to end in mid-2023. At this point, it's unknown how much of these costs will fall on patients' shoulders.

In this issue, you'll also find information on new drug approvals, including Airsupra, the only rescue inhaler approved to treat symptoms of asthma and to help prevent asthma attacks; an update on much-needed fentanyl-based opioid use disorder guidance; and an overview of the hype and demand surrounding GLP-1 receptor agonists. Learn about new HIV treatment and prevention recommendations and get your CPE credit with this month's article on new therapeutic agents marketed in 2022.

The authority of pharmacists to test to treat COVID-19 in pharmacies is an important addition to the expanding scope of pharmacy practice. These roles require pharmacists to quickly learn new information and skills to keep up with a changing practice landscape. I encourage you to check out helpful APhA resources such as the Pharmacist Decision Making Support Tool, which is available at apha.us/Paxlovid, or pursue additional education in testing to treat COVID-19 and other conditions through APhA's Test and Treat Certificate Training Program, which is available at pharmacist.com/certificate-training-programs.

Have a great *Today!* ■



Kristin Wiisanen
PharmD, FAPhA, FCCP
***Pharmacy Today* editor in chief**

Springtime brings renewal

Springtime, blue skies, and this year's Annual Meeting & Exposition are here, and with them the promise of new growth, expansion, and an invitation to open one's arms to welcome change. Excitement, opportunities, and inspiration are all abuzz here in Phoenix as we gather at APhA2023 to celebrate accomplishments, address challenges, and connect with new and known colleagues.

Our theme, "Rise! Advancing in the Face of Adversity," is evident in the entrepreneurial and pioneering practices we see in our profession. This innovation in pharmacy, humming and reaching far and wide, drives the top use of our knowledge and skills.

There is a digital transformation gaining momentum in health care, and technology continues to be employed in new ways across the health care system.

Telehealth services exploded during the pandemic, supported by wide-ranging technology systems, and are expected to be prominent moving forward. Digital therapeutics are poised to impact the treatment of conditions in new ways, and pharmacists are increasing their involvement with digital monitoring devices and corresponding assessment services. Importantly, there are renewed efforts to rebuild the information superhighway for the seamless exchange of clinical data needed to effectively care for patients.

As we are seeing effective use of automation and artificial intelligence in a way that frees up the pharmacist, allowing them to focus on clinical services, there remain hurdles as well as tremendous room for growth in all practice settings.

Pharmacists and pharmacy teams need to be included in these trailblazing endeavors. We're reimagining pharmacy practice models and pharmacy team member roles with inclusion in mind.

To be part of the play on the field and help patients to the best of our abilities, pharmacists need access.

Most recently, APhA sent a letter to HHS and The White House to clarify whether federal PREP Act coverage for pharmacists and pharmacy team members to test, treat, and immunize adults and children ages 3–18 years old will continue past May 11, 2023.

APhA emphasized that ending federal PREP Act coverage compromises the federal government's commitment to the public health response and promoting health equity. While many states have updated their laws to authorize members of the pharmacy team to perform the services authorized under the PREP Act, this is a work in progress.

These promising and great strides before us can only happen with a strong pharmacy workforce and an updated pharmacy payment and reimbursement model.

There is room for improvement stabilizing and maintaining pharmacist and pharmacy technician well-being and resilience to effectively care for patients. This is complex, and APhA is committed to doing the additional work required to meaningfully support pharmacists and their teams.

As the leading voice and advocate for the profession, APhA's primary focus in 2023 is driving the change needed to make a difference for pharmacy team members and pharmacy as the central role in patient care.

Gathering together to share our stories, strategies, and support, we "Rise!" to advance our profession! ■

ILISA BG BERNSTEIN
PharmD, JD, FAPhA
Interim Executive Vice President and CEO
American Pharmacists Association

NEW DRUGS

BEXAGLIFLOZIN
(Brenzavvy—TheracosBio)

Drug class: Brenzavvy is a sodium-glucose cotransporter-2 (SGLT-2) inhibitor.

Indication: Brenzavvy is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Recommended dosage and administration: The recommended dose is 20 mg once daily, taken in the morning, with or without food. The tablet should not be crushed or chewed. Renal function should be assessed prior to initiation of Brenzavvy and as clinically indicated. Correct volume depletion before initiation occurs.

Common adverse effects: The most common adverse reactions in patients taking Brenzavvy are female genital mycotic infections, urinary tract infection, and increased urination.

Warnings and precautions: Brenzavvy is not recommended in patients with type 1 diabetes mellitus as it may increase the risk of diabetic ketoacidosis in these patients. Use of Brenzavvy is also not recommended in patients with an eGFR <30 mL/min/1.73 m^2. Brenzavvy is contraindicated in patients with a hypersensitivity to bexagliflozin or any excipient in Brenzavvy and patients on dialysis. Patients of reproductive potential should be advised of the potential risk to a fetus especially during the second and third trimesters of pregnancy. Brenzavvy is not recommended during the second and third trimesters of pregnancy or while breastfeeding. In geriatric patients, there is a higher incidence of adverse reactions related to volume depletion. In patients with renal impairment, there is a higher incidence of adverse reactions related to reduced renal function. Brenzavvy is not recommended for use in patients with hepatic impairment.

Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue, evaluate, and treat promptly. Before initiating treatment with Brenzavvy, consider risk factors for ketoacidosis. Patients may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. Consider factors that may increase the risk for amputations before initiating Brenzavvy. Monitor patients for signs and symptoms of infection or ulcers of the lower limbs and discontinue if these occur. Before initiating Brenzavvy, assess and correct volume status in patients with impaired renal function or low systolic blood pressure, older patients, or those on diuretics.

Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. Consider a lower dose of insulin or insulin secretagogue to reduce the risk of hypoglycemia when used in combination with Brenzavvy. Serious, life-threatening cases of necrotizing fasciitis of the perineum have occurred in both females and males treated with SGLT-2 inhibitors.

Assess patients presenting with pain, tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. Monitor and treat genital mycotic infections as appropriate.

PIRTOBRUTINIB
(Jaypirca—Loxo Oncology)

Drug class: Jaypirca is a kinase inhibitor.

Indication: Jaypirca is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least 2 lines of systemic therapy, including a BTK inhibitor.

Recommended dosage and administration: The recommended dosage is 200 mg orally once daily, swallowed whole with water, with or without food. Reduce dose in patients with severe renal impairment.

Common adverse effects: The most common adverse reactions in patients with MCL are fatigue, musculoskeletal pain, diarrhea, edema, dyspnea, pneumonia, bruising, decreased neutrophil count, decreased lymphocyte count, and decreased platelet count.

Warnings and precautions: Avoid concomitant use with strong CYP3A inhibitors. If concomitant use is unavoidable, reduce the Jaypirca dose. Avoid concomitant use with strong or moderate CYP3A inducers. If concomitant use is unavoidable, increase the Jaypirca dose. For substrates where minimal concentration changes may increase the risk of adverse reactions, follow recommendations for coadministration with CYP2C8, CYP2C19, CYP3A, P-gp, or BRCP inhibitors provided in their approved product labeling. Monitor for signs and symptoms of infection, evaluate promptly, and treat. Monitor for bleeding as hemorrhage may occur. Monitor complete blood counts during treatment. Monitor for symptoms of arrhythmias such as atrial fibrillation and atrial flutter. Other malignancies have developed, including skin cancers and other carcinomas. Monitor and advise patients to use sun protection. Jaypirca can cause fetal harm. Advise patients of reproductive potential of possible risk to a fetus and to use effective contraception. Jaypirca should not be used while breastfeeding.

ELACESTRANT
(Orserdu—Stemline Therapeutics)

Drug class: Orserdu is an estrogen receptor antagonist.

Indication: Orserdu is indicated for treatment of postmenopausal women or adult men, with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

Recommended dosage and administration: The recommended dosage of Orserdu is one 345 mg tablet taken orally, once daily, with food.

Dose interruption, reduction, or permanent discontinuation may be required due to adverse reactions.

Common adverse effects: The most common adverse reactions in patients taking Orserdu were musculoskeletal pain, nausea, increased cholesterol, increased AST, increased triglycerides, fatigue, decreased hemoglobin, vomiting, increased ALT, decreased sodium, increased creatinine, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flashes, and dyspepsia.

Warnings and precautions: Orserdu can cause fetal harm. Patients should be advised of the potential risk to a fetus and to use effective contraception. Patients should be advised not to breastfeed while taking Orserdu. Avoid use in patients with severe hepatic impairment. Reduce the dosage for patients with moderate hepatic impairment. Avoid concomitant use with strong or moderate CYP3A4 inducers and inhibitors. Orserdu may cause hypercholesterolemia and hypertriglyceridemia. Monitor lipid profile prior to starting treatment and periodically thereafter.

NEW DOSAGE FORMS

RISPERIDONE
(Rykindo—Luye Pharma)

Drug class: Risperidone is an atypical antipsychotic.

Indication: Rykindo is indicated for the treatment of schizophrenia in adults and as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder in adults.

Recommended dosage and administration: Prior to initiating treatment with Rykindo, patients must show tolerability with oral risperidone. Rykindo should be administered by I.M. injection in the gluteal muscle by a health care provider. The recommended dosage of Rykindo is 25 mg I.M. every 2 weeks. Patients not responding to 25 mg may benefit from 37.5 mg or 50 mg. Dosage should not be titrated more frequently than every 4 weeks. The maximum recommended dosage is 50 mg every 2 weeks. The first dose of Rykindo should be administered along with 7 days of oral risperidone. In patients with renal or hepatic impairment, titrate with oral risperidone up to at least 2 mg prior to initiating treatment with Rykindo. A starting dose of 12.5 mg may be appropriate for some patients.

Common adverse effects: The most common adverse reactions in patients with schizophrenia were headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increase, pain in extremity, and dry mouth. The most common adverse reactions in patients with bipolar disorder were increased weight, tremor, and parkinsonism.

Boxed warning: Older patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Rykindo is not approved for use in patients with dementia-related psychosis.

Other warnings and precautions: Rykindo is contraindicated in patients with a known hypersensitivity to risperidone, paliperidone, or to any components in Rykindo. When taken with strong CYP2D6 inhibitors, there may be an increased risperidone plasma concentration. When taken with strong CYP3A4 inducers, there may be a decreased plasma concentration of risperidone. Rykindo may cause extrapyramidal and withdrawal symptoms in neonates with third trimester exposure. There is an increased risk of cerebrovascular adverse reactions in older patients with dementia-related psychosis. If neuroleptic malignant syndrome occurs, manage with immediate discontinuation and close monitoring. Tardive dyskinesia may occur. Monitor for hyperglycemia, dyslipidemia, and weight gain. Prolactin elevations may occur and persist during chronic administration of Rykindo. Hyperprolactinemia, when associated with hypogonadism, can lead to decreased bone density in males and females. Monitor heart rate and blood pressure and warn patients with known cardiovascular disease or cerebrovascular disease, and risk of dehydration or syncope. Perform complete blood cell counts in patients with a history of clinically significant low white blood cell count or history of leukopenia or neutropenia. Consider discontinuing Rykindo if a clinically significant decline in white blood cell count occurs in the absence of other causative factors. There is potential for cognitive and motor impairment so patients should use caution when operating machinery. Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Priapism has been reported during postmarketing use of other risperidone products. Severe priapism may require surgical intervention. ■

Also in this issue

Airsupra: The first and only rescue inhaler approved to treat symptoms of asthma (page 16)

Sleep aids to the rescue?

Mary Warner

According to CDC, 8.4% of adults took sleep medication either every day or most days to help them fall or stay asleep in 2020. Women (10.2%) were more likely than men (6.6%) to take medication for sleep, and the use of sleep medication generally rose with increasing age.

Diphenhydramine and doxylamine both lose their effectiveness over time, with their sedative effect noticeably decreasing within days of repeated use.

Insomnia can be caused by stress and by both prescription and nonprescription medications, including antidepressants, antihypertensive agents, and decongestants such as pseudoephedrine and phenylephrine. Drinking caffeinated beverages in the late afternoon or evening hours can also cause insomnia, as can late-night exercise and late-evening meals.

Sleep specialists often suggest that patients practice sleep hygiene, such as daily sleep routines and environmental adjustments (e.g., dim light and cool temperatures) before beginning to use a sleep aid. The Sleep Foundation recommends following a consistent nightly routine, having a fixed wake-up time, prioritizing sleep, and avoiding naps during the day to catch up on sleep. Unplugging electronics and avoiding caffeine within a few hours of bedtime can also improve sleep.

For patients who have trouble falling or staying asleep, nonprescription sleep aids can be an effective solution. OTC sleep aids commonly include one of two antihistamines, diphenhydramine or doxylamine, to treat insomnia. Natural supplements, most often melatonin or valerian (*Valeriana officinalis*), are also available as sleep aids, though their efficacy is questioned.

Antihistamine sleep aids

Both diphenhydramine and doxylamine affect sleep by competitively blocking histamine-1 receptors and are well absorbed, typically taking effect within an hour after a dose. The usual dosage for patients 12 years and older is 50 mg diphenhydramine or 25 mg doxylamine, taken 30 minutes prior to bedtime.

Diphenhydramine is available as tablets, rapidly dissolving tablets, capsules, and liquid, while doxylamine is available only as tablets. Doxylamine has similar efficacy as diphenhydramine, but it has a longer half-life and may have residual effects. Adverse effects to both medications are those associated with antihistamine use, including dry mouth, nose, and throat; dizziness; nausea and vomiting; and constipation.

Combination products containing diphenhydramine plus acetaminophen, ibuprofen, or aspirin are also widely available. These are most often labeled with "PM," such as Tylenol PM, Advil PM, or Excedrin PM, and contain 25 mg or 50 mg of diphenhydramine along with the analgesic medication.

Natural supplements

Complementary therapies such as melatonin, valerian, and chamomile (*Matricaria recutita*) are often promoted as sleep aids. The American Academy of Sleep Medicine clinical guideline, published in 2017, recommends against the use of melatonin or valerian for treatment of insomnia in adults based on insufficient evidence of their efficacy.

The recommendation against melatonin is based on 2 mg doses, which reduced sleep onset by an average of 9 minutes versus placebo but with only small improvements in sleep quality. Melatonin is likely most useful in shifting circadian rhythm.

Clinical trials using valerian and chamomile also show no statistically significant differences with placebo for sleep onset, duration, or efficiency according to a meta-analysis by Leach and Page published in the December 2015 issue of *Sleep Medicine Reviews*. Adverse events, including diarrhea, were more common when valerian was used versus placebo.

What to tell your patients

Advise patients to practice good sleep hygiene before trying OTC sleeping aids, including avoiding caffeine for several hours before bed. Ensure that patients understand that diphenhydramine and doxylamine both lose their effectiveness over time, with their sedative effect noticeably decreasing within days of repeated use. Patients with chronic insomnia should visit a physician specializing in sleep disorders to explore causes and potential treatment.

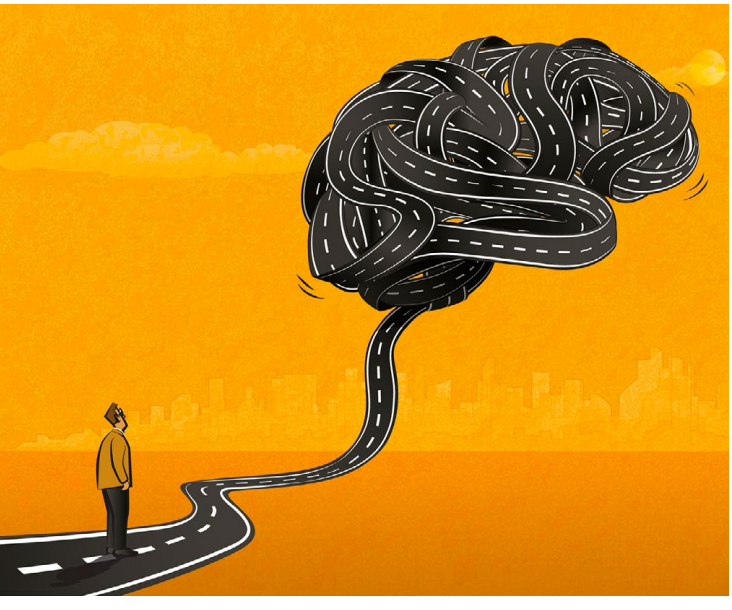
For further information, please see Chapter 46 of APhA's *Handbook of Nonprescription Drugs*, available in print via the bookstore on pharmacist.com or online through Pharmacy Library. ■

SAMe: The same old, same old?

Mickie Cathers

S-adenosyl-L-methionine (SAMe) is a compound found naturally in the body, produced in the liver. As a supplement, SAMe is advertised as supporting a healthy mood and emotional well-being. Some products also promise a liver detox cleanse as well as a joint and brain boost. But how does SAMe measure up?

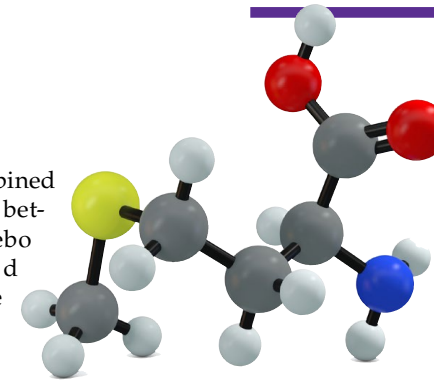
SAMe is created within the body from methionine, an amino acid found in foods, and helps produce and regulate hormones and maintain cell membranes. SAMe facilitates dopamine and norepinephrine synthesis in the central nervous system and as the principal methyl donor in methyltransferase reactions, SAMe has been shown in studies to restore hepatic glutathione deposits and modulate liver injury.



Is there a benefit?

Research on SAMe has mostly focused on potential beneficial effects related to depression, liver diseases, and osteoarthritis, with mixed results.

A 2020 systematic review of double-blind, randomized controlled trials comparing SAMe to placebo and other antidepressants by Cuomo and colleagues in *Annals of General Psychiatry* examined the evidence concerning the efficacy of SAMe in treatment of major depressive disorder (MDD). Eight trials were evaluated with a total of 1,011 participants. Studies ranged between 2 and 12 weeks with a daily dose of SAMe from 20 mg to 3,200 mg. Three out of 5 studies showed significant improvement over placebo. Four comparisons showed no significant difference over antidepressants such as imipramine or escitalopram. One study concluded that SAMe combined with SSRI was better than placebo administered with SSRI. The study authors commented that larger, double-blind randomized controlled studies were warranted to confirm the antidepressant effectiveness of SAMe.



A 2020 double-blind, randomized controlled trial by Sarris and colleagues published in *Psychopharmacology (Berlin)* tested the efficacy of SAMe versus placebo in patients with MDD and mild to moderate levels of depressive symptoms who are not currently taking antidepressants. This 8-week, double-blind, randomized controlled trial focused on 800 mg/day of SAMe monotherapy versus placebo. The study showed a high placebo efficacy rate of over 50% and although a differential reduction in depression symptoms seemed to favor SAMe, the results were not statistically significant.

Liver disease and osteoarthritis

A 2015 systematic review and meta-analysis in *PLoS One* by Guo and colleagues evaluated 20 years of randomized controlled trials of chronic liver disease treatment. Their findings suggest that SAMe could be used as the basis of a medication regimen for liver function improvement due to its safety profile but that it demonstrated limited clinical value in treatment of certain chronic liver diseases.

Several randomized controlled trials also assessed the efficacy of SAMe compared with placebo or NSAIDs in the treatment of osteoarthritis. A meta-analysis by Soeken and colleagues in the *Journal of Family Practice* revealed that only 2 out of 11 trials concluded that SAMe appears to be as effective as NSAIDs in reducing pain and improving joint function in patients with osteoarthritis without the adverse effects often associated with NSAIDs. They noted that most studies weren't well-designed and included small population sizes.

What to tell your patients

While research doesn't consistently support any benefit of using SAMe for depression, liver disease, or osteoarthritis, the supplement is safe with mild and transient adverse effects such as nausea or upset stomach. SAMe is available as a capsule, tablet, or liquid in 200 mg to 400 mg dosages.

Patients should be aware that SAMe may interact with antidepressants and can possibly increase anxiety and mania in patients with bipolar disorder.

Those with weakened immune systems may be at increased risk of infection as SAMe may encourage the growth of the bacteria pneumocystis. Contraindications include antidepressants and other drugs and supplements, such as St. John's Wort, that increase levels of serotonin, as well as antipsychotics, amphetamines, dextromethorphan, levodopa, and narcotics such as meperidine and tramadol. ■

Breathing easy with Airsupra

Lauren Howell, PharmD

For years, patients with asthma have been prescribed regimens that include several different inhalers, requiring them to remember the correct timing and situation for using each one. The development of combination inhalers has allowed patients to carry fewer inhalers and has significantly simplified regimens. While combination inhalers are not necessarily new, Airsupra (AstraZeneca) is the first and only rescue inhaler that is approved to treat symptoms of asthma, including airway tightening, and to help prevent asthma attacks.

How it works and recommended dosage

Airsupra is a combination of a beta$_2$ adrenergic agonist called albuterol and a corticosteroid called budesonide. Albuterol works to combat the symptoms of asthma by relaxing the smooth muscles of airways while budesonide works to decrease inflammation and prevent future attacks.

Airsupra is packaged as a pressurized metered dose inhaler that delivers 90 µg of albuterol and 80 µg of budesonide per actuation. The recommended dosage is 2 actuations (180 µg albuterol/160 µg budesonide) by oral inhalation as needed for asthma symptoms. No more than 6 doses or 12 inhalations should be used in a 24-hour period.

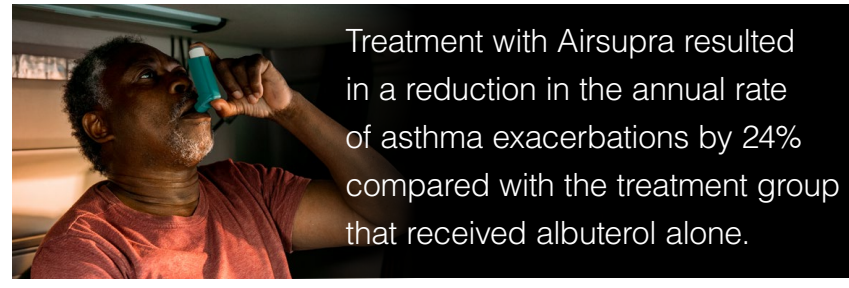
Drug interactions

Airsupra should be used with caution in combination with strong CYP3A4 inhibitors, as this may cause systemic corticosteroid effects. Additionally, Airsupra should be used judiciously with other short-acting beta agonists. If a patient is taking a beta-blocker, the effectiveness of Airsupra may be decreased and severe bronchospasm may occur.

In patients using Airsupra, consider alternatives to beta-blockers and if no alternative is available, consider the use of a cardioselective beta-blocker. The use of Airsupra with diuretics may potentiate hypokalemia or ECG changes. If used with digoxin, serum digoxin levels may be decreased. Use Airsupra with extreme caution if using concomitantly with monoamine oxidase inhibitors or tricyclic antidepressants.

Adverse effects and contraindications

Airsupra is contraindicated in patients with a hypersensitivity to albuterol, budesonide, or to any of the excipients. The most common adverse reactions in patients using Airsupra are headache, oral candidiasis, cough, and dysphonia. In patients with hepatic impairment, systemic exposure to budesonide may increase. Cardiovascular effects may occur so use with caution in patients sensitive to sympathomimetic drugs and patients with cardiovascular disorders. Use with caution in patients with convulsive disorders, hyperthyroidism, diabetes mellitus, and ketoacidosis. Hypokalemia may occur. Use with caution in patients with potential of worsening infections. Monitor patients with major risk factors for decreased bone mineral content. Glaucoma and cataracts may occur.



Clinical trials

The efficacy of Airsupra was evaluated in both the MANDALA and DENALI trials. MANDALA was a phase III, randomized, double-blind, multicenter, parallel-group, event-driven trial. In MANDALA, treatment with Airsupra, compared to treatment with albuterol alone, demonstrated significantly reduced risk of severe asthma exacerbations as assessed by the time to first severe asthma exacerbation. There were reductions in severe asthma exacerbation risk regardless of exacerbation history, baseline lung function, and asthma severity. Treatment with Airsupra resulted in a reduction in the annual rate of asthma exacerbations by 24% compared with the treatment group that received albuterol alone.

DENALI was a phase III, randomized, double-blind, placebo-controlled, multicenter, parallel-group trial that was designed to evaluate the efficacy and safety of Airsupra compared to its components on improvement in lung function. In this trial, Airsupra demonstrated a statistically significant improvement in lung function measured by forced expiratory volume in one second, compared to the individual components albuterol and budesonide, and compared to placebo. Onset of action and duration of effect were similar for both Airsupra and albuterol. The safety and tolerability of Airsupra was consistent with the known profiles of the components.

Patient counseling

Patients should be advised to seek medical attention immediately if treatment with Airsupra becomes less effective for symptomatic relief or if symptoms become worse. Additionally, patients should be advised not to exceed 6 doses in a 24-hour period. Patients should be instructed to prime the inhaler before using for the first time, when the inhaler has not been used for more than 7 days, is dropped, or after cleaning, and to shake well before each spray. Advise patients to rinse the mouth with water, if available, without swallowing after inhaling Airsupra to help reduce the risk of thrush. ■

Fentanyl-based OUD guidance needed in light of crisis

Loren Bonner

The latest CDC data find that deaths involving synthetic opioids like fentanyl increased by a staggering 80% over the past 2 years. These drugs were involved in more than two-thirds of the overdose deaths in the year ending March 2022. But fentanyl isn't just causing fatal overdoses; it's also making it harder for patients to start treatment for opioid use disorder (OUD).

Due to its potency and increased prevalence of misuse, fentanyl has presented challenges in starting patients on medications for opioid use disorder (MOUD) like buprenorphine.

"Patients started on buprenorphine following fentanyl use often experience significant precipitated withdrawal, which can lead the patient to not continue the buprenorphine or to return to fentanyl use," said Sarah Melton, PharmD, a professor of pharmacy practice at the Gatton College of Pharmacy at East Tennessee State University. "Because the precipitated withdrawal felt so horrible, many patients will refuse to ever try buprenorphine again."

Individuals with fentanyl OUD are at higher risk of overdose and death, creating an urgent situation that warrants evaluation of improved treatment approaches in addition to expanding and improving access to evidence-based care.

Individuals with fentanyl OUD are at higher risk of overdose and death.

"Guidance is needed as the overdose rates are skyrocketing from fentanyl and fentanyl-analogues," said Melton. "Traditional treatment with methadone and buprenorphine is not as straightforward as with prescription opioids such as oxycodone or morphine." She said it's paramount that fentanyl-based OUD guidance for prescribers and pharmacists be published and distributed.

In late 2022, Congress passed the Mainstreaming Addiction Treatment Act, which would eliminate DEA's "X-waiver." Melton said more health care professionals will be able to prescribe buprenorphine for OUD with limited training now that this requirement is removed.

Microdosing protocol

"Fentanyl has a distinct pharmacological profile compared with other opioids that contributes to this high risk of precipitated withdrawal from buprenorphine administration," said Melton, who also practices as a clinical pharmacist at a community health center.

Fentanyl is 100 times more potent than morphine and has a gradual release from lipid tissue, which increases the half-life.

"When patients refuse to continue to take buprenorphine because of a severe precipitated withdrawal, it is considered a 'failed induction,'" said Melton.

In order to treat patients who use fentanyl—and in the absence of sufficient research, data, and guidance—many clinicians have begun using microdosing approaches.

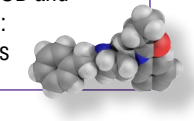
In a microdosing protocol, the patient receives a low dose of buprenorphine, which is gradually increased over several days to the target dose. A patient can continue to take a full dose of fentanyl until the therapeutic dose of buprenorphine has been achieved. At that point, the full opioid agonist or fentanyl is discontinued.

Melton said the microdosing process usually takes 3 to 10 days to work. According to the theory behind the approach, gradually adding buprenorphine on to the μ receptors using very small doses that are escalated daily will avoid displacement of the full agonist all at once, which is what triggers precipitated withdrawal, said Melton. "There are many proposed microdosing regimens that are being used in clinical practice and the literature does not support one over another," she said.

While the research is continuing to evaluate the best way to prevent precipitated withdrawal in patients who are using high potency fentanyl, the approach has helped clinicians treat patients during this time.

Melton recommends all interested health care professionals become familiar with Providers Clinical Support System (pcssnow.org) and review education about treatment of OUD, especially education on microdosing of buprenorphine for those using fentanyl.

APhA–APPM's Pain, Palliative Care and Addiction Special Interest Group offers a resource for pharmacists that is designed to provide evidence-based information addressing misconceptions surrounding OUD and MOUD and reduce stigma available at: apha.us/OpioidsResources



Stigma

For patients seeking treatment for OUD, stigma continues to be an issue.

"Pharmacists need to be on the front line to fight stigma by stocking buprenorphine in their pharmacies, being willing to dispense it, educating patients about and providing fentanyl test strips, providing naloxone, and collaborating with prescribers to ensure patients are getting comprehensive substance use treatment," said Melton.

She said stigma will only worsen as the prevalence of fentanyl, combined with the drug xylazine, spreads across the United States.

Individuals who use these drugs in combination present with severe ulcers and wounds when injected, and the combination is increasing the severity of substance use disorders and making treatment more difficult, according to Melton. ■

Overlapping gabapentin and opioid prescriptions have been on the rise

Loren Bonner

Ninety-five percent of gabapentin prescriptions are written for off-label pain management, despite studies questioning gabapentin's effectiveness for managing pain, and reports of its misuse with simultaneous opioid therapy.

Authors of a new study published November 2022 in *JAMA Internal Medicine* wanted to find out how common it was for both gabapentin and opioids to be prescribed at the same time for patients. They found consistent growth in the concurrent prescription of opioids and gabapentin throughout the 13-year study period.

"While opioid analgesic episodes plateaued and eventually began to decline, gabapentin episodes continually rose and the overlap between the two increased," said lead author Evan Peet, PhD, from the RAND Corporation. "This trend, combined with the fact that it is concentrated in high poverty, rural, and predominantly non-Hispanic white areas, suggests that this is a form of substitutionary prescribing, which is occurring in response to the opioid crisis and the associated supply-side restrictions to opioid prescribing."

Between 2006 and 2018, Peet and his research team found that the total volume of opioid prescriptions initially rose but began to plateau before falling at the end of the observational period. In tandem, the number of gabapentin prescriptions increased 5-fold. Though the total volume of opioid prescriptions was stable before eventually falling, the number of episodes of overlapping gabapentin and opioid prescriptions more than tripled.

The research team analyzed national deidentified pharmacy claims data, capturing approximately 90% of prescriptions filled at retail pharmacies across the United States.

"While the decrease in opioid prescriptions is promising, the alarming upward trajectory of gabapentin use tempers the collective progress made in reducing patients' exposure to opioids," wrote authors of an accompanying editorial in *JAMA Internal Medicine*.

"Prescribers must recognize the risks associated with gabapentin and its limited efficacy in treating chronic pain. The sense of urgency to continue to address the opioid crisis should not override the need to find nonpharmacologic agents or other treatment modalities to manage chronic pain effectively and safely."

A trend

Mark Garofoli, PharmD, a pain management expert, said that naturally other pain management prescription medications would replace opioid prescriptions amid the opioid epidemic and the crackdown on opioid overprescribing.

He said it was revealing in the study that pain specialists—those with the top level of pain management expertise—were shown as the highest percentage of physicians prescribing both opioids and gabapentin.

"[It] really emphasizes the reality that at some point, patients in pain need multi-modal multiple prescription treatment options," said Garofoli, a clinical assistant professor at West Virginia University School of Pharmacy.

Additionally, the highest patient age group using both prescription opioids and gabapentin was among older adults.

The study focused only on trends, making the results simple yet strong, said Peet.

"The results are consistent with anecdotal evidence and a growing number of overdose mortalities in which both opioids and gabapentin are observed," Peet said.

He noted that the data represent the largest and most accurate representation of these trends that have been published to date, and provide a foundation for future research exploring the causes of these trends.

Awareness

According to Peet, all providers need to know the risks associated with concurrent use of opioids and gabapentin.

In many states, gabapentin is not a controlled substance and is therefore not reported to prescription drug monitoring programs. "This means that prescribers may be unaware that they are concurrently prescribing gabapentin with opioids," said Peet.

West Virginia, one of only 7 states recognizing gabapentin as a controlled substance, started tracking gabapentin-related overdose deaths in the 2010s.

"West Virginia's tracking of gabapentin-related deaths—key word 'related'—does not mean that a multitude of people are overdosing solely upon gabapentin utilization, rather that gabapentin has been found in the toxicology reports of those who had a multi-drug overdose, which is very similar in concept to benzodiazepines being utilized concurrently with opioids," said Garofoli.

Though the total volume of opioid prescriptions was stable before eventually falling, the number of episodes of overlapping gabapentin and opioid prescriptions more than tripled.

Gabapentin's mechanism of action is similar to that of other controlled substances, such as benzodiazepines and barbiturates, leading to an opportunity for misuse and abuse. Taken in combination with opioids, gabapentin increases the risk of respiratory depression and death in patients.

Garofoli pointed out that pregabalin—a "structural cousin" to gabapentin—was reclassified as a controlled substance.

"However, [a reclassification of gabapentin] would not inherently mean tightening the spigot, rather respecting the pharmacology and incorporating [that] into clinical decisions and patient care conversations," Garofoli said. ■

Interruption or continuation of antithrombotic therapy in perioperative patients?

Ariel L. Clark, PharmD

Too often, clinicians question whether they are making the right decision about a patient's anticoagulation therapy with planned, nonemergent surgical procedures. Clinicians must determine when to interrupt the regimen to protect patients from unnecessary post-procedural bleeding, for how long, and if bridging is necessary. Until now, guidance has not been inclusive to this wide range of possible situations.

In their August 11, 2022, update to the clinical practice guideline on the perioperative management of antithrombotic therapy, the American College of Chest Physicians (CHEST) aimed to expand recommendations to better capture the variety of instances—from 11 to 43 PICO (patient/problem/population, intervention, comparison, outcome) questions—when practitioners must decide between interruption versus continuation or interruption and bridging of antithrombotics.

These guidelines are intended to provide clinicians with a frame of reference to help them make decisions for their patients' individual care.

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Vitamin K antagonists

Recommendations from CHEST for patients receiving a vitamin K antagonist (e.g., warfarin) with a low-to-moderate bleed risk and high bleed risk are the same in cases when the planned operation is likely to result in bleeding.

The executive summary of the recommendations suggest discontinuation of the drug 5 days prior to the day of the procedure, with some exceptions in patient-specific cases such as in older adults, and a restart within 24 hours afterward at the same dose.

Direct oral anticoagulants

CHEST exclusively recommends interruption of therapy in patients on direct-acting oral anticoagulant (DOAC) therapy in the update. Individual drugs in this class of medication have variable half-lives and the updated clinical practice guidance suggests that each should be assessed uniquely for when to interrupt and when to restart therapy for elective procedures.

Antiplatelets

Drugs in the antiplatelet class include aspirin, clopidogrel, and prasugrel. CHEST recommends that clinicians almost exclusively interrupt therapy of these before surgery, with one exception: in patients who are preparing for an elective, noncardiac procedure at a low-bleed risk or for a coronary artery bypass graft procedure.

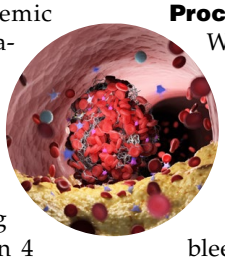
In these cases, the aspirin regimen can continue uninterrupted. Similar to DOACs, each antiplatelet drug has a unique interruption date prior to the procedure and restart date after surgery.

Clinicians should also note that in cases in which patients are on dual-antiplatelet therapy, such as when a coronary stent is placed, the guidance says to either continue both drugs for an elective procedure or to interrupt one of them prior to the procedure based on the individual patient's bleed risk. When the stent(s) were placed within the last 3 to 12 months, the $P2Y_{12}$ inhibitor should be stopped.

Bridging

In general, the updated guidance suggests against the use of either low-molecular weight heparin (LMWH) or unfractionated heparin (UFH) bridging except in specific patient cases, including when patients have a high risk for thromboembolism,

had a recent stroke or ischemic attack, had a prior perioperative clotting event, or have a CHA2DS2-VASc score greater than 7.



When bridging is indicated, the updated CHEST guidelines suggest stopping intravenous UFH more than 4 hours prior to surgery and restarting more than 24 hours after surgery. In LMWH patient cases, the dose prior to surgery should be more than 24 hours before at half the dose and restarted at least 24 hours after surgery.

Minor procedures

In cases of minor procedures—such as dental procedures—or ones for which postoperative bleeding is expected to be minimal, the updated guidance suggests continuation of therapeutic warfarin, DOACs, and antiplatelets over interruption of therapy.

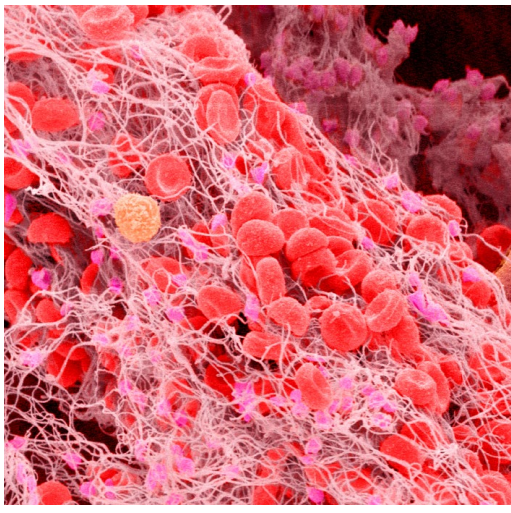
Procedural bleed risk

With any surgical procedure, there is at least some level of risk for bleeding. However, some procedures have a higher bleeding risk than others.

Procedures with a high bleed risk include any major surgery, including orthopedic or thoracic procedures, biopsies or resections, or other surgeries in which the total procedure time exceeds 45 minutes.

CHEST suggests that clinicians should refer to the Risk Stratification for Procedural Bleed Risk Based on the International Society on Thrombosis and Haemostasis, Inc. (ISTH) Guidance Statements.

As pharmacy professionals play their part in helping to avoid unnecessary and potentially dangerous bleeds in patients, they must also take an active role in assuring medications are restarted and bridged appropriately.

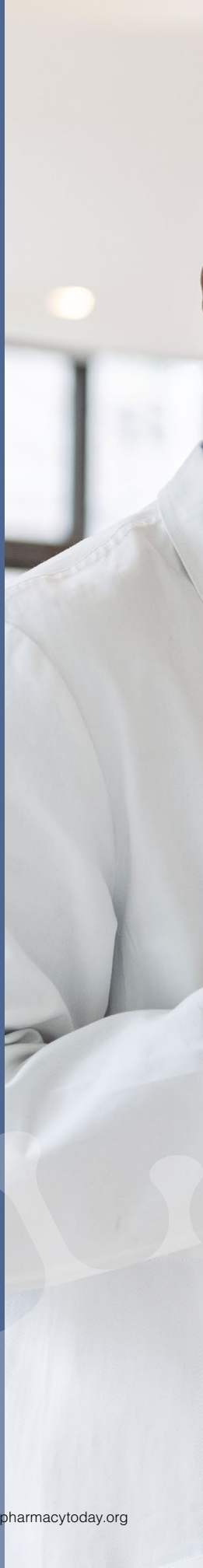


These updated guidelines can help providers determine what's right for their patients. ■

Community pharmacists prescribe and dispense Paxlovid **despite hurdles**

Sonya Collins

Every at-home COVID-19 test that leaves Moose Pharmacy in Charlotte, NC, carries a sticker bearing a QR code. Beside the code, the text reads, "Test POSITIVE for COVID-19? At Moose Pharmacy, we offer a $75 consultation to see if you are eligible for Paxlovid. If eligible, the pharmacist can prescribe and dispense the antiviral medication right to you! Scan here to schedule your consultation."



During assessments for Paxlovid (Pfizer) eligibility, Tory Grooms, PharmD, runs through an exhaustive list of conditions.

"If you take an antidepressant, that counts. If you have any sort of mood disorder, or even ADHD, that counts, too. They've pretty much lowered all the barriers to qualifying for Paxlovid," Grooms said. She attributes the expanded access to increased supply and ongoing data to support the benefits of the antiviral medication.

According to CDC, from December 2022 to February 2023, weekly COVID-19 deaths averaged 3,756. New hospital admissions during that time averaged 3,953 a day, which underscores the ongoing need for easy access to Paxlovid.

While federal agencies have made it simpler for patients to qualify to receive the antiviral, pharmacies still face major barriers to prescribing and dispensing the drug. But those who offer the medication say that the benefits for patients and for the pharmacy profession may make the trouble worthwhile.

Paxlovid in the pharmacy

The Coronavirus Aid, Relief, and Economic Security (CARES) Act gives pharmacists the authority to prescribe Paxlovid to eligible patients.

To check for eligibility, pharmacists must first get confirmation of a COVID-19 infection. This happens via a positive test result or, in rare instances, individuals with a recent known exposure who develop signs and symptoms consistent with COVID-19 may be diagnosed by a health care provider as having COVID-19 even if they have

PAXLOVID PRESCRIPTION

Qualifying conditions to receive Paxlovid

- Asthma
- Cancer
- Cerebrovascular disease
- Chronic kidney disease
- Chronic lung diseases limited to
  - Bronchiectasis
  - Chronic obstructive pulmonary disease
  - Interstitial lung disease
  - Pulmonary embolism
  - Pulmonary hypertension
- Chronic liver diseases limited to
  - Cirrhosis
  - Non-alcoholic fatty liver disease
  - Alcoholic liver disease
  - Autoimmune hepatitis
- Cystic fibrosis
- Diabetes mellitus, type 1
- Diabetes mellitus, type 2
- Disabilities, including Down syndrome
- Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)
- HIV
- Mental health conditions limited to
  - Mood disorders, including depression
  - Schizophrenia spectrum disorder
- Neurologic conditions limited to dementia
- Obesity (BMI ≥30 kg/m^2 or ≥95th percentile in children)
- Physical inactivity
- Pregnancy and recent pregnancy
- Primary immunodeficiencies
- Smoking, current and former
- Solid organ or blood stem cell transplantation
- Tuberculosis
- Use of corticosteroids or other immunosuppressive medications

Source: CDC. COVID-19: Underlying medical conditions associated with higher risk for severe COVID-19: Information for healthcare professionals.

Medications without clinically relevant interactions

These medications may be coadministered without dose adjustment and without increased monitoring.[a] This list is not inclusive of all noninteracting medications within each drug category.

Acid reducers
- Famotidine
- Omeprazole
- Pantoprazole

Allergy
- Cetirizine
- Diphenhydramine
- Fexofenadine
- Loratadine

Anti-infectives
- Azithromycin
- Cidofovir
- Hydroxychloroquine
- Tecovirimat
- Valacyclovir

Cardiovascular
- Aspirin
- Atenolol
- Carvedilol
- Furosemide
- Hydrochlorothiazide
- Irbesartan
- Isosorbide dinitrate
- Lisinopril
- Losartan
- Metoprolol
- Prasugrel

Diabetes
- Empagliflozin
- Insulin
- Metformin
- Pioglitazone

Immunosuppressants
- Abrocitinib
- Baricitinib
- Methotrexate
- Mycophenolate
- Prednisone

Lipid-modifiers
- Ezetimibe
- Pitavastatin
- Pravastatin

Migraine
- Frovatriptan
- Naratriptan
- Rizatriptan
- Sumatriptan

Neuropsychiatric
- Amitriptyline
- Bupropion
- Citalopram
- Duloxetine
- Escitalopram
- Fluoxetine
- Gabapentin
- Lorazepam
- Nortriptyline
- Olanzapine
- Paroxetine
- Sertraline
- Venlafaxine

Pain
- Acetaminophen
- Aspirin
- Codeine
- Ibuprofen
- Meloxicam
- Naproxen

Respiratory
- Corticosteroids (inhaled)
- Formoterol
- Montelukast

Miscellaneous
- Allopurinol
- Contraceptives (oral)[b]
- Cyclobenzaprine
- Donepezil
- Enoxaparin
- Finasteride
- Levothyroxine

Most monoclonal antibody products[c]
- Ondansetron

[a]This list is primarily based on the most common medication searches by U.S. users on the Liverpool COVID-19 Drug Interactions website between January 1 and July 31, 2022 (internal communication, August 2022).

[b]The FDA EUA for ritonavir-boosted nirmatrelvir suggests that individuals who use contraceptive products containing ethinyl estradiol consider using a backup, nonhormonal contraceptive method because coadministration may result in low ethinyl estradiol levels. However, the low level is not expected to be clinically significant during the 5 days of therapy. The progestin concentration of a combined hormonal contraceptive is expected to remain similar or increase with coadministration, which would maintain the effectiveness of the oral contraceptive.

[c]Ritonavir-boosted nirmatrelvir interacts with certain conjugated monoclonal antibodies, such as those conjugated to the drug monomethyl auristatin E (or vedotin). These include brentuximab vedotin, enfortumab vedotin, polatuzumab vedotin, and tisotumab vedotin. Before coadministering ritonavir-boosted nirmatrelvir and any of these conjugated monoclonal antibodies, refer to the drug's FDA prescribing information and consult with the patient's specialist providers as needed.

Source: NIH. COVID-19 treatment guidelines: Drug–drug interactions between ritonavir-boosted nirmatrelvir (Paxlovid) and concomitant medications.

a negative test result. Next, they check that the patient has risk factors for progression to severe disease. As this often means the patient is taking other medications, the pharmacist has to review the medication to list to make sure there aren't any that might interact with Paxlovid. The list of contraindicated medications is lengthy.

"There are whole classes of drugs that interact with it," said Grooms, "so we have to be cautious about those patients who are already complex with their medication regimens."

OTC medications make the list, too, said Coleman Cutchins, PharmD, lead pharmacist with the Alaska Department of Health and Social Services. "You have to do a very thorough medication review—all prescriptions, all over-the-counters, all herbal supplements—to check for interactions. Pharmacists are very good at that. We deal with it every day."

Finally, pharmacists need access to patients' lab values to confirm that their kidney and liver function are sufficient to metabolize the drug.

"That's the greatest barrier and what makes it hard for some pharmacies to do this because it takes digging and you've got to have the time to be able to do that," Grooms said.

Those who offer the medication say that the benefits for patients and for the pharmacy profession may make the trouble worthwhile.

As an independent pharmacy, Moose Pharmacy has relationships with many of the local medical centers and access

PAXLOVID PRESCRIPTION

Paxlovid: An oral antiviral for COVID-19

Paxlovid, an oral antiviral that contains a combination of nirmatrelvir and ritonavir, is a SARS-CoV-2 protease inhibitor that prevents replication of the coronavirus.

In the clinical trials that earned the drug its EUA from FDA, Paxlovid twice daily for 5 days and started within 5 days of symptom onset reduced COVID-19–related hospitalizations and deaths in unvaccinated people who had the Delta variant by 89% for 28 days.

More recently, NIH research has found that Paxlovid reduces the risk of severe COVID-19 illness, hospitalization, and death in adults over age 50 infected with the Omicron variant by 44%. These risks were 81% lower in people who weren't vaccinated. Notably, hospitalization and death in general were less likely among people infected with the Omicron variant compared to those infected with Delta. Among the 44,500 people whose medical records were analyzed for this study, hospitalizations and deaths were below 1%. ■

PAXLOVID PRESCRIPTION

Who can get Paxlovid?

Once recommended only for older adults, Paxlovid is now indicated for anyone age 12 or older who has a condition that might put them at risk for progression to severe disease. The list of conditions is sweeping and includes some that clinicians might expect to see and others that may be surprising, such as mood disorders, obesity, and physical inactivity.

"There's really good data to show that, across the board, vaccinated or not, especially if you're over 50, Paxlovid will reduce your risk even further," said Coleman Cutchins, PharmD, lead pharmacist with the Alaska Department of Health and Social Services. "Anyone, especially if they have high-risk criteria—age being the number one risk factor for severe disease—should get tested if they have symptoms and be offered Paxlovid." ■

to patients' electronic health records (EHR). When Grooms cannot access a patient's record, she encourages them to register for their health care facility's patient portal and share lab results with her directly.

"Pharmacists can be proactive about this, too, by encouraging patients to sign up for their patient portal even outside of the Paxlovid assessment," Cutchins added. "Ask them, 'Have you had your COVID-19 vaccines? Do you have a plan for if you were to get COVID-19? Do you have access to your patient portal?'"

When Grooms is not able to complete all the steps to determine a patient's eligibility for Paxlovid, she contacts their physician for lab values or refers them to urgent care for a Paxlovid prescription. But both strategies run the risk of pushing patients past the 5-day window to start the medication.

Barriers to better patient care

While patients face fewer hurdles to eligibility for Paxlovid, many barriers are still firmly in place for the pharmacies where the drug is prescribed and dispensed.

Since Paxlovid earned EUA status, the federal government has provided it to participating pharmacies at no cost to the pharmacy or the patient. Thus far, patients have received the prescription for free, and pharmacies have billed insurance for the cost of dispensing.

However, this year, the federal government will stop paying for the antiviral drug, which it gets from Pfizer at the discounted price of $530 per course. Patients and insurers will have to cover the cost (as of press time, Pfizer has not yet released that figure). It remains to be seen how much of the undisclosed cost will fall to patients.

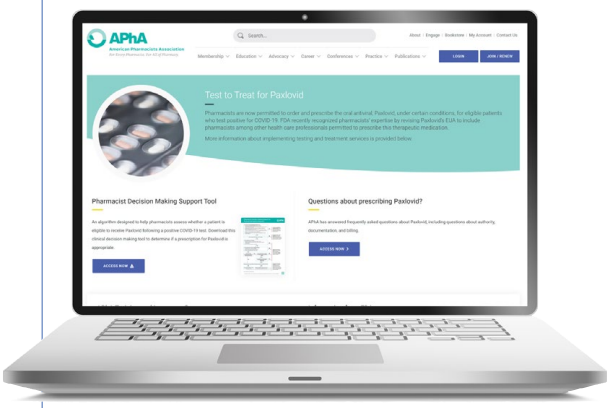
Government funding of the treatment is expected to end sometime in mid-2023. Until then, select pharmacies will continue to dispense the drug for free.

To prescribe the drug, pharmacies typically also charge patients a cash fee for the assessment for eligibility that they are required to do but for which they aren't reimbursed by insurance. This may prevent some pharmacies from choosing to become Paxlovid prescribers at all.

"We all need to acknowledge the sustainability of these clinical services," Cutchins said. "It takes a lot of time to assess the patient, do a full medication review, and make those clinical assessments, and that medical encounter isn't universally reimbursed for pharmacists."

If they are not able to bill for these services, pharmacies may not be able to hire the staff necessary to carry out the services. "You don't want to be the only pharmacist in a [community pharmacy] and have to spend 30 minutes assessing a patient for Paxlovid, while you're also handling dispensing duties on top of that," he added.

For uninsured patients, pharmacies used to bill the Health Resources and Services Administration's (HRSA) COVID-19 Claims Reimbursement program for the



APhA has created several resources to help pharmacists implement these services and assess patients for treatment with Paxlovid. Access apha.us/Paxlovid and apha.us/TreatmentPrescribingConsiderations for pharmacist decision-making support tools, training resources, information on APhA advocacy surrounding Paxlovid, and information from FDA.

cost of dispensing until federal funding for that program ran out.

"Pharmacists are in a pickle here," Grooms said. "The HRSA funding is dry, so we are no longer paid to offer COVID-19 vaccines or treatments to patients who are uninsured, but we are still required to provide these services at no cost to the patient, so we are forced to provide these services at a loss."

Other rules made by individual payers cause problems, too. Some insurers, for example, set a limit of only one course of Paxlovid per patient every 6 months. "If patients need a repeat, we still have to fill the prescription, but we can't bill the insurance plan for it. We just have to eat the cost," said Stephanie Rice-Erlenbusch, CPhT, from Fred Meyer Pharmacy in Portland, OR.

Raising the profile of the profession

The CARES Act has expanded pharmacists' scope of practice in several ways. Pharmacists have led the charge in vaccinating adults and children against COVID-19. They've prescribed and administered COVID-19 treatments including Paxlovid and monoclonal antibody therapy.

Cutchins sees the use of CLIA-waived tests to test and treat COVID-19 with Paxlovid as an opportunity to advance the profession that pharmacists should seize.

"Since the 90s, as a pharmacy profession, we've been saying we need to provide more medical care, we need to advance our practice, we need to fill in gaps in primary care," he said. "This is another big opportunity to do that."

"Anything we can do to increase access is going to help patients and advance the profession."

While the requirements pharmacists must meet to prescribe Paxlovid may seem difficult to achieve, Grooms stresses the importance of leaning on support staff for every step of the process that does not require a pharmacist.

Pharmacies that don't have the staff necessary to assess for Paxlovid every day can choose to provide the service only on certain days. "Anything we can do to increase access is going to help patients and advance the profession," Cutchins said.

Better outcomes for patients

Prescriptive authority for Paxlovid is also an opportunity to help more patients at risk of severe illness, hospitalization, and death from COVID-19.

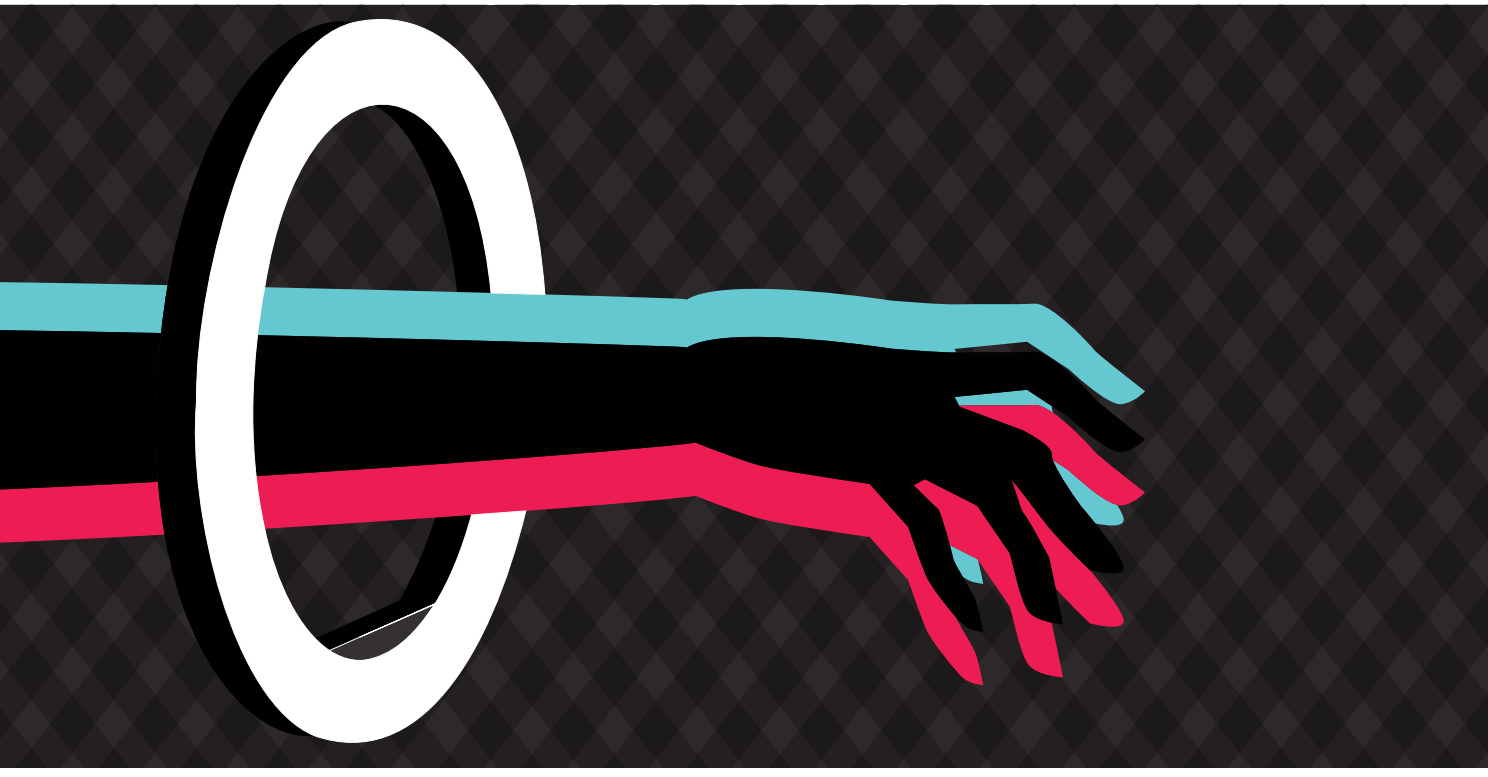
Patients at risk of severe illness from COVID-19 and seeking Paxlovid have a few options: They can try to see their regular doctor; they can go to urgent care; or they can see a pharmacist who prescribes Paxlovid.

Patients may not want to risk the time it could take to see or get a prescription from their physician, and urgent care is costly. A man who called Moose Pharmacy was in exactly this predicament. He was concerned about his 80-year-old mother as they waited for a call back from her doctor.

"He was nervous because she was so old and fragile. The son drove his mother over, we retested, got a positive result, pulled up her EHR, current med list, and lab values, and got Paxlovid out the door in about 30 minutes," Grooms said. "It was so fast in comparison to the broken health care system that people are used to, and that normally works in most circumstances, but that doesn't work well in a pandemic."

For all the trouble Rice-Erlenbusch has had chasing down reimbursement for Paxlovid dispensing fees at Fred Meyer Pharmacy in Portland, OR, the pharmacy technician says providing the service is the pharmacy's duty.

"Our number one priority is to take care of our community," she said. "Even though it does make it hard on the business side when we do not receive reimbursement, it is something that we owe our community in order to help them if they need that medication." ■



GLP-1 receptor agonists: Breaking down the hype and demand

Loren Bonner

For pharmacists like Candis Morello who are treating patients using GLP-1 receptor agonists, it's been a challenging few months navigating the shortage of this class of medications.

"This particular class of drugs is in such high demand right now; I don't think manufacturers expected this outcome," said Morello, PharmD, APh, CDCES, FCSHP, FASHP, a professor of clinical pharmacy at the University of California San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences.

Morello said that because of GLP-1 receptor agonist drug shortages, she's been unable to initiate new starts or increase a patient's dose for the last several months.

"I've had to delay initiation or delay titration in my patients. I start them off with a lower dose and can only use the lower doses," said Morello, who is a clinical pharmacist and director of the Diabetes Intense Medical Management Clinic at the Veterans Affairs San Diego Healthcare System.

Because the drugs are so highly effective, the American Diabetes Association now recommends GLP-1 receptor agonists as a first injectable over insulin for the majority of patients with type 2 diabetes.

In addition to being effective diabetes medications, GLP-1 drugs have demonstrated superior weight loss results for obesity. A March 2021 study published in *NEJM* found that adults using 2.4 mg of semaglutide lost an average of 35 pounds, or 15% of their body weight, within 15 months. The medications mimic the hormones that the intestines produce when eating, and together with a relatively safe adverse effect profile, have made this third generation of medication attractive compared with older drugs for those wishing to lose weight.

"Shortages are also happening because of social media," said Jennifer Goldman, PharmD, CDCES, BC-ADM, FCCP, a professor of pharmacy practice at Massachusetts College of Pharmacy and Health Sciences and a clinical pharmacist at Well Life. She said the social media platform TikTok has dedicated pages for the use of these drugs for weight loss.

Like Morello, Goldman has had to keep her patients on lower doses of GLP-1 receptor agonists for the time being.

"A lower dose temporarily is not a bad thing," she said. "Work with the doses available—you can go up and down—these drugs are safe and don't cause low blood glucose reactions, typically. Plus, the differences between the doses are small."

Evidence

In 2021, FDA approved Wegovy semaglutide (Novo Nordisk) for weight loss. Ozempic (Novo Nordisk), which was approved 4 years earlier for type 2

diabetes, also contains semaglutide, but at a higher dose—2.4 mg—than Wegovy.

Although GLP-1 receptor agonist medications have existed since 2005 with exenatide (Byetta—AstraZeneca) and liraglutide (Victoza, Saxenda—Novo Nordisk) for patients with type 2 diabetes, the Cleveland Clinic noted on their Health Essentials blog that newer, longer-acting once-weekly GLP-1 receptor agonist medications like dulaglutide (Trulicity—Eli Lilly) have appeared to be more effective in treating obesity and lowering blood glucose.

In addition to the GLP-1 receptor agonists, FDA recently approved a GIP/GLP-1 receptor agonist combination called tirzepatide (Mounjaro—Eli Lilly) for people with type 2 diabetes. This weekly injection has also become popular for weight loss—outcomes of studies showed patients experienced up to 25% of body weight loss on tirzepatide.

In general, evidence from clinical trials with GLP-1 receptor agonists demonstrated safety and efficacy of controlling patient's glucose, but also have shown multiple benefits of reducing weight and improving cardiovascular health, according to Morello. "Especially for someone with type 2 diabetes, if you can protect the heart and reduce weight, the benefits are all encompassing and positive outcomes can be achieved with diabetes and associated comorbidities."

On average, people with type 2 diabetes have twice the risk of cardiovascular disease as people without diabetes.

Cost

One major barrier to patients accessing GLP-1 receptor agonists medications is cost. The subcutaneous, weekly injections list for around $1,200 per month for one dose. Higher doses will cost more, and insurance coverage can also be limited.

Most patients use manufacturer coupon cards to purchase GLP-1 receptor agonists. "There are coupons available for the lower doses, which can give pharmacists time to work with the provider to place a prior authorization request for use with the insurance company," said Morello.

Providers can prescribe these medications off-label for patients who need to lose weight, but Goldman points out the tricky position pharmacists might find themselves in when patients use coupon cards.

"What happens on the pharmacy end if a pharmacist fills it for obesity and it's not indicated for that? Is someone going to come back and recoup that money?" said Goldman. "If a pharmacist has to check a box saying the patient has diabetes to have the savings card—that puts them in the middle. They can call the provider, but the provider can say they can write the prescription for whatever they want." She said the demand for these medications also highlights how desperate people with obesity are for effective treatment.

"One of the things I've seen particularly coming into 2023 is that many insurance companies are starting to require [diabetes] diagnosis before they will approve," said Theresa Tolle, BPharm, FAPhA, 2022–2023 APhA president and owner of Bay Street Pharmacy in Sebastian, FL, during a January 2023 APhA webinar on drug shortages.

Rarely will an insurer cover a GLP-1 receptor agonist for weight loss purposes. In addition, manufacturers have tightened access amidst the shortages. In early 2023, it was reported that Eli Lilly was limiting tirzepatide for only those patients with type 2 diabetes.

Pharmacists' role

"As the complexity of drugs increases and patient's comorbidities increase, these are all areas of opportunities for a pharmacist's knowledge and skill sets to help patients," said Morello.

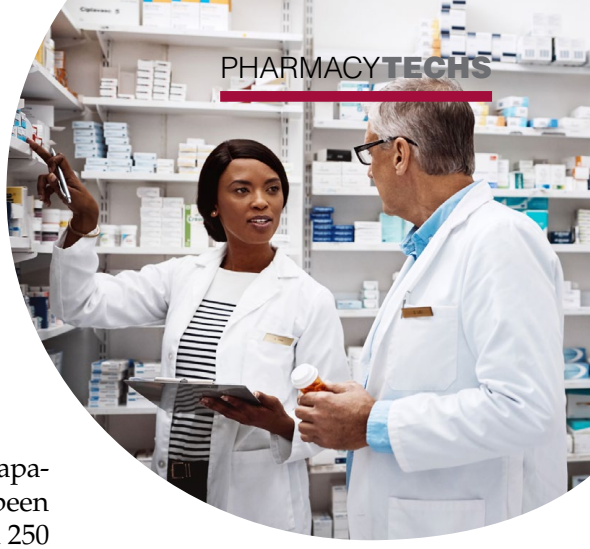
According to the Cleveland Clinic, GLP-1 receptor agonists don't have as many adverse effects as other diabetes medications. Because they work by stimulating hormones in a person's gut, the most common adverse effects are limited to digestion and can include abdominal pain, constipation, diarrhea, and nausea.

For patients with type 2 diabetes taking these medications, pharmacists should also be aware of the risk of a patient's blood glucose levels going too low, especially when they are used in combination with other diabetes medications such as insulin or sulfonylureas.

"Especially for someone with type 2 diabetes, if you can protect the heart and reduce weight, the benefits are all encompassing."

Morello said pharmacists also need to remember the importance of counseling. "I tell patients we want to access your motivation—it's not just a drug that will help you lose weight," she said. "These drugs work well, but they need to be coupled with long term lifestyle changes."

"We have to look at the whole picture and take a holistic approach. GLP-1s are good for heart health, weight loss, kidney protection, and diabetes, but I never want us to lose sight of educating on the importance of a healthy diet and regular physical activity," said Morello. "When pharmacists provide counseling on these drugs, we need to include these other components. All of these efforts combined can produce astounding results." ■



Win–win: Permanent PREP Act declarations benefit pharmacy staff, patients, and more

Ariel L. Clark, PharmD

The value in expansion and protection of pharmacy technicians' capabilities provided by the ninth amendment to the PREP Act has been incalculable in the face of the COVID-19 pandemic. As more than 250 million doses of the COVID-19 vaccines were provided by pharmacists, pharmacy technicians, and student pharmacists, their role as protectors of public health became clear despite critical staffing shortages and a number of other challenges.

Most pharmacy leaders would agree that these provisions need to become permanent, especially in preparation for future public health crises. Christina Madison, PharmD, founder and CEO of the Public Health Pharmacist, noted in a recent *Pharmacy Times* article that pharmacy staff should seek out their state and federal lawmakers and ask them to protect the public by ensuring all capable pharmacy staff can continue to provide these and other lifesaving services.

The case for permanence

With the declaration of the PREP Act in March 2020, it became clear that public access to vaccinations was vitally important. With the first EUA for the Pfizer vaccine, followed by the additional EUAs for Moderna and Johnson & Johnson vaccines, Madison observed that pharmacy personnel were soon overwhelmed by the sheer volume of vaccinations provided daily at more than 40,000 pharmacy locations across the United States.

Pharmacy technicians came to the rescue with their inclusion as "qualified persons" in the ninth amendment to the PREP Act and were soon providing (in some cases) the vast majority of COVID-19 vaccines at these pharmacies.

"Technicians have now been directly involved in tens of millions of tests, immunizations, and other tasks," said William Schimmel, executive director and CEO of the Pharmacy Technician Certification Board.

Research also supports the expanded roles of pharmacy technicians.

In the October 2021 issue of *JAPhA*, Demarco and colleagues compiled available research on pharmacy technicians' roles in vaccine administration. With adequate training, pharmacy technicians improved pharmacy workflow, allowing pharmacists to focus on other clinical tasks, and felt empowered in their role when performing immunizations. This systematic review went on to highlight patients' perspectives of pharmacy technicians, which was positive due to reduced wait times and their "trusting relationship with the pharmacy team."

"This is a mountain of data to validate [pharmacy technicians'] willingness and skill to continue this larger role," said Schimmel.

A survey commissioned by the National Alliance of Chain Drug Stores found that 70% of Americans are in support of these expanded roles, and 68% are in favor of them becoming permanent. This far outperformed many other standard health care providers, particularly in rural communities, showing that patients rely heavily on trusted pharmacy personnel to provide them with necessary services they wouldn't be able to receive otherwise.

"According to PTCB's 2022 Pharmacy Technician Workforce Survey, most technicians across all pharmacy settings believed that their work during this public health crisis had a much greater impact on patient care. And despite the increased workload and responsibilities, most technicians felt a stronger sense of pride and accomplishment," said Schimmel.

Patients rely heavily on trusted pharmacy personnel to provide them with necessary services they wouldn't be able to receive otherwise.

Progress thus far

In an effort to ensure pharmacy personnel, including technicians, can continue to provide critical services, nearly 100 different organizations signed a letter of support to HHS Secretary Xavier Becarra in June 2022.

This letter called for PREP Act provisions to be granted through October 2024. Signers noted their support of the continuation of the PREP Act declarations to ensure that those who want them have continued access to pharmacy personnel able to provide vaccination services.

Schimmel noted that "more than 20 states have made permanent some or all of the scope of practice additions that are part of the PREP Act" and that "continuing this progress would acknowledge pharmacy technicians as trusted health care providers who play a vital role in patient safety."

The COVID-19 pandemic has shown that the practice of pharmacy and the role of pharmacy technicians is crucial to the protection of public health both as part of the current pandemic, but also in the event of future public health emergencies.

Without the permanent provisions allowed by the PREP Act, patients across the United States could easily find themselves without access to the care that they need. ■

New HIV treatment and prevention recommendations promote medication adherence

Clarissa Chan, PharmD

Antiretroviral therapy (ART) recommendations from the International Antiviral Society from December 2022 highlight novel long-acting injectables for PrEP and HIV treatment. These HIV therapies, which have advanced considerably, provide many patients convenience, improved adherence, and reduced stigma.

"Long-acting injectable cabotegravir for PrEP and cabotegravir/rilpivirine for treatment are game changers. They help reduce pill burden and decrease stigma associated with taking daily oral agents," said Anna Staudt, PharmD, AAHIVP, allied health manager and lead pharmacist at Heart of Ohio Family Health in Columbus, OH, who did not contribute to the recommendations.

The long-acting injectable cabotegravir/rilpivirine (Cabenuva–Viiv Healthcare) offers a non-oral option for patients with HIV who have no previous treatment failure history and no known resistance to either drug component. Cabenuva offers patients an option to receive an intragluteal injection every 1 or 2 months, said Maksida Sabackic, PharmD, AAHIVP, pharmacy operations regional director at AIDS Healthcare Foundation in Los Angeles, who was also not involved with the new recommendations.

"Although treatment failure risk is low, it is still possible with Cabenuva, especially with 2-month dosing intervals. All patients should be informed of this risk prior to initiating treatment," she said.

Switching to Cabenuva creates an important adherence challenge: ensuring scheduled appointments are not missed. "Many patients with jobs may have difficulty taking time off for regular injection appointments," said Sabackic. "Pharmacists can be a solution by receiving training in intragluteal injection technique and providing injections outside of provider office hours when patients have more availability."

Novel PrEP therapy

Like Cabenuva, cabotegravir (Apretude–Viiv Healthcare) is an injectable option approved for PrEP and may be considered for patients with adherence challenges.

"In certain states, pharmacists have the ability to furnish PrEP independent of a medical provider, increasing access to PrEP," said Sabackic. "Communities with disproportionately high HIV incidence rates need more PrEP-related resources and guidance."

Pharmacists can help prevent HIV transmission by advocating for and educating patients on best practices and providing available resources to increase access to treatment and reduce barriers to care.

Accessibility and maintaining adherence to ART in patients who are at risk of HIV has historically been a challenge for providers.

ART accessibility and adherence advancements

Despite the options, some patients may not have access to HIV therapies due to socioeconomic or environmental factors. Since patients with HIV are among the most vulnerable populations, providing ongoing monitoring and support will promote adherence, said Sabackic.

"I have many patients with or at risk for HIV [who] struggle with medication access, transportation, and stable housing," said Staudt. "It's a necessity to assess [SDOH] and offer assistance and linkage to resources to improve care and outcomes."

Accessibility and maintaining adherence to ART in patients who are at risk of HIV has historically been a challenge for providers. "When we assess a patient, we must look at the complete picture," said Sabackic. "What is the lifestyle of my patient? Where do they live and sleep at night? How often do they have access to meals? These questions and others are needed for deciding appropriate ART regimens."

Pharmacists can promote adherence by providing pill boxes, medication packs, and prescription delivery; helping patients set calendar reminders; helping patients apply for assistance programs to reduce drug costs; understanding community resources available for housing, food, insecurity, and social work; and providing ongoing compassionate care with stigma-free support, Sabackic said.

Influence of substance use disorders

Screening for substance use disorders can be easily overlooked during appointments.

"Pharmacists have a significant role in the patient's overall wellbeing by understanding risks and drug–drug interactions with opioids and other illicit substances, and being able to counsel and offer stigma-free support to patients who are willing to open up about their substance misuse," said Sabackic. "Pharmacists also have the ability to furnish naloxone within all 50 states."

Although stigma still exists surrounding patients purchasing clean needles from pharmacies, it is important to understand the public health perspective on syringes to prevent diseases like HIV from spreading that may occur with sharing needles, said Sabackic.

Pharmacists may provide community resources to help patients seek out addiction treatment clinics and licensed practitioners in their area, she said. ■

Pharmacists can improve the care patients receive in memory disorder clinics

Loren Bonner

Few neurology practices in the United States have embedded pharmacists on their care teams, but a study published December 11, 2022, in the *Journal of the American College of Clinical Pharmacy* demonstrates how clinical pharmacists could positively affect patients in these settings.

Out of 180 patients included in the study, pharmacists made recommendations for nearly half of them, most commonly laboratory monitoring recommendations or medication discontinuations or substitutions.

"We were struck by the large number of [potentially inappropriate medications] that were identified—332 in 180 patients, which is a little less than 2 per patient," said lead author Traci Aladeen, PharmD, BCPP, clinical pharmacist at DENT Neurosciences Research Center in Amherst, NY. "This speaks to the acute need for medication optimization in this patient population."

Of the 192 total pharmacist recommendations, 32% were accepted by providers within the memory disorder clinic, a subspecialty clinic located within a neurology group practice.

Aladeen said many patients in these clinics are taking anticholinergic medications, which can exacerbate cognitive problems. Other medications can increase fall risk or require age-related dose adjustments, for example.

"We are learning more about the potential impact that medications can have on risk for Alzheimer disease, with some research now showing that anticholinergic medications can increase risk of [Alzheimer disease] long before cognitive problems present," said Aladeen.

Additionally, new medications for Alzheimer disease with complex monitoring parameters are entering the market.

Aladeen and her team were also struck by the disparity between the number of potentially inappropriate medications that were identified during initial screening using tools like the Beers Criteria (332) versus how many were deemed actionable by clinical pharmacists (111).

"This speaks volumes to the complexity of delivering appropriate and actionable recommendations to prescribers," said Aladeen. "While tools such as the Beers Criteria can help provide a starting place, it is clear that they require careful interpretation in order to perform a risk/benefit analysis considering individual patient characteristics."

"Although this was outside of the scope of our study, it would be great to see a similar study conducted in a controlled fashion with a comparator group and scheduled follow-ups to collect outcomes such as cognitive testing, falls risk assessment, and hospitalizations consistently to better evaluate the effect of pharmacist interventions," said Aladeen.

She noted that future studies could explore opportunities to improve how recommendations by pharmacists are accepted by providers.

"The intervention studied here was conducted via chart review prior to the patient visit," said Aladeen. "Based on studies in inpatient settings and more highly integrated outpatient settings, it is possible that the recommendation acceptance rate would have been higher if we had been able to conduct interventions involving direct patient contact and delivered concurrently with a prescriber visit.

"This speaks to the acute need for medication optimization in this patient population."

The task can't be automated by electronic medical record alert systems either, she said, or delegated to those without pharmacotherapeutic expertise or access to medical records.

Memory disorder clinics

Patients with memory disorders or dementia are particularly vulnerable to adverse effects from potentially inappropriate medications. In her clinic setting, where the study was carried out, Aladeen said the team frequently comes across patients with memory disorders who could benefit from a medication review by a pharmacist.

"Patients can connect with the clinic for an examination and evaluation of their memory problems including neuroimaging and cognitive testing, and work with the clinic to develop a treatment plan," said Aladeen.

The clinic staff consists of a neurologist specializing in the treatment of memory disorders, physician assistants, nurse practitioners, social workers, a neuropsychologist, and a care coordinator.

"This may have further improved trust, communication, and coordination between the pharmacist, prescriber, and patient."

Tailored care

Aladeen said that one of the neurologists they collaborate with shared that the drug–disease interaction information received from embedded clinical pharmacists in the clinic was much more tailored than the calls received from retail colleagues, which primarily concern major drug–drug interactions.

"While these sorts of drug interactions are important, the neurologist found the enhanced medication review provided by the embedded clinical pharmacists were more comprehensive, clinically relevant, and useful in practice," she said.

"We hope pharmacists, pharmacist trainees, and training programs will consider neurology as a viable clinical specialty for pharmacists, and that pharmacists as well as prescribers and other stakeholders will recognize the great impact that pharmacists can make within this specialty," Aladeen said. ■

Ears, eyes, nose, and throat

Nonprescription products offer preparations to treat a wide range of ears, eyes, nose, and throat (EENT)–related disorders. People with ocular complaints commonly consult a pharmacist for specific management recommendations and an estimated 40.9 million people use contact lenses in the United States. EENT discomfort is a well-documented impetus for patients to seek OTC relief in the pharmacy.

Eye drops for allergies .....(n = 540)

Alcon (Pataday/Zaditor)	51%
Visine	9%
Bausch + Lomb	7%
Refresh	3%
Clear Eyes	2%

Snoring cessation aid .....(n = 431)

Breathe Right	32%
Nicorette	1%
CVS Health	1%
SleepRight	1%

Eye drops for redness .....(n = 636)

Visine	42%
Alcon (Systane)	12%
Clear Eyes	10%
Refresh	4%
Lumify	3%

Snoring treatment .....(n = 460)

Breathe Right	30%
CPAP	1%
SnoreStop	1%
Walgreens	1%
Smart Nora	1%

Contact lens solution.....(n = 529)

Bausch + Lomb	37%
Alcon	19%
Boston	2%
Acuvue	1%
Equate	1%

Ear ringing treatment (tinnitis) (n = 454)

Lipo-Flavonoid	16%
Similasan	4%
Hyland's	1%
CVS Health	1%
Sundown Naturals	1%

Earache relief.....(n = 463)

Similasan	14%
Debrox	7%
Hyland's	6%
Tylenol	3%
Motrin IB	2%

Water-blocked ear treatment ...(n = 531)

Swim Ear	21%
Debrox	16%
Auri-Dri	6%
Walgreens	1%
CVS Health	1%

Eye drops for dry eyes .....(n = 547)

Alcon (Systane)	25%
Refresh	23%
Visine	11%
Clear Eyes	4%
TheraTears	3%

Self-care survey redux

This section of *Pharmacy Today*'s Self-Care Product Survey is reprinted from the full survey results published in the January 2023 issue of the magazine and available online at pharmacytoday.org.

The current survey was conducted using scientifically valid methodology and determines those nonprescription products most often recommended by pharmacists in the United States to consumers.

The winners were selected based on a survey of 1,682 pharmacists practicing in the United States who gave their unaided write-in opinions on which brands they'd recommend to patients in 86 categories. The highest share of citations as Most Trusted in the category determined the winner. If the margin of citation share between the leading brands did not exceed the estimate of sampling error at 90% statistical confidence, a tie was declared.

The n value given for each category represents the total number of responding pharmacists' recommendations.

Please also see APhAs *Handbook of Nonprescription Drugs*, the definitive source of professional information about OTC products. The Handbook is available online at PharmacyLibrary.com or in print in the bookstore at www.pharmacist.com.

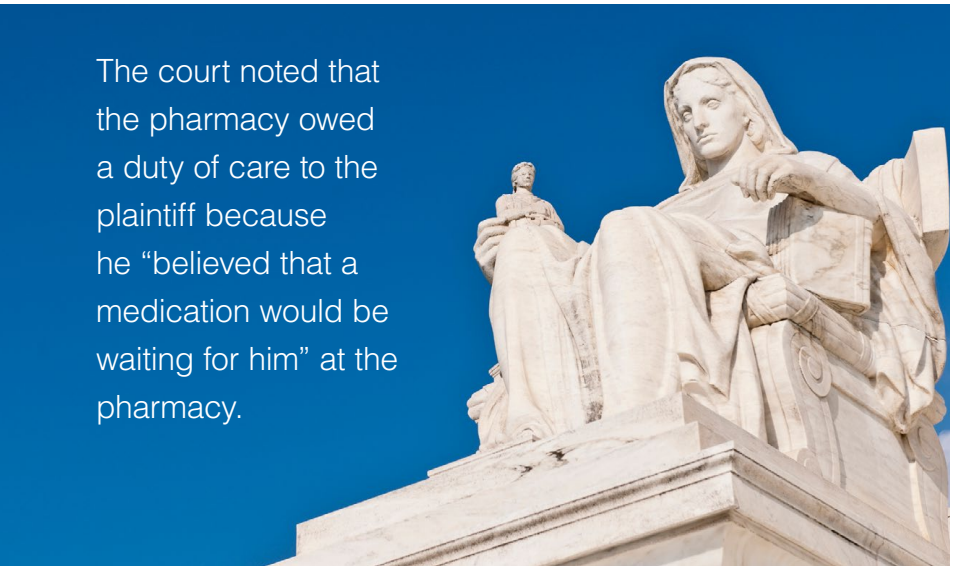
Court recognizes potential liability for unfilled prescription

David B. Brushwood, BSPharm, JD

The Ninth Judicial District of the Court of Appeals of Ohio recently reversed the dismissal of a plaintiff's lawsuit against a pharmacy that allegedly failed to provide the plaintiff with prescribed medication.

Background

The plaintiff worked at a slaughterhouse where he "smashed the index finger on his left hand." He was transported by the employer to an urgent care facility. A physician's assistant (PA) stitched the finger that was severed "down to the bone" and ordered an X-ray. The PA concluded that the finger was not fractured, and the plaintiff was discharged without a prescription for medication and was transported back to work. A radiologist later read the X-ray and diagnosed a fracture. The PA then instructed a nurse to phone in a prescription for amoxicillin/clavulanate to the defendant pharmacy.



There was disagreement regarding when the nurse made this call. Although there was no documentation of any telephone call on that day, the nurse testified that her "regular practice" would be to immediately transmit the prescription to the pharmacy and to contact the employer to inform them that the patient should pick up the prescription at the pharmacy on the following day.

When the plaintiff went to the pharmacy the next day, having been instructed by his employer to do so, he was told that the pharmacy had no record of a prescription for him.

The pharmacy later explained that they "received a voicemail message" about the prescription one hour after the plaintiff had been turned away, but they had no contact information for the plaintiff, who did not return to the pharmacy.

The plaintiff never received his medication.

Two days later, the plaintiff "developed a severe infection that had spread through his body and eventually led to the amputation of both his legs below the knees and the partial amputation of his fingers." He sued the pharmacy, alleging that they had either received the prescription on the first day and had failed to process it in a timely manner, or that they had a duty to obtain his contact information on the second day and to notify him when the prescription was received.

The pharmacy moved for dismissal of the case, contending that they owed no duty to the plaintiff, whom they characterized as a "potential customer" with whom they had "no prior relationship." The trial court granted dismissal of the case, and the plaintiff appealed.

Rationale

The appellate court considered whether there was sufficient evidence of liability to reverse dismissal of the case and to remand the case for further proceedings.

The court reasoned that the plaintiff's appearance at the pharmacy on the day following his injury was evidence that the employer had been informed by the nurse of the prescription to be picked up at the pharmacy. This evidence supported an interpretation that the prescription could have been transmitted to the pharmacy by the nurse on the day of the injury.

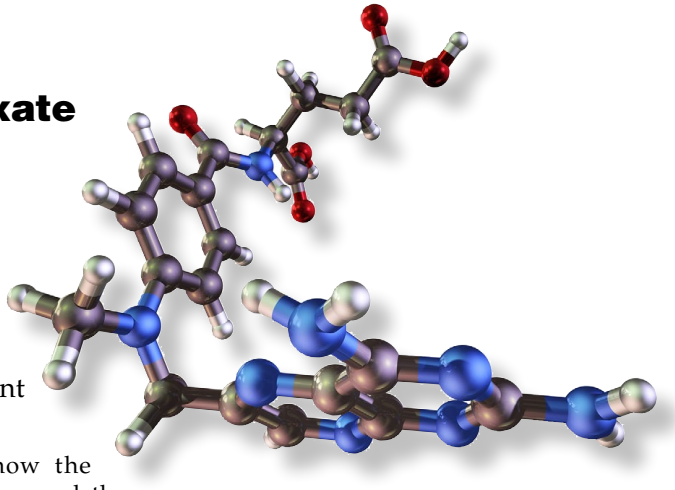
In addition, the court noted that the pharmacy owed a duty of care to the plaintiff because he "believed that a medication would be waiting for him" at the pharmacy. That duty could include investigating the matter further and asking the plaintiff for his contact information. The court ruled that genuine issues of material fact had not yet been resolved.

Takeaways

The ruling in this case is more suggestive than determinative. The pharmacy's exposure to liability has not yet been established. The cautionary tale of this case is that the court seemed very receptive to the argument that a pharmacy owes a legal duty to a person who believes a prescription has been transmitted to the pharmacy, even if the pharmacy has no prior relationship with that person. Based on this ruling, the prudent step is to thoroughly investigate the possibility that the person's prescription has been misplaced and to retain the person's contact information in case the prescription is eventually found. ■

Patient harm from taking methotrexate daily after wrong-drug error

Institute for Safe Medication Practices, Horsham, PA

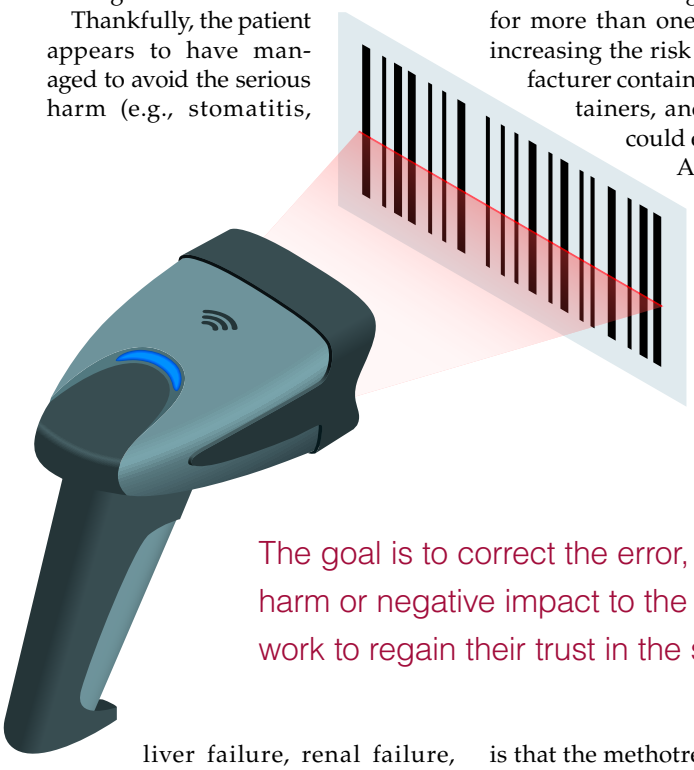


A patient recently reported that they had been inadvertently taking 2.5 mg of methotrexate—an antineoplastic and immunosuppressant agent—daily for nearly 3 months instead of 10 mg of prasugrel, an antiplatelet agent that had been prescribed.

A community pharmacy dispensed the incorrect drug after applying the patient's prasugrel prescription label to a manufacturer bottle of methotrexate. The patient experienced worsening adverse effects from the methotrexate, including arm and joint pain and hair loss. At the time of the report, the patient was still not feeling well.

Thankfully, the patient appears to have managed to avoid the serious harm (e.g., stomatitis, liver failure, renal failure, myelosuppression, GI bleeding, life-threatening pulmonary symptoms, and death) that other patients have suffered when methotrexate was inadvertently taken daily.

Also, the patient did not experience a thrombotic cardiovascular event despite not taking the prescribed prasugrel for 3 months.



While we do not know the details of how the error occurred, the patient indicated that the methotrexate bottle looked like the prasugrel bottle they routinely received. For example, Mylan uses unique blue-colored bottles for their medications, which may contribute to look-alike similarities. It is also plausible that the pharmacy staff was working on prescriptions for more than one patient at a time, increasing the risk of errors as manufacturer containers, pharmacy containers, and pharmacy labels could easily be mixed-up. Another possibility is that the methotrexate bottle was on the pharmacy counter because it was pulled in anticipation of using it for a different patient's prescription.

What we do know is that despite the patient reporting this event to the pharmacy, they have only received a message stating that a district manager would be in contact. To prevent this type of error, it is critical that pharmacy staff generate prescription labels for one patient at a time and then fill that patient's prescription(s) to avoid affixing the wrong label to a bottle of medication intended for another patient. Baskets or trays can be used to keep labeled containers, stock bottles, and documentation for one patient together until final verification.

When affixing the pharmacy label to a manufacturer's container, avoid covering critical information, including the drug name and strength. Return unused or partially used medication bottles to the pharmacy shelves as quickly as possible to reduce the potential for wrong-drug errors. If you encounter look-alike containers, investigate ordering one of the containers from a different manufacturer.

If not already done, install and use barcode verification during production. Scan each package or container (e.g., bottle, carton) used to fill a prescription, including each manufacturer carton or bottle that may be dispensed to a patient. Standardized processes should be developed to guide the pharmacist's final verification of a medication.

At the point-of-sale, have the patient review the pharmacy labels and contents of each prescription container to check that the medication is correct, even if this requires opening the bag. When a patient reports a potential or actual error, respond to the patient in a timely manner with transparency and honesty.

The goal is to correct the error, minimize any harm or negative impact to the patient, and work to regain their trust in the system. ■

The goal is to correct the error, minimize any harm or negative impact to the patient, and work to regain their trust in the system.

Inpatient*Insights*

Hydroxychloroquine and the risk for incident retinopathy

Patients with systemic lupus erythematosus and other inflammatory conditions are often prescribed medications such as hydroxychloroquine to address joint pain, rashes, lupus flares, and fatigue. However, retinopathy has been observed in some patients taking hydroxychloroquine for long periods, and screening is recommended by the American Society of Opthalmology after 5 years of treatment.

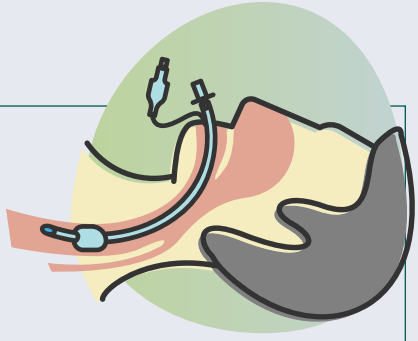
A nationwide group of researchers led by April M. Jorge, MD, of Harvard Medical School and Ronald B. Melles, MD, of Kaiser Permanente Northern California conducted a cohort study to characterize the long-term risk for incident hydroxychloroquine retinopathy and how accurately the average hydroxychloroquine dose within the first 5 years of treatment predicts this risk.

The study, published on January 17, 2023, in *Annals of Internal Medicine*, examined the pharmacy records of more than 3,300 adult patients who had been taking hydroxychloroquine for 5 years or more. Risk for hydroxychloroquine retinopathy was estimated over 15 years of medication use according to hydroxychloroquine weight-based dose using the Kaplan–Meier estimator.

Of the patients in the study group, 81 developed hydroxychloroquine retinopathy, mostly mild, with overall cumulative incidences of 2.5% and 8.6% at 10 and 15 years, respectively.

The authors concluded that higher hydroxychloroquine dose was associated with progressively greater risk for incident retinopathy. ■

Can rapid-onset opioids replace neuromuscular blockers during intubation?



Tracheal intubation is an effective way to prevent aspiration of gastric contents during surgery; however, concerns have been raised about potential adverse effects, including anaphylaxis and respiratory complications, related to the neuromuscular blockers commonly used in intubation. In a recent study, published in the January 3, 2023, issue of *JAMA*, a group of French researchers investigated whether rapid-onset opioids would meet the criteria for successful tracheal intubation without major complications.

The randomized, open label, noninferiority trial involved 1,150 adults at risk of aspiration (e.g., fasting for <6 hours, bowel occlusion, recent trauma, or severe gastroesophageal reflux) who underwent tracheal intubation in the operating room at 15 hospitals in France from October 2019 to April 2021.

Patients received neuromuscular blockers (1 mg/kg of succinylcholine or rocuronium) or remifentanil (3–4 µg/kg) immediately after injection of a hypnotic drug. The primary outcome was successful tracheal intubation on the first attempt without major complications, defined as lung aspiration of digestive content, oxygen desaturation, major hemodynamic instability, sustained arrhythmia, cardiac arrest, or severe anaphylactic reaction.

Results of the study indicated that the rate of tracheal intubation on first attempt without major complications was 66.1% in the remifentanil group and 71.6% in the neuromuscular blocker group, a difference that did not meet the prespecified noninferiority margin of –7% and was consistent with statistical inferiority of remifentanil. An adverse event of hemodynamic instability was recorded in 19 of 575 patients (3.3%) with remifentanil and 3 of 575 (0.5%) with neuromuscular blockers.

The authors concluded, however, that although remifentanil was statistically inferior to neuromuscular blockers, the wide confidence interval around the effect estimate remains compatible with noninferiority and limits conclusions about the clinical relevance of the difference. ■

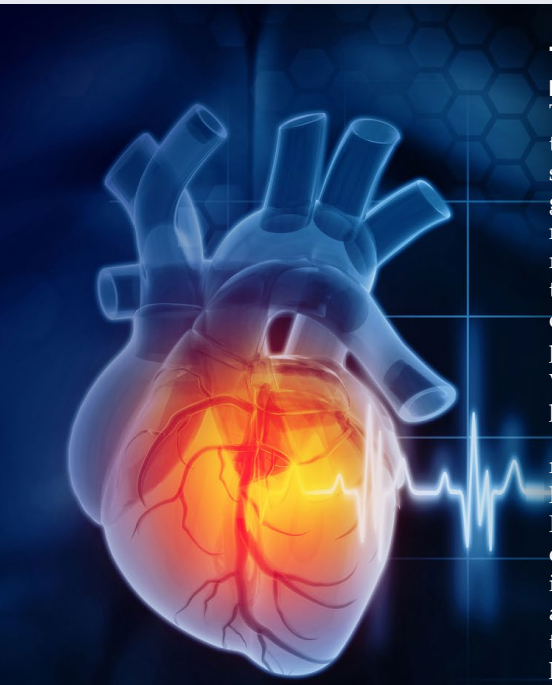
Baxdrostat may hold promise for treatment of resistant hypertension

Because high levels of aldosterone can cause hypertension, inhibition of aldosterone synthase is essential for controlling BP. According to the authors of a recent paper in the February 2, 2023, issue of *NEJM,* selective inhibition is difficult to achieve because cortisol synthesis is catalyzed by another enzyme that shares 93% sequence similarity with aldosterone synthase. However, preclinical and phase 1 studies have shown that baxdrostat holds promise for reducing plasma aldosterone levels but not cortisol levels.

The BrigHTN Investigators conducted a multicenter, placebo-controlled trial involving 248 patients who had treatment-resistant hypertension with BP of 130/80 mm Hg or higher and who were receiving stable doses of at least 3 antihypertensive agents, including a diuretic. Key exclusion criteria were a mean seated systolic BP of at least 180 mm Hg or a diastolic BP of at least 110 mm Hg, an estimated glomerular filtration rate of less than 45 mL per minute per 1.73 m^2 of body-surface area, and uncontrolled diabetes.

Patients were randomly assigned to receive baxdrostat (0.5 mg, 1 mg, or 2 mg) once daily for 12 weeks or placebo, with a primary end point of the change in systolic BP from baseline to week 12 in each baxdrostat group compared with the placebo group.

Patients in the 1-mg and 2-mg baxdrostat group showed significantly greater decreases in systolic BP than those in the placebo group, while patients in the 0.5-mg group showed smaller decreases. No deaths occurred during the trial, and no serious adverse events were attributed by the investigators to baxdrostat. ■



Torsemide versus furosemide after discharge in patients hospitalized with HF

The majority of patients with symptomatic heart failure (HF) are prescribed loop diuretics to relieve congestion, with furosemide being the most commonly used. However, some recent studies have suggested that torsemide may have beneficial effects on myocardial fibrosis, aldosterone production, sympathetic activation, ventricular modeling, and natriuretic peptides.

Members of the TRANSFORM-HF research group, led by Robert J. Mentz, MD, of the Duke Clinical Research Institute and Kevin J. Anstrom, PhD, of the University of Chapel Hill's Gillings School of Public Health, conducted an open-label, pragmatic randomized trial involving almost 3,000 patients hospitalized with HF (regardless of ejection fraction) at 60 hospitals in the United States to determine whether torsemide results in decreased mortality compared with furosemide among this patient population. The study was published in the January 17, 2023, issue of *JAMA.*

Over the 12 months following randomization, all-cause mortality or all-cause hospitalization occurred in 47.3% of patients in the torsemide group and 49.3% patients in the furosemide group. In addition, there were 940 total hospitalizations among 536 participants in the torsemide group and 987 total hospitalizations among 577 participants in the furosemide group. The authors concluded that among patients discharged after hospitalization for HF, torsemide did not result in a significant difference in all-cause mortality over 12 months compared with furosemide. However, they said, interpretation of these findings is limited by loss to follow-up and participant crossover and nonadherence. ■

Certain treatments for critically ill patients with COVID-19 could improve long-term health outcomes

Olivia C. Welter, PharmD

A new study published in *JAMA* investigated how various treatment interventions affected long-term outcomes in critically ill patients with COVID-19.

Since the beginning of the pandemic in 2020, patients and providers alike have had an interest in learning about how contracting the virus could impact an individual's future health, even after recovering from infection.

"Long COVID," formally known as post-acute SARS-CoV-2 infection, has since become recognized as a diagnosable condition. Long COVID is an illness in which patients previously diagnosed with COVID-19 continue to have symptoms—like fatigue and brain fog—for a month or longer.

While long COVID is certainly a concern for any patient recovering from COVID-19, researchers of the study focused on big-picture health endpoints specifically for patients with COVID-19 who had been admitted to an ICU. The study found that interleukin-6 (IL-6) receptor antagonists and antiplatelet agents yielded the most favorable results, while some antiviral agents were associated with potential patient harm.

Treatments assessed

Enrolled patients in the study could receive treatment interventions from several domains: corticosteroid, immune modulation, antiviral, immunoglobulin, anticoagulation, or antiplatelet. Each domain contained various intervention options patients could receive. For example, a patient who fell under the antiviral domain could receive either lopinavir/ritonavir, hydroxychloroquine, combination therapy, or no antiviral therapy. Eligible patients could also receive treatments from multiple domains.

The identified domains align with treatments that patients had been receiving throughout the pandemic for COVID-19 infection. While health care professionals were aware that these interventions may not have been effective in the short-term, they often didn't have a chance to evaluate how they affected patients several months following hospitalization.

Outcomes evaluated

The primary outcome of the study was mortality status at 180 days. While researchers were most interested in learning whether certain treatments increased a patient's chance of survival 6 months after infection, they also assessed mortality status at 90 days, health-related quality of life (HRQoL), and disability. HRQoL evaluation focused on each patient's mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These assessments give health care professionals insight into which treatment options are associated with the best outcomes for critically ill patients with COVID-19.

Which treatments yielded the best outcomes?

Among all the potential treatments that patients could have received, the authors of the study determined that certain domains could be associated with lower mortality and greater HRQoL at the specified endpoints. IL-6 receptor antagonists, a medication class included under the immune modulators domain, were found to be the intervention that had the greatest probability of improving outcomes at 180 days. In fact, the probability of improved mortality was greater than 99.9%. IL-6 receptor antagonists were also correlated with higher HRQoL scores and lower instances of disability.

Closely following IL-6 receptor antagonists, the antiplatelet domain was found to have a 95% probability of improving mortality 6 months after treatment.

Conversely, researchers determined that hydroxychloroquine alone or in combination with lopinavir/ritonavir had high potential to cause harm. The probability of causing harm was a consistent finding for the antiviral domain across all evaluated outcomes: mortality, quality of life, and disability.

Health care professionals should give careful consideration to the treatments they use for critically ill patients with COVID-19.

Impact on COVID-19 care

Based on the findings of this study, health care professionals should give careful consideration to the treatments they use for critically ill patients with COVID-19. The researchers commented that this study is likely the largest to be conducted investigating long-term outcomes of COVID-19 treatments, meaning the results have a higher level of credibility.

Throughout the pandemic, regulatory agencies including FDA have issued statements cautioning that taking medication like hydroxychloroquine to treat COVID-19 could be associated with negative effects such as an irregular heart rhythm. This study provides evidence that hydroxychloroquine should be avoided in patients with COVID-19 infection, particularly patients who are considered to be critically ill.

IL-6 receptor antagonists and antiplatelet agents were shown in the study to yield the most favorable outcomes; providers can consider using medications such as tocilizumab or clopidogrel in their critically ill patients with COVID-19. ■

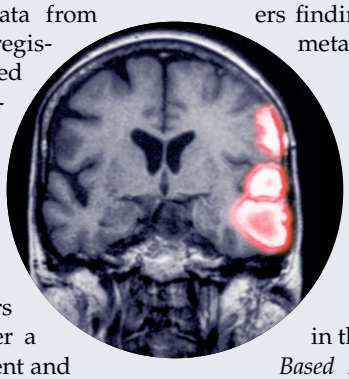
Do statins have an effect on hemorrhagic stroke? New study raises the question, again

Corey Diamond, PharmD

Cardiovascular disease (CVD) is a significant global health issue. The most recent statistics attribute it to over 18 million deaths worldwide. While statins continue to be the cornerstone therapy in CVD prevention by reducing cholesterol levels, concerns have arisen over the risk of intracranial hemorrhage (ICH) in patients receiving statin therapy. Findings from a December 7, 2022, study published in *Neurology* by Boe and colleagues found that statin use was associated with a lower risk of ICH, particularly with longer treatment durations.

Design and results

Boe and colleagues conducted a retrospective nested case-control registry analysis that included data from the Danish nationwide registries, which incorporated data from over 1.2 million patients in the South Denmark region. The authors included patients aged 55 or older who had a "first-ever" ICH event between 2009 and 2018.



About 1,000 statin users were identified with either a lobar or non-lobar ICH event and had their demographics matched with about 40,000 control subjects each. The authors used a conditional logistical regression analysis to adjust for potential confounders.

The analysis revealed that statin use was associated with an overall 17% and 16% relative reduction in odds of having a lobar and non-lobar ICH event, respectively. However, a subgroup analysis showed that the odds reduction relationship was only statistically significant in patients who had been taking statins for more than 5 years. Additionally, a dose response association could not be demonstrated, as the adjusted odds ratios were not observed to significantly change when stratifying the analysis by different statin dose intensities.

Significance and limitations

The current literature is unclear on the use of statins and the risk of ICH. Overall, studies have been mixed, with some suggesting an increased risk of ICH among statin users and others finding no association. A meta-analysis published in the *Journal of Evidence-Based Medicine*—also from December 2022—pooled data from 29 studies and found a lack of significant all cause bleeding and ICH events with statin use. However, the meta-analysis did find a small, but statistically significant increased risk of ICH among statin users with a history of prior stroke.

Several mechanisms have been proposed to explain the potential association between statin use and ICH. Statins have been shown to have anti-inflammatory and antithrombotic effects, which could lead to a decrease in the risk of stroke.

However, those positive effects could be a double-edged sword, leading to a weakening of the structural integrity of blood vessels. Deleterious downstream effects of statins, such as the formation of micro tears in vessel walls, have been theorized to increase the risk of hemorrhage. Curiously, this risk relationship has not yet been observed with more potent cholesterol lowering medications such as PCSK9 inhibitors.

The majority of patients who take statins do not experience ICH. In general, the risk of ICH may be higher in older individuals, those with a history of stroke or head injury, and those taking anticoagulant or antiplatelet medications.

"We found that lower ICH risk was restricted to patients receiving both statins and concurrent antihypertensive drugs. Conversely, in analyses of oral anticoagulant co-medications, only patients who were not concurrently on anticoagulants had a lower risk of ICH in association with statin use," stated Boe and colleagues in their article. They go on to say that their positive results could have been biased by the stronger effects of anti-hypertensive use or lack of anticoagulant use. "Finally, our results may not be generalizable to other populations, as the Danish population is of mainly European ancestry," they wrote.

> The decision to hold statins should be made on a case-by-case basis.

Recommendations

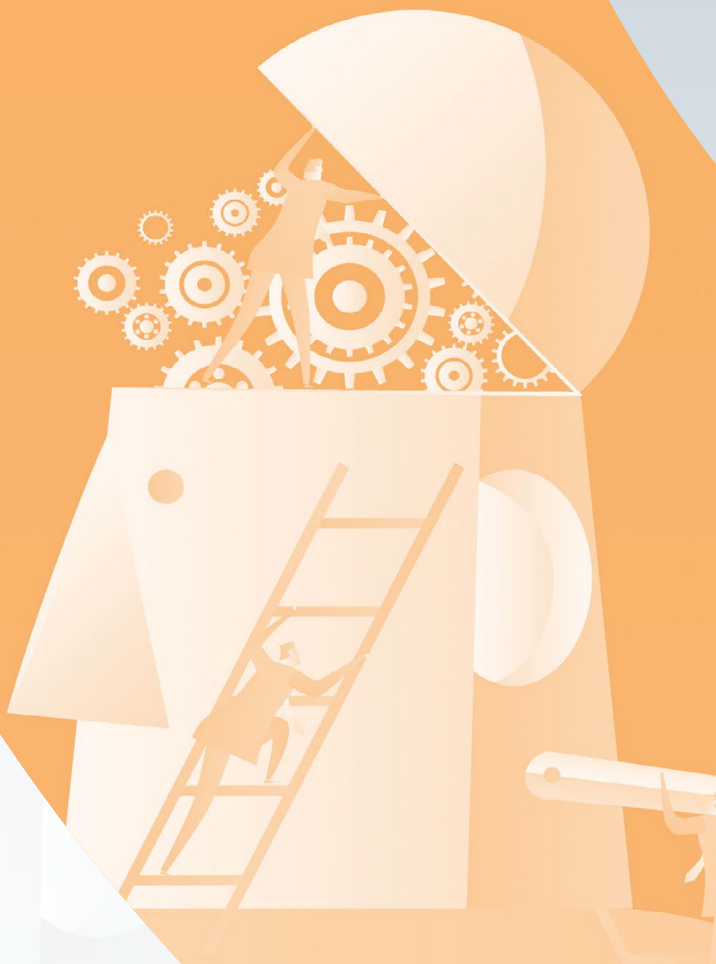
Ultimately, further research is needed to determine whether the increased risk of ICH among statin users is truly due to the drugs or is a result of other factors.

The decision to hold statins should be made on a case-by-case basis. It is important for practitioners and pharmacists to help patients weigh the potential benefits and risks of statin use when making treatment decisions.

For some individuals, the benefits of statin therapy in reducing the risk of CVD may outweigh any potential increased risk of ICH. However, for others, the potential increased risk may be a concern, and alternative treatments may need to be considered. ■

NEW RELEASE!

Evidence-Based Learning Strategies for Student Pharmacists



Using effective, evidence-based learning strategies while studying can make all the difference in academic success. This book, which draws from the author's experience as an academic coach and faculty member, will teach students how to use the latest evidence-based learning strategies and best practices to enhance learning and performance in courses.

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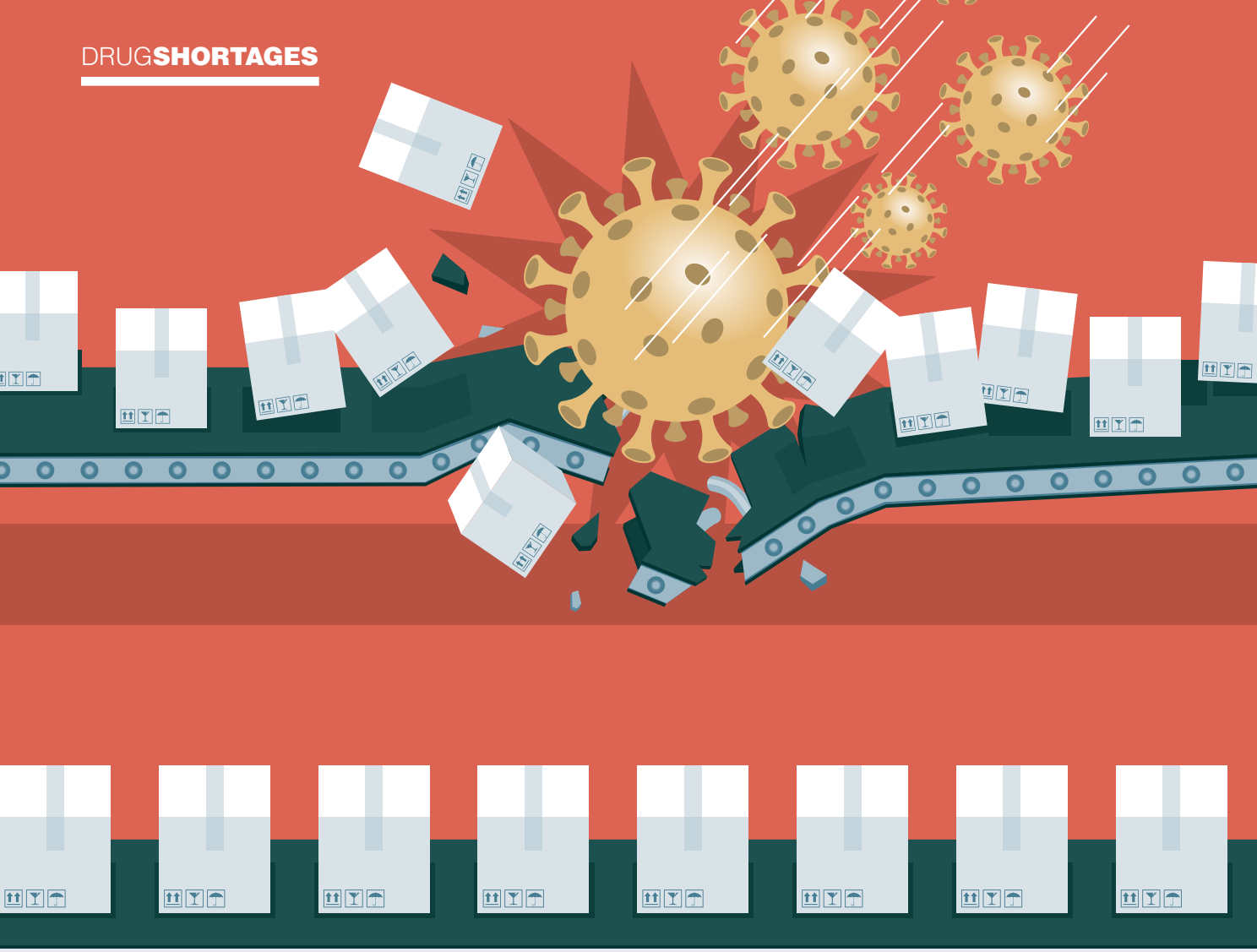


Experts give the scoop on drug shortages

Morgan Carson-Marino, PharmD, MS

On January 4, 2023, APhA hosted an open forum as part of the Pulse on Practice and Policy Open Forum Series to discuss the drug shortages that pharmacies are facing nationwide. The shortage and accessibility of various medications continues to affect patients and health care systems, which are struggling to find alternative therapies and mitigate the impact of these drug shortages.

The scarcity of essential medications, in particular, has sparked questions about contributing factors. For example, there have been concerns voiced about the supply chain and its intermediaries, the nature of manufacturing, and the role of FDA and the government.

During the open forum, experts, including Valerie Jensen, RPh, FDA's associate director of the drug shortages staff, answered some of the top questions about drug shortages and the work being done to mitigate them.

What causes drug shortages?

Drug shortages can be caused by a variety of factors, including production delays, manufacturing issues, raw material shortages, and unexpected increases in demand.

How can health systems and compounding pharmacies prepare for and mitigate drug shortages?

Health systems can prepare for drug shortages by maintaining an up-to-date list of drugs that are in short supply and developing contingency plans for how to manage the shortages. This may include identifying alternative treatment options, conserving supplies of the affected drug, and coordinating with other health systems to share limited supplies.

Compounding pharmacies can help address and alleviate drug shortages by preparing customized medications, for example, with alternative formulations and doses. FDA is responsible for regulating compounding pharmacies, such as their standards for quality and safety, but Medicare, Medicaid, and private insurance companies are responsible for determining which medications may be covered.

Compounded medications are covered if deemed medically necessary and if no alternative treatment is available.

503B outsourcing facilities, or compounding pharmacies registered with FDA, can step in during shortages to manufacture medications that

are in short supply or use alternative ingredients. Moreover, these facilities can collaborate with hospitals and other pharmacies to identify shortages and prioritize manufacturing efforts accordingly.

What are the best resources for predicting and proactively managing drug shortages?

The FDA's Drug Shortage website is a helpful resource for staying up to date on current and potential drug shortages. Many hospitals and health systems have established protocols for managing drug shortages and may have additional resources available to help predict and proactively manage shortages.

> The FDA's Drug Shortage website is a helpful resource for staying up to date on current and potential drug shortages.

What role does overseas manufacturing play in drug shortages?

Many drugs used in the United States are manufactured overseas, and supply chain disruptions or manufacturing issues in these countries can contribute to drug shortages.

Additionally, the increasing global demand for drugs and other medical products has put pressure on manufacturing capacity, which can also lead to shortages. FDA is working to ensure the drug supply chain is robust and is taking measures to protect smaller sites. Overseas manufacturing and importation plays a role in the current drug shortage, and FDA is considering different options to ensure adequate drug supply, including moving manufacturing back to the United States.

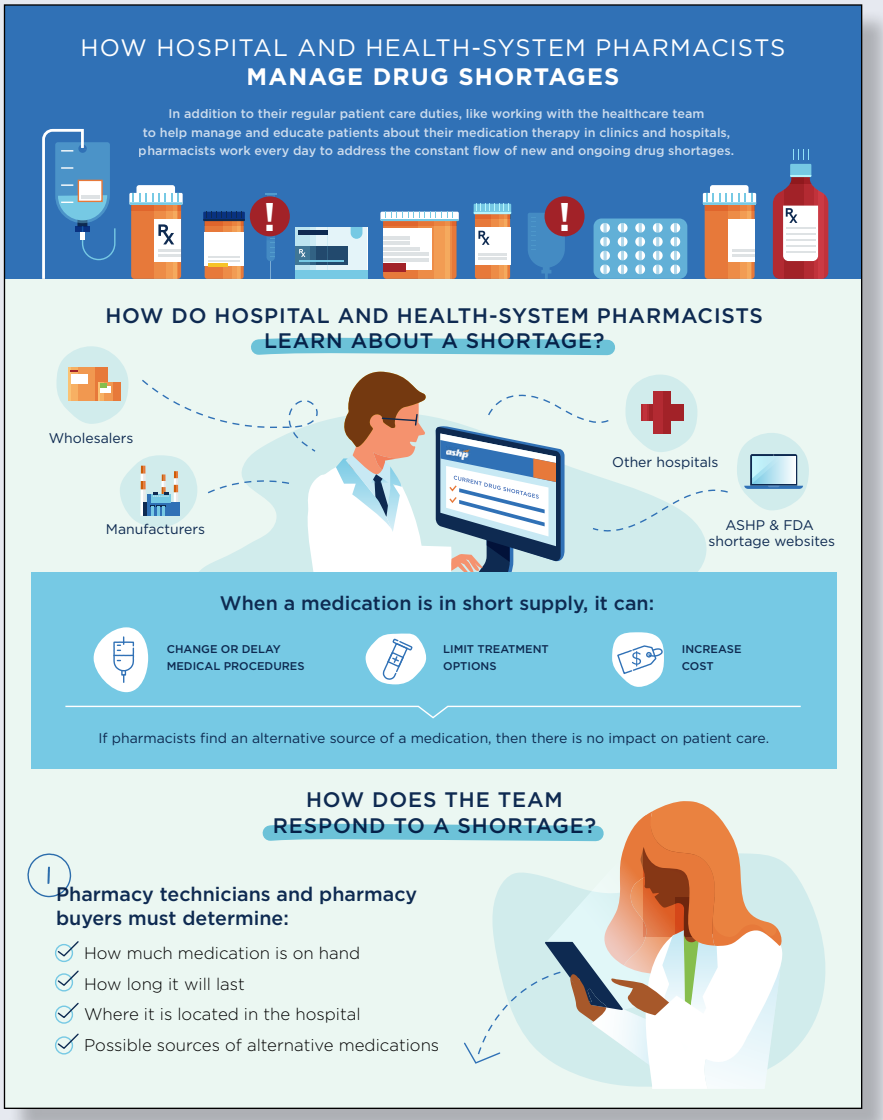
How can pharmacists inform prescribers about shortages and improve communication?

Pharmacists can regularly check FDA's Drug Shortage website and other resources and share this information with prescribers. It is also important for pharmacists to stay in close communication with their colleagues and other health care professionals to share updates about shortages and discuss potential alternative treatment options. Many health systems have established protocols for managing drug shortages and may have systems in place for communicating with prescribers about shortages and alternative treatments.

Taken together, FDA determines which drugs to put on the shortage list based on reports from manufacturers, wholesalers, and other stakeholders and this is a process that takes time to be reported and listed. In the meantime, shortage management practices can be implemented in health systems and these contingency plan strategies can be shared among pharmacy teams and other health care professionals.

As the demand for certain medication continues, communication with both patients and providers about alternatives is important and pharmacists can deliver updates as needed.

As pharmacists, it is important to stay informed about any changes to DEA regulations and their effect on prescription validity. Overall, changes in the shortage crisis are complex and may be caused by a variety of factors and the best resources for staying updated include the FDA's shortage list and establishing relationships with suppliers. ■



Excerpt from ASHP.org/Drug-Shortages

Zinc for patients with COVID-19?

Lauren Howell, PharmD

Over the course of the pandemic, researchers raced to find effective treatments for patients with COVID-19. While many different strategies have been investigated, few have proven to be beneficial to health outcomes in these patients. But one simple, readily available, low-cost OTC supplement could change that narrative.

A study published November 4, 2022, in *Clinical Infectious Diseases* showed that in patients with COVID-19, oral zinc can decrease 30-day death, ICU admission rate, and shorten symptom duration. Previous studies have shown that serum zinc is inversely correlated with outcomes in sepsis, leading researchers to hypothesize that zinc could provide value to patients with COVID-19.

Study design

VIZIR was a prospective, randomized, double-blind, placebo-controlled, multicenter trial, conducted from February to May of 2022.

To be included, patients had to be 18 years or older and have a diagnosis of COVID-19. Patients were excluded from the trial if symptoms started more than 7 days before inclusion or if they had symptoms that immediately qualified them for ICU admission.

The included patients were randomly assigned to receive either 25 mg of elemental zinc twice daily for 15 days or a placebo capsule twice daily for 15 days.

All patients received supportive care as recommended by national guidelines, including corticosteroids, prophylactic anticoagulation, supplemental oxygen, and other treatments as clinically indicated.

Primary outcome measures were death rate, ICU admission rate, and combined outcome within 30 days after randomization. Secondary outcomes included length of stay in the hospital and protocol treatment safety. In outpatients, duration of COVID-19 symptoms, need for hospitalization, and oxygen therapy were also included as secondary outcomes. A total of 470 patients were included in this intention to treat analysis.

Study findings and clinical implications

The study found that 30-day mortality was 6.5% in the zinc group compared to 9.2% in the placebo group—despite similar severity of illness between the two groups. The ICU admission rate was 5.2% in the zinc group and 11.3% in the placebo group. The trial also found evidence of a treatment positive effect with zinc, as compared with placebo, in inpatients, patients older than 65, patients with a comorbidity, and those requiring oxygen at baseline. Among outpatients, the duration of COVID-19 symptoms was found to be shorter in the zinc group. The rate of hospital admission was similar between both the patients treated with zinc and those given placebo. There was no significant difference in rates of adverse events between the two groups.

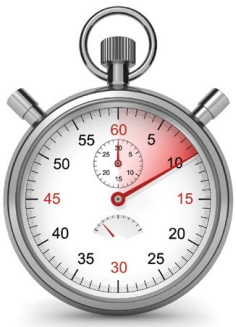
> Zinc should be considered as a strategy in the treatment of patients with COVID-19.

Based on the findings of this trial, zinc should be considered as a strategy in the treatment of patients with COVID-19. The finding showed consistent results among both high- and low-risk patients, showing that there is potential for zinc to be used among a wide variety of patients. Additionally, zinc is readily available at a low price to most patients.

Thirty-day primary outcome

Variable	Zinc (n = 231)	Placebo (n = 239)
Death, n (%)	15 (6.5)	22 (9.2)
ICU admission, n (%)	12 (5.2)	27 (11.3)
Composite outcome, n (%)	24 (10.4)	40 (16.7)

In the future, more studies should be performed to evaluate the efficacy and safety of higher and lower doses of zinc. Additionally, a longer span of treatment, beyond the 15 days used in this trial, could be considered for further studies. While there is certainly more research to be done, the absence of a curative treatment for COVID-19 makes the findings of this study relevant to many pharmacists and patients. ■



A minute with ...

Aimee Dawson, PharmD

Associate Professor of Pharmacy Practice, Massachusetts College of Pharmacy and Health Sciences, Worcester; and Pharmacist, Holyoke Health Center, Holyoke, MA

Member since 2013

"Being a member of APhA is one of the things I can point to and say this had one of the biggest impacts on my professional career development. My experiences at APhA helped me grow as a leader and network with pharmacists across the country. It is something that happens gradually over time. When I first joined APhA, I would have never imagined the opportunities it would have led to 10 years later."

How has APhA helped you establish meaningful connections?

APhA has made it very easy to get involved, stay involved, and continue to establish meaningful connections. Through the Special Interest Group (SIG) community, I was able to serve as a volunteer for the Medication Therapy Management and Diabetes Management (DM) SIGs. After a few years of being a volunteer, I was ready to serve as a cochair of a committee. After a few years of that, I was ready to run for election to serve as the coordinator of the DM SIG. Within all of these experiences, I had the opportunity to work with amazing pharmacists and APhA staff. Everyone I have gotten to know throughout the years has been great to work with and incredibly helpful.

How does APhA help you thrive in your everyday practice?

APhA is the place to go when you don't know where else to go. I think everything we have learned about billing for clinical services has been through our connections or continuing education programs at APhA. I always know that if I have a question that I can't answer, I can post it on the Engage platform and someone will have an answer.

What excites you about the profession of pharmacy?

I love how adaptable pharmacy is. We saw how we rose to the challenge during the COVID-19 pandemic. I am excited to see how else pharmacists can make an impact on patient care.

Can you share a meaningful story about a time you interacted with a patient? Perhaps a time you felt like you really made a difference for them?

There was a patient at my health center who had recently transferred to a new primary care provider (PCP). Her new PCP called in a panic, as this patient had over 45 medications on her active medlist from her previous provider. During her first visit with her PCP, I worked with the patient to reconcile her medication list to match the 25–30 medications she was actually taking. Many of these were PRN medications and I suspected many were treating adverse effects of her other medications.

I met with this patient each month when she picked up her medboxes and, little by little, we worked collaboratively with her PCP and specialists to adjust and manage her medications and reduce the polypharmacy. Her health conditions improved and she was feeling better. From a medical perspective, it was a win. However, the patient could not have cared less about the interventions we were making on her medications and disease states. What she valued the most each month was knowing she was going to see me and feel heard. Patients always value your communication skills, empathy, and active listening, more than your clinical knowledge. She would keep me updated with her family life and show me pictures of her nieces and nephews. I share this story to show that you don't always need to have a clinical intervention to make a difference for people; sometimes they just need that connection. ■

Get involved

Preceptor SIG

The primary purpose of the APhA Preceptor Special Interest Group (SIG) is to serve as an interactive community where pharmacists who precept students and residents can communicate and receive feedback on precepting strategies, precepting challenges and solutions, and opportunities for preceptor growth and development. This community also serves as a conduit for APhA to identify practice-based teaching models that support the advancement of patient-care services and address training and development needs of preceptor pharmacists in order to continually improve the quality of experiential teaching within the profession of pharmacy. Members of the SIG can choose to be further involved in either the communications or education committee, where they will work to identify resource needs and develop valuable toolkits and resources for learning.

Interested in getting involved in the Preceptor SIG? Please visit apha.us/PreceptorSIG to learn more. ■

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APhA publishes annually between 10 and 15 printed and digital textbooks and professional references for pharmacists, pharmacy technicians, and student pharmacists in these fields. APhA titles include Krinsky et al., *Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care*; Franks, *The APhA Complete Review for Pharmacy*; Allen, *The Art, Science, and Technology of Pharmaceutical Compounding*; Cohen, *Medication Errors*; -Kowalsky, *Weatherman, Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*; and Trissel, *Trissel's Stability of Compounded Formulations*.

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Doug R. Hacking, PharmD, MBA
Founder, Relationship Resonance
Presentation: PharmTalk: Lessons on Leadership: Building a High Performing Team
Sunday, March 26, 2023
1:00 PM – 2:00 PM PT

Diana Isaacs, PharmD
Endocrine Clinical Pharmacy Specialist/CGM Program Coordinator, Cleveland Clinic
Presentations: DigitalHealth.Rx Summit: Digitally-Enabled Care: Pharmacy Case Studies
Thursday, March 23, 2023
2:45 PM – 4:00 PM PT

Digital Technology in Diabetes Care
Friday, March 24, 2023
2:15 PM – 3:45 PM PT

Christopher M. Jones, PharmD, DrPH, MPH
Director, National Center for Injury Prevention and Control (NCIPC), CDC
Presentation: Update on the 2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain
Sunday, March 26, 2023
2:15 PM – 3:15 PM PT

Adrijana Kekic, PharmD
Pharmacogenomics Clinical Specialist, Mayo Clinic
Presentation: The Future is Now: AI and Machine Learning in Medicine
Friday, March 24, 2023
8:00 AM – 9:00 AM PT

Bill Stilling, MS, JD
Partner, Stilling & Harrison, PLLC
Presentation: The Dobbs Decision: Impact for Pharmacists
Friday, March 24, 2023
1:00 PM – 2:00 PM PT

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New therapeutic agents marketed in 2022: Part 1

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Four new therapeutic agents are considered in this review, the first in a series of articles on new therapeutic agents marketed in 2022: tirzepatide (Mounjaro–Eli Lilly and Company), daridorexant hydrochloride (Quviviq–Idorsia), tenapanor hydrochloride (Ibsrela–Ardelyx), and vonoprazan fumarate in co-packaging with amoxicillin, and amoxicillin and clarithromycin (Voquezna–Phathom Pharmaceuticals).

Following the review of each new therapeutic agent, the new drug is compared with the older medication(s) with which it is most similar in properties and uses, and its advantages and disadvantages are identified. (Advantages and disadvantages are identified at the time the new drug is first marketed and do not reflect approval of additional new drugs and/or changes that occur after the drug is initially marketed.)

Antidiabetic agent

Glucagon-like peptide-1 (GLP-1), a peptide hormone released soon after eating a meal, has multiple actions that include suppressing glucagon secretion, stimulating glucose-dependent insulin secretion, slowing gastric emptying, and promoting satiety. The class of GLP-1 receptor agonists includes exenatide (immediate-release formulation Byetta–AstraZeneca and the extended-release formulation Bydureon–AstraZeneca), liraglutide (Victoza–Novo Nordisk), dulaglutide (Trulicity—Eli Lilly and Company), and semaglutide (Ozempic–Novo Nordisk). These agents are administered subcutaneously as adjuncts to diet and exercise to improve glycemic control in patients with type 2 diabetes. Dulaglutide, semaglutide, and extended-release exenatide are administered once a week, whereas liraglutide is administered once a day and immediate-release exenatide is administered twice a day. An orally administered formulation of semaglutide (Rybelsus–Novo Nordisk) is also available; it is administered once a day.

GLP-1 receptor agonists have assumed an increasingly important role in the treatment of diabetes because in addition to their multiple actions that improve glycemic control, dulaglutide, semaglutide, and liraglutide have also been approved to reduce the risk of major adverse cardiovascular events (MACE) in patients

Learning objectives

At the conclusion of this knowledge-based activity, the pharmacist will be able to

- Identify the new therapeutic agents and explain their appropriate use.
- Identify the indications and mechanisms of action of the new agents.
- Identify the most important adverse events and other risks of the new therapeutic agents.
- State the route of administration for each new drug and the most important considerations regarding dosage and administration.
- Compare the new therapeutic agents with older medications to which they are most similar in properties and/or use and identify the most important advantages and disadvantages of the new drugs.

Preassessment questions

Before participating in this activity, test your knowledge by answering the following questions. These questions will also be part of the CPE assessment.

1. Which of the following agents should be administered immediately prior to a meal?

a. Tirzepatide
b. Daridorexant
c. Tenapanor
d. Vonoprazan

2. Which of the following agents is administered subcutaneously?

a. Tirzepatide
b. Daridorexant
c. Tenapanor
d. Vonoprazan

3. Which of the following statements is correct regarding daridorexant?

a. It acts as an orexin receptor agonist.
b. In comparison with other drugs with a similar action, it is considered to have an intermediate duration of action.
c. It has been demonstrated to be more effective than eszopiclone.
d. It is eliminated in unchanged form in the urine.

with type 2 diabetes and established cardiovascular disease, and formulations of semaglutide (Wegovy–Novo Nordisk) and liraglutide (Saxenda–Novo Nordisk) have been approved as adjuncts to a reduced-calorie diet and increased physical activity for chronic weight management in patients with or without diabetes.

Tirzepatide is the most recent addition to the class of GLP-1 receptor agonists; however, unlike its predecessors, it is a dual-targeted treatment that also activates glucose-dependent insulinotropic polypeptide (GIP) receptors. It is a 39-amino acid modified peptide based on the GIP sequence, and it is administered subcutaneously as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Tirzepatide is administered subcutaneously in the abdomen, thigh, or upper arm, and the injection site should be rotated with each dose. As with dulaglutide, subcutaneous semaglutide, and extended-release exenatide, it is administered once a week. The recommended starting dosage is 2.5 mg injected once a week; however, it should be noted that this dosage is for treatment initiation and is not intended for glycemic control. After 4 weeks, the dosage is increased to 5 mg once a week. If additional glycemic control is needed, the dosage may be increased in 2.5 mg increments after at least 4 weeks on the current dose. The maximum dosage is 15 mg once a week. If the new drug is used concurrently with insulin, the products should be administered as separate injections and should not be mixed with tirzepatide.

Tirzepatide injection is available in prefilled single-dose pens containing 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg per 0.5 mL. The drug should be stored in a refrigerator in its original carton of 4 single-dose pens.

The effectiveness of tirzepatide was evaluated in five 40- or 52-week clinical trials as either a stand-alone therapy or as an add-on to other medications for diabetes. Three doses of the new drug (5 mg, 10 mg, 15 mg) were evaluated, and it was compared with placebo, semaglutide, insulin degludec (Tresiba–Novo Nordisk), and insulin glargine (e.g., Lantus–Sanofi). Patients receiving the maximum recommended dosage of 15 mg once a week of tirzepatide experienced, on average, a lowering of their hemoglobin A1C by 1.6% more than placebo, 0.5% more than semaglutide, 0.9% more than insulin degludec, and 1% more than insulin glargine.

Many patients with diabetes are overweight, and obesity was common among the participants in the clinical trials, with an average BMI of 32–34 kg/m^2 at the time of enrollment. Some antidiabetic agents (e.g., insulin, sulfonylureas) have been associated with weight gain during treatment, but those treated with a GLP-1 receptor agonist often experience weight loss. In patients treated with the maximum recommended dosage, the average weight loss with tirzepatide was 15 pounds more than with a placebo, 12 pounds more than semaglutide, 29 pounds more than insulin degludec, and 27 pounds more than insulin glargine.

Notwithstanding the likely greater weight loss with tirzepatide, chronic weight management is not a labeled indication for the new agent at present, as it is with semaglutide and liraglutide. It has not yet been determined whether tirzepatide reduces the risk of MACE, whereas this is a labeled indication for dulaglutide, semaglutide, and liraglutide in patients with diabetes and established cardiovascular disease.

The limitations of use for tirzepatide are similar to those of other agents with GLP-1 receptor agonist activity, and it should not be used in patients with type 1 diabetes. Acute pancreatitis has been infrequently reported with these agents, and they have not been studied

in patients with a history of pancreatitis. If pancreatitis is suspected, treatment with tirzepatide should be promptly discontinued. Other antidiabetic agents should be considered in patients with a history of pancreatitis.

In studies in rodents, tirzepatide and other GLP-1 receptor agonists have been reported to cause thyroid C-cell tumors, but it is not known whether they cause these tumors in humans. However, the labeling for these agents includes a boxed warning about this possibility and for contraindications in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.

The most commonly reported adverse events in the studies of tirzepatide (and their incidence with the weekly dosage of 10 mg and 15 mg, respectively) include nausea (15%, 18%), diarrhea (13%, 17%), decreased appetite (10%, 11%), vomiting (5%, 9%), constipation (6%, 7%), dyspepsia (8%, 5%), and abdominal pain (5%, 5%). The new agent has not been studied in patients with severe GI disease, including severe gastroparesis, and its use is not recommended in these patients. Acute kidney injury and worsening of chronic renal failure have been infrequently reported in patients treated with GLP-1 receptor agonists; most of these events have occurred in patients who had experienced GI adverse events such as vomiting and diarrhea that resulted in dehydration. Renal function should be monitored when initiating or increasing the dosage of tirzepatide in patients with renal impairment who also report severe GI adverse events.

Additional risks associated with the use of tirzepatide and other GLP-1 receptor agonists include hypersensitivity reactions, complications in patients with a history of diabetic retinopathy, and acute gallbladder disease (e.g., cholelithiasis, cholecystitis). There are insufficient data to evaluate the safety of using tirzepatide during pregnancy or lactation, but based on animal studies its use during pregnancy may be associated with adverse developmental effects.

As with semaglutide, the effectiveness and safety of tirzepatide in patients younger than 18 years have not been established. However, dulaglutide, extended-release exenatide, and liraglutide are indicated for patients 10 years and older who have type 2 diabetes.

Following subcutaneous administration, the mean absolute bioavailability of tirzepatide is 80%. It is metabolized via proteolytic cleavage, beta-oxidation, and amide hydrolysis, and it is eliminated as metabolites in the feces and urine. Dosage adjustment is not necessary in patients with hepatic or renal impairment.

Tirzepatide and the other GLP-1 receptor agonists are not likely to cause hypoglycemia. However, there is an increased risk of hypoglycemia if they are used in combination with insulin or an insulin secretagogue, and a reduction in dosage of the latter agent may be necessary.

Because the GLP-1 receptor agonists delay gastric emptying, a potential exists for altered absorption and activity of concomitantly administered oral medications. The delay in gastric emptying caused by tirzepatide is greatest after the first dose and this effect diminishes over time. Patients who are concurrently treated with oral medications dependent on threshold concentrations for efficacy and/or with a narrow therapeutic index (e.g., warfarin) should be monitored for a potential change in activity. The labeling for tirzepatide advises that patients using oral hormonal contraceptives switch to a non-oral contraceptive method, or add a barrier method of contraception, for 4 weeks after initiation and for 4 weeks after each dosage increase with tirzepatide.

Comparison of tirzepatide with dulaglutide and semaglutide

Advantages

- It is more effective in reducing hemoglobin A1C and causing weight loss than semaglutide, insulin degludec, and insulin glargine based on comparative clinical studies.
- It has dual-targeted mechanisms of action (i.e., it is an agonist of both GLP-1 and GIP receptors).

Disadvantages

- It is not indicated in pediatric patients, whereas dulaglutide is indicated for use in patients 10 years and older with type 2 diabetes.
- Labeled indications are more limited (i.e., it is not yet approved for chronic weight management, and it has not been determined whether it reduces the risk of MACE).

Hypnotic

Orexins are naturally occurring neuropeptides that act in a signaling mechanism as a central promoter of wakefulness. This wake-promoting action results from the binding of orexin A and orexin B to OX1R and OX2R receptors. Daridorexant hydrochloride (Quviviq–Idorsia) is the third orexin receptor antagonist to be approved for the treatment of patients with insomnia, joining suvorexant (Belsomra–Merck) and lemborexant (Dayvigo–Eisai Inc.). By blocking the binding of orexins to their receptors, these agents are thought to suppress the wake drive. Like its predecessors, daridorexant is indicated for the treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

Daridorexant hydrochloride is supplied in film-coated tablets in quantities equivalent to 25 mg and 50 mg of daridorexant.

The effectiveness of daridorexant was evaluated in 2 placebo-controlled trials in which the primary efficacy endpoints were the change from baseline to month 1 and month 3 in latency to persistent sleep (LPS, a measure of sleep induction) and wake after sleep onset (WASO, a measure of sleep maintenance). A secondary endpoint was patient-reported subjective total sleep time (sTST) that patients evaluated every morning at home using a sleep diary questionnaire.

In the first study, doses of 25 mg and 50 mg of daridorexant showed a statistically significant improvement compared with placebo on LPS, WASO, and sTST at months 1 and 3. In the second study, a dose of 25 mg of the new drug showed a statistically significant improvement compared with placebo on WASO and sTST but

not LPS at months 1 and 3. (The 50 mg dose was not evaluated in this study.) Patients treated with daridorexant in both studies reported longer total sleep time (about 10–20 minutes) and better sleep quality than those receiving a placebo.

The 3 orexin receptor antagonists as well as hypnotics such as eszopiclone and temazepam are considered to have an intermediate duration of action in comparison with agents such as triazolam and ramelteon, which have a short duration of action, and flurazepam, which has a long duration of action.

The loss of orexin receptors has been reported in individuals with narcolepsy, and antagonism of orexin receptors by daridorexant may be associated with signs of narcolepsy or cataplexy. Symptoms similar to mild cataplexy, such as periods of leg weakness, can occur with daridorexant and the other orexin receptor antagonists, and their use is contraindicated in patients with narcolepsy. Sleep paralysis—an inability to speak or move for several minutes during sleep-wake transitions—and hallucinations have also been infrequently reported.

Adverse events experienced most often with daridorexant (and their incidence with the 25 mg and 50 mg doses, respectively) include headache (6%, 7%) and somnolence or fatigue (6%, 5%). In a controlled study of the nighttime administration of daridorexant on next-morning driving performance, using a driving simulator, both doses of the drug caused a statistically significant impairment of next-day driving skills after the first dose. Although the mean effect on driving performance was not statistically significant after 4 consecutive nights of treatment with either dose, driving ability was impaired in some individuals. In view of the individual variation in sensitivity to daridorexant, patients should be cautioned about the potential for next-morning driving impairment. Patients should also be cautioned about central nervous system (CNS) depressant effects and related risks that increase with dosage and concurrent use with other CNS depressants. Patients should be advised not to consume alcohol because coadministration with daridorexant may result in additive effects on psychomotor performance.

The use of hypnotics, including daridorexant, has been associated with the occurrence of complex sleep behaviors, including sleepwalking, sleep-driving, and engaging in other activities while not fully awake (e.g., preparing and eating food, phone conversations) which patients do not usually remember. Treatment should be immediately discontinued if patients experience these effects.

Worsening of depression and suicidal ideation has been associated with the use of hypnotics. Appropriate precautions must be observed in evaluating, treating, and monitoring patients for these risks. Like suvorexant and lemborexant, daridorexant is classified as a schedule IV controlled substance. However, in clinical trials of chronic administration of the new drug, discontinuation of treatment was not associated with withdrawal signs or symptoms, and it appears unlikely to cause physical dependence.

The respiratory depressant effect of daridorexant was evaluated in patients with mild to moderate obstructive sleep apnea (OSA) not requiring continuous positive airway pressure (CPAP) and in patients with moderate chronic obstructive pulmonary disease (COPD); it was well-tolerated. However, it has not been studied in patients with severe OSA or those requiring CPAP, or in patients with severe COPD, and it must be used with caution in patients with compromised respiratory function.

Sufficient data are not available to assess the risk of daridorexant use during pregnancy and lactation. The risk of adverse events if used during pregnancy appears to be low, but those who are exposed to the drug during pregnancy are advised to register in the company's pregnancy registry by calling 1-833-400-9611. It is likely that daridorexant and its metabolites will be present in human milk, and infants exposed to the drug through breast milk should be monitored for excessive sedation. The effectiveness and safety of the new drug in pediatric patients have not been established.

Following oral administration, daridorexant has a prompt onset of action and it has an absolute bioavailability of 62%. It is extensively metabolized via the CYP3A4 pathway, and approximately 60% of a dose is recovered in the feces and 30% in the urine. Dosage adjustment is not necessary in patients with renal impairment, but it should be used in a lower dosage in patients with moderate hepatic impairment. The new agent has not been studied in patients with severe hepatic impairment, and its use in these patients is not recommended.

As with suvorexant and lemborexant, the activity of daridorexant is increased by drugs that are CYP3A4 inhibitors and decreased by CYP3A4 inducers. Concurrent use of daridorexant or suvorexant with a strong CYP3A4 inhibitor (e.g., clarithromycin, itraconazole) should be avoided, but the hypnotic may be used in a lower dosage in patients being treated with a moderate CYP3A4 inhibitor (e.g., diltiazem, fluconazole). The labeling for lemborexant recommends that concurrent use with a strong or moderate CYP3A4 inhibitor be avoided, and that it be used in a lower dosage in patients taking a weak CYP3A4 inhibitor. The use of daridorexant or lemborexant should be avoided in patients treated with a strong or moderate CYP3A4 inducer (e.g., carbamazepine, rifampin, St. John's wort), whereas the labeling for suvorexant cautions that its efficacy may be reduced by the concurrent use of a strong CYP3A4 inducer.

Unlike daridorexant and lemborexant, suvorexant is a P-glycoprotein (P-gp) inhibitor, and it may increase the serum concentration and activity of P-gp substrates such as digoxin.

The maximum concentration and time to sleep onset of daridorexant may be delayed if it is taken with or soon after a meal. The recommended dosage is 25 mg or 50 mg once per night, taken within 30 minutes before going to bed, with at least 7 hours remaining prior to planned awakening. In patients with moderate hepatic impairment

Comparison of daridorexant with suvorexant and lemborexant

Advantages

- It may be used in a lower dosage in patients treated concurrently with a moderate CYP3A4 inhibitor (compared with lemborexant).

Disadvantages

- Concurrent use with strong or moderate CYP3A4 inducers should be avoided compared with suvorexant, for which the labeling does not preclude concurrent use with a CYP3A4 inducer.
- It has not been directly compared with other hypnotics in clinical studies.

and in those also being treated with a moderate CYP3A4 inhibitor, the maximum recommended dosage is 25 mg once per night.

Agent for IBS

Irritable bowel syndrome (IBS) is a GI disorder in which abdominal pain is associated with constipation and/or diarrhea as well as sometimes other GI symptoms such as bloating. IBS with constipation (IBS-C) affects more than 11 million people in the U.S., many of whom do not experience adequate relief from dietary modification and use of laxatives. Medications that have been approved for the treatment of IBS-C include the secretagogues lubiprostone (indicated in women at least 18 years old), a chloride channel activator, and the guanylate cyclase-C agonists linaclotide (Linzess–AbbVie) and plecanatide (Trulance–Salix Pharmaceuticals). The serotonin-4 receptor agonist tegaserod (Zelnorm–Alfasigma) is effective in some patients with IBS-C; however, because it may cause cardiovascular adverse events, its use is restricted to women less than 65 years old who do not have a history of serious cardiovascular problems.

The sodium/hydrogen exchanger 3 (NHE3) is expressed on the apical surface of the small intestine and colon, and it is primarily responsible for the absorption of dietary sodium. Tenapanor hydrochloride (Ibsrela–Ardelyx) is the first NHE3 inhibitor to be approved and is administered orally. It is minimally absorbed and acts locally in the GI tract. By reducing the absorption of sodium, it causes an increase in water secretion into the intestinal lumen, which accelerates intestinal transit time and results in a softer stool consistency. In studies in animals, it has also been reported to reduce abdominal pain.

Tenapanor hydrochloride is supplied in tablets in a quantity equivalent to 50 mg of tenapanor. The labeling for linaclotide and plecanatide provides instructions for mixing the drugs with applesauce or water for patients who have difficulty swallowing capsules or tablets or who have a nasogastric or gastric feeding tube. However, such instructions are not provided for tenapanor.

The recommended dosage of tenapanor is 50 mg orally twice a day, and the drug should be administered immediately before breakfast or the first meal of the day and immediately before dinner. Linaclotide and plecanatide are administered once a day, and linaclotide should be administered at least 30 minutes prior to the first meal of the day.

The effectiveness of tenapanor was evaluated in 2 placebo-controlled clinical trials having identical designs during the first 12 weeks of treatment. The primary endpoint was the proportion of responders, which were defined as a patient achieving both the stool frequency and abdominal pain intensity criteria in the same week for at least 6 of the first 12 weeks of treatment. The stool frequency responder criterion was defined as a patient who experienced an increase of at least 1 complete spontaneous bowel movement (CSBM) in a weekly average from baseline, and the abdominal pain responder criterion was defined as a patient who experienced at least a 30% reduction in the weekly average of abdominal pain score compared with baseline. In one of the trials, 37% of the patients treated with tenapanor were responders, with 47% being CSBM responders and 50% being abdominal pain responders, compared with 24%, 33%, and 38%, respectively, of those receiving a placebo. In the other trial, the corresponding percentages of responders treated with tenapanor were 27%, 34%, and 44%, compared with 19%, 29%, and 33% of those receiving placebo.

Lubiprostone, linaclotide, and plecanatide are also indicated for the treatment of chronic idiopathic constipation in adults, and lubiprostone is also indicated for the treatment of opioid-induced constipation in adults with chronic noncancer pain. However, these are not labeled indications for tenapanor at present.

Tenapanor was approved by the FDA in 2019 but the company was also conducting studies of its use to control serum phosphorus in patients with chronic kidney disease (CKD) who are on dialysis, and it delayed marketing the drug with the hope that the additional indication for the drug would soon be approved. However, when the indication for patients with CKD (that was considered of greater importance) was still not approved by 2022, the drug was marketed for the treatment of IBS-C.

The effectiveness and safety of tenapanor, linaclotide, and plecanatide in patients less than 18 years have not been established. However, the 3 drugs are associated with a risk of serious dehydration in pediatric patients; in studies in juvenile mice and rats, the drugs have caused deaths due to dehydration. The labeling for each of the drugs includes a boxed warning regarding this risk. Tenapanor and plecanatide are contraindicated in patients less than 6 years, and the use of these agents should be avoided in patients aged 6–12 years and less than 18 years, respectively. Linaclotide is contraindicated in patients less than 2 years. All 3 drugs are also contraindicated in patients with known or suspected mechanical GI obstruction.

The adverse events most often reported in the studies of tenapanor include diarrhea (16%), abdominal distension (3%), flatulence (3%), and dizziness (2%). Severe diarrhea occurred in 2.5% of patients and, if severe diarrhea occurs, treatment should be suspended and the patient should be rehydrated. Tenapanor is minimally absorbed, and its use is not expected to cause risk during pregnancy or result in a clinically relevant

Comparison of tenapanor with linaclotide and plecanatide

Advantages

- It has a unique mechanism of action (i.e., it is a sodium/hydrogen exchanger 3 [NHE3] inhibitor).

Disadvantages

- It is administered more frequently (i.e., twice a day), whereas linaclotide and plecanatide are administered once a day.
- Instructions for use in patients with swallowing difficulties are not provided.
- It may reduce the effectiveness of OATP2B1 substrates (e.g., enalapril).
- It has not been directly compared with previous agents in clinical trials.
- Its labeled indications are more limited (linaclotide and plecanatide are also indicated for chronic idiopathic constipation).

exposure to breastfed infants.

Most of a dose of tenapanor is excreted in the feces as unchanged drug, with less than 10% recovered in the urine primarily as metabolites. Tenapanor is an inhibitor of intestinal uptake transporter organic anion transporter polypeptide 2B1 (OATP2B1), and concurrent use with a substrate of this transporter (e.g., enalapril) is likely to reduce exposure and effectiveness of the latter agent, possibly necessitating an increase in dosage of enalapril.

Gastric acid suppressant

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium that is a common cause of infection in the stomach. It is estimated to affect more than 100 million people in the U.S. It does not usually cause symptoms but may cause inflammation and local tissue damage that result in gastritis and/or peptic ulcer, and an association with certain gastric cancers. Symptomatic *H. pylori* infections are most commonly treated with a combination of a gastric acid suppressant (e.g., omeprazole, lansoprazole) with one or more antimicrobial agents (e.g., amoxicillin, clarithromycin, metronidazole, tetracycline, rifabutin). There has been increased resistance of *H. pylori* to clarithromycin and (to a lesser extent) to metronidazole. Bismuth quadruple therapy with the combination product that contains bismuth subcitrate potassium, metronidazole, and tetracycline (Pylera–AbbVie) plus omeprazole or another PPI is usually considered the preferred treatment for *H. pylori* infection.

PPIs such as omeprazole block the final step of gastric acid production. Vonoprazan fumarate is a type of gastric PPI that is designated as a potassium-competitive acid blocker. It acts to suppress acid secretion at the surface of the gastric parietal cell by reducing potassium binding at the hydrogen-potassium-ATPase enzyme system (i.e., proton pump). It is the first gastric acid suppressant with this mechanism of action, and it provides a higher intragastric pH and has a longer half-life than the other PPIs.

Vonoprazan is not marketed as a single agent in the U.S., but rather as a copackaged product that includes the new drug with amoxicillin capsules (Voquezna Dual Pak–Phathom Pharmaceuticals) and as a copackaged product with amoxicillin capsules and clarithromycin tablets (Voquezna Triple Pak–Pharthom Pharmaceuticals).

The products have been approved for the treatment of *H. pylori* infection in adults and are used in a 14-day course of treatment.

The effectiveness of the 2 vonoprazan-containing copackaged products as well as a regimen of lansoprazole, amoxicillin, and clarithromycin (LAC) was evaluated in treatment-naive *H. pylori*–positive adult patients with at least one clinical condition (e.g., peptic ulcer, dyspepsia).

H. pylori eradication was confirmed with a negative ^{13}C urea breath test conducted at least 27 days following the completion of treatment. The vonoprazan triple and dual combination products were shown to be noninferior to LAC in patients who did not have a clarithromycin or amoxicillin resistant strain of *H. pylori* at baseline, with eradication rates of 85%, 79%, and 79%, respectively. However, the vonoprazan products were superior to LAC in patients who had a clarithromycin resistant strain of *H. pylori* at baseline, with eradication rates of 66%, 70%, and 32%, respectively. Although the regimens have not been directly compared in clinical trials, the results of the studies with the individual regimens suggest that the vonoprazan regimens are less effective than the bismuth quadruple therapy regimen.

The adverse events most often experienced in the clinical trial—and their incidence with the vonoprazan triple combination, vonoprazan dual combination, and LAC, respectively—include diarrhea (4%, 5%, 10%), dysgeusia (5%, 1%, 6%), vulvovaginal yeast infections (3%, 2%, 1%), and abdominal pain (2%, 3%, 3%). The properties and the risks of adverse events and drug interactions with amoxicillin and clarithromycin are

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Development: This home-study CPE activity was developed by APhA.

Comparison of vonoprazan plus clarithromycin and/or amoxicillin with LAC

Advantages

- Regimens are more effective in patients who have a clarithromycin resistant strain of *H. pylori* at baseline.
- Vonoprazan has a unique mechanism of action (i.e., it is a potassium-competitive acid blocker).

Disadvantages

- It may be less effective than bismuth quadruple therapy (based on noncomparative studies of individual regimens);
- Vonoprazan is not available as a single agent.

well-recognized as a result of their long-term use, and most of the concerns (e.g., QT prolongation, hepatotoxicity) identified in the labeling of the new products pertain to the inclusion of clarithromycin in the triple combination product. The properties of vonoprazan that are relevant to its use in combination regimens are the primary focus in the following discussion.

There are insufficient data in patients who are pregnant or breastfeeding to determine if there are risks of developmental events or adverse effects in nursing infants. However, because of the risks with clarithromycin, the triple regimen including this agent should not be used during pregnancy. It is likely that vonoprazan will be present in human milk; based on concerns from studies in animals, breastfeeding is not recommended during treatment. A lactating patient can pump and discard breast milk during treatment and for 2 days after the completion of treatment, and the infant can be fed with stored human milk collected prior to treatment or with formula.

Although amoxicillin and clarithromycin are each indicated for treating infections in pediatric patients, the effectiveness and safety of the vonoprazan combination regimens have not been established in patients less than 18 years old.

Following oral administration and absorption, vonoprazan is metabolized via multiple pathways including CYP3A4/5 and CYP2C19. Approximately 67% of a dose is recovered in the urine and 31% in the feces, primarily as metabolites. Its use in combination with clarithromycin and/or amoxicillin should be avoided in patients with severe renal impairment and in patients with moderate and severe hepatic impairment.

As a CYP3A substrate, the activity of vonoprazan as well as that of clarithromycin may be reduced by strong or moderate CYP3A4 inducers (e.g., carbamazepine), and concurrent use should be avoided. Vonoprazan is a weak CYP3A inhibitor and clarithromycin is a strong inhibitor of this pathway; they may increase the exposure and risks of CYP3A substrates.

Concurrent use with CYP3A4 substrates—during which small changes in concentration may result in serious toxicity (e.g., cyclosporine, tacrolimus)—should be closely monitored.

Vonoprazan is a CYP2C19 inhibitor and may reduce the conversion of clopidogrel to its active metabolite via this pathway and possibly decrease its antiplatelet activity. However, it may increase exposure of drugs that are substrates for this pathway (e.g., citalopram, cilostazol).

Because vonoprazan reduces intragastric acidity, it may reduce the absorption and serum concentration of rilpivirine, and concurrent use is contraindicated. The new drug may also reduce the absorption of drugs such as itraconazole which are dependent on an acidic medium for optimum absorption. Conversely, the reduction in intragastric acidity increases chromogranin A levels and may cause false positive results in diagnostic investigations for neuroendocrine tumors.

Vonoprazan fumarate is supplied in tablets in an amount equivalent to 20 mg of vonoprazan. The Voquezna Dual Pak is copackaged containing vonoprazan tablets (20 mg) and amoxicillin capsules (500 mg); the recommended dosage is vonoprazan 20 mg twice a day (morning and evening) plus amoxicillin 1,000 mg 3 times a day (morning, midday, and evening) with or without food for 14 days. The Voquezna Triple Pak is copackaged containing vonoprazan tablets (20 mg), amoxicillin capsules (500 mg), and clarithromycin tablets (500 mg); the recommended dosage is vonoprazan 20 mg plus amoxicillin 1,000 mg plus clarithromycin 500 mg, each administered twice a day (morning and evening, 12 hours apart) with or without food for 14 days. ■

CPE information

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CPE Assessment

This assessment must be taken online; please see "CPE information" in the sidebar on the previous page for further instructions. The online system will present these questions in random order to help reinforce the learning opportunity. There is only one correct answer to each question.

1. Which of the following agents acts as a potassium-competitive acid blocker?
a. Tirzepatide
b. Daridorexant
c. Tenapanor
d. Vonoprazan

2. Which of the following agents is indicated for the treatment of patients with type 2 diabetes?
a. Tirzepatide
b. Daridorexant
c. Tenapanor
d. Vonoprazan

3. Which of the following agents should be administered immediately prior to a meal?
a. Tirzepatide
b. Daridorexant
c. Tenapanor
d. Vonoprazan

4. Which of the following agents is contraindicated in patients with narcolepsy?
a. Tirzepatide
b. Daridorexant
c. Tenapanor
d. Vonoprazan

5. Which of the following agents is administered subcutaneously?
a. Tirzepatide
b. Daridorexant
c. Tenapanor
d. Vonoprazan

6. Which of the following statements is correct regarding tirzepatide?
a. It is indicated for use in patients 10 years and older.
b. Dizziness is the adverse event most often associated with its use.
c. It is administered once a week.
d. Following initiation of treatment, maintenance doses of 2.5 mg should be administered.

7. Which of the following statements is correct regarding daridorexant?
a. It acts as an orexin receptor agonist.
b. In comparison with drugs with a similar indication, it is considered to have an intermediate duration of action.
c. It has been demonstrated to be more effective than eszopiclone.
d. It is eliminated in unchanged form in the urine.

8. Which of the following statements is correct regarding tenapanor?
a. It is extensively metabolized via hepatic CYP3A4 metabolic pathways.
b. Nausea is the adverse event most often associated with its use.
c. It is administered once a day.
d. It acts as a sodium/hydrogen exchanger 3 inhibitor.

9. Which of the following statements is correct regarding vonoprazan?
a. It is used in combination with omeprazole and metronidazole.
b. It is indicated for use in the treatment of infections caused by *Clostridioides difficile*.
c. Concurrent use with rilpivirine is contraindicated.
d. It is administered once a day.

10. Which of the following statements is correct regarding the comparison of tirzepatide and semaglutide?
a. Both agents have been demonstrated to reduce the risk of major adverse cardiovascular events.
b. Hypoglycemia is the most important adverse event with the use of both agents.
c. Both agents act as GLP-1 receptor agonists, but tirzepatide also acts as an SGLT-2 inhibitor.
d. Tirzepatide has been demonstrated to cause greater weight loss than semaglutide in a comparative study.

Across

8 Twins of the zodiac
9 COVID-19 therapeutic
10 The "S" in ISMP
11 Xanax is an example of this type of word
12 OTC meds promote this kind of care
13 Dried
17 Joint stabilized by the ACL
18 Pharmacist at many independent pharmacies
19 HIV causes this syndrome
21 Cells that protect or enclose organs
23 1/28 of an ounce
24 Inflamed bronchial tubes can cause this
28 Inaccurate data can ____ results
29 Sleeplessness
30 In slang, a drink laced with an incapacitating drug

Down

1 Special delivery?
2 Adverse consequence of treatment
3 Oval track for horse races
4 October birthstone
5 Impulse transmitter
6 The "h" in q.h.
7 Shot that's difficult to miss
14 Common hospital name
15 Genetic carrier
16 Aspirin and ibuprofen
20 Metformin is used to treat this
22 Adenine or guanine, for example
25 Diagnostic tracer gas
26 Improve a skill
27 Drop of salty liquid

Solution is available online at pharmacytoday.org.