PharmacyToday
An official publication of the **American Pharmacists Association**
SEPTEMBER 2023

PHARMACISTS' ROLE IN HIV PrEP GROWING

CONTINUING PHARMACY EDUCATION
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Preventing and managing stress and burnout

TREATING PEDIATRIC T2D
New class of meds available

TEST AND TREAT
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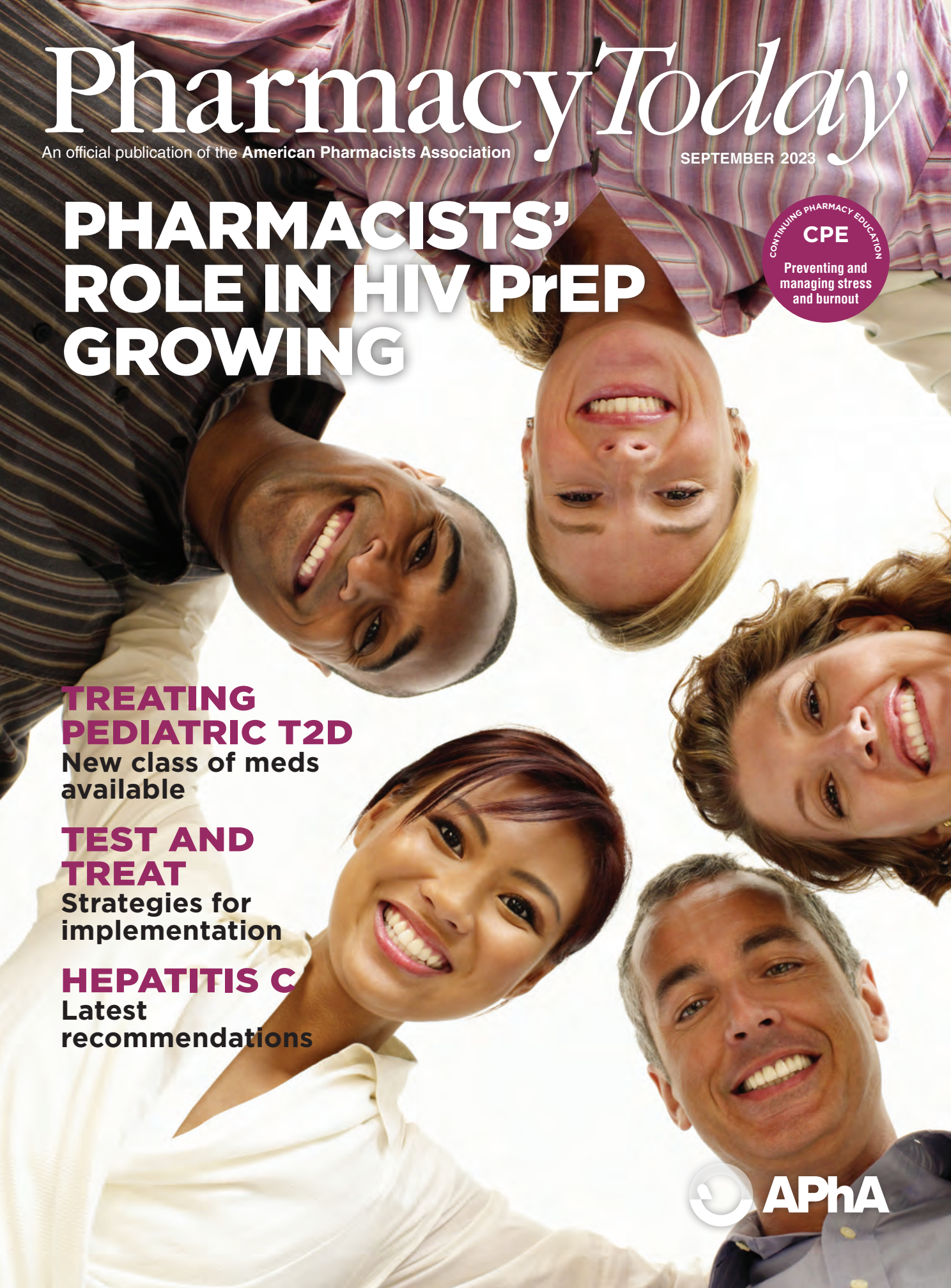


APhA

BulletinToday

WHO says global childhood vaccinations closer to prepandemic levels

Childhood vaccinations worldwide are rising to coverage levels close to those seen before the COVID-19 pandemic, according to new data from WHO and UNICEF.

The agencies estimate that 4 million more children received full vaccination in 2022 compared with the previous year, but recovery is not keeping pace in low-income countries. Approximately 20.5 million children globally still missed at least one vaccine constituting a part of routine immunization in 2022, although that is better than the 24.4 million children who missed at least one dose in 2021.

The data also concluded that 14.5 million children did not receive a single dose of diphtheria, tetanus, and pertussis (DTP) vaccine, which is used as the marker of overall immunization coverage, compared with 18 million who received no DTP doses in 2021.

The new coverage levels remain below those prior to the COVID-19 pandemic when 18.4 million children missed out on at least one vaccination. They are also far short of the United Nations' target to slash the global number of "zero-dose children" by 50% by 2030.

According to the report, the only vaccine to gain ground was the HPV vaccine. The UN hopes to see HPV vaccine rates rise to 90% of girls worldwide by 2030. ■

Weekly insulin found safe, effective for T2D

Research published June 24, 2023, in *JAMA* shows that once-weekly insulin icodec is safe for people with T2D. It also showed that individuals with T2D who used insulin icodec maintained healthier blood glucose levels compared with people who received daily injections of insulin degludec.

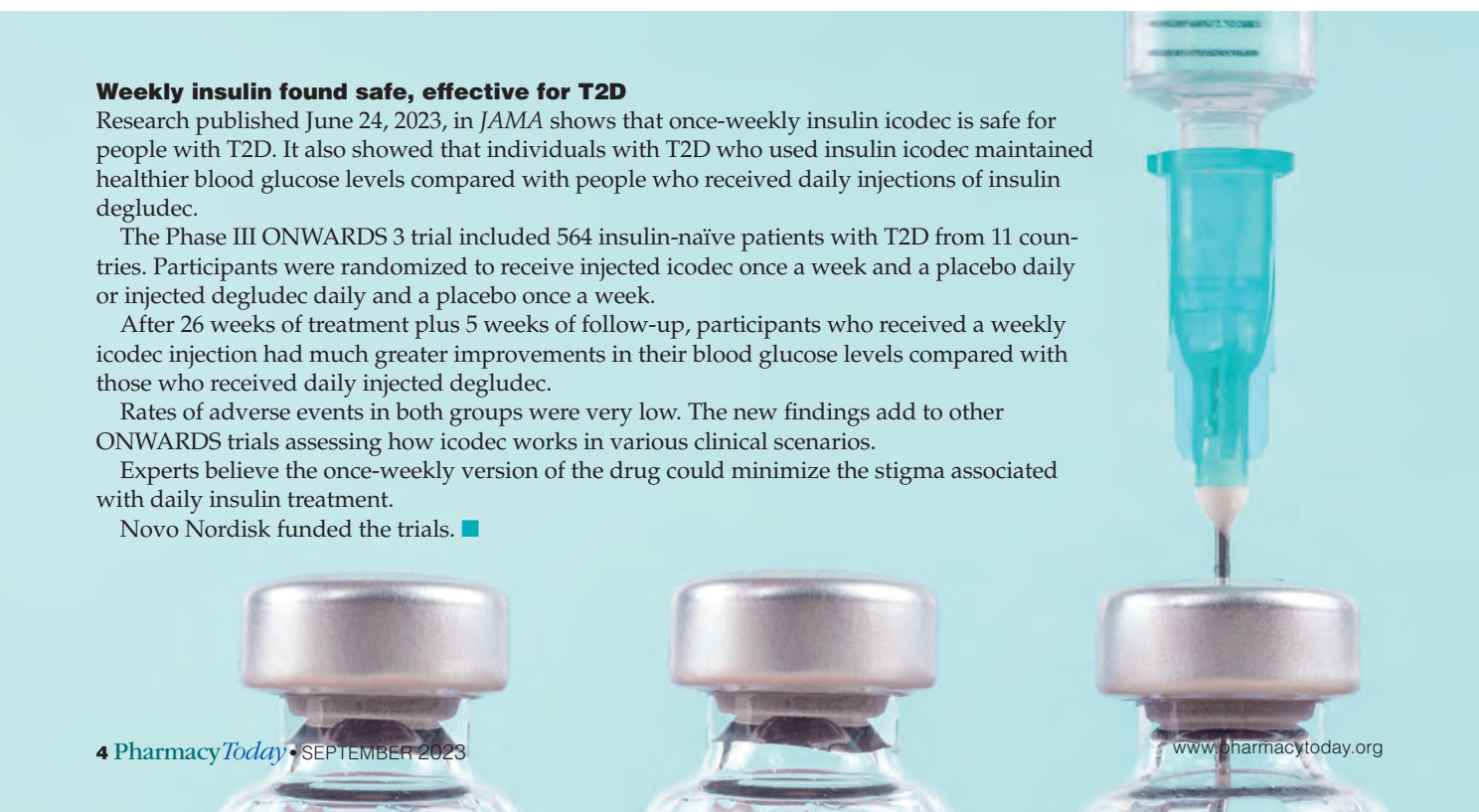
The Phase III ONWARDS 3 trial included 564 insulin-naïve patients with T2D from 11 countries. Participants were randomized to receive injected icodec once a week and a placebo daily or injected degludec daily and a placebo once a week.

After 26 weeks of treatment plus 5 weeks of follow-up, participants who received a weekly icodec injection had much greater improvements in their blood glucose levels compared with those who received daily injected degludec.

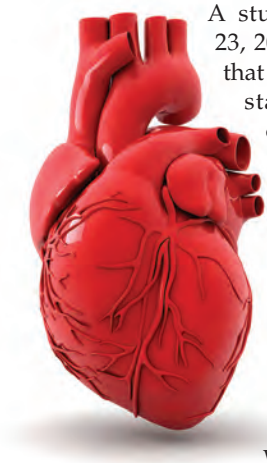
Rates of adverse events in both groups were very low. The new findings add to other ONWARDS trials assessing how icodec works in various clinical scenarios.

Experts believe the once-weekly version of the drug could minimize the stigma associated with daily insulin treatment.

Novo Nordisk funded the trials. ■



Daily statin reduces heart disease risk among adults living with HIV



A study published July 23, 2023, in *NEJM* found that cholesterol-lowering statin drugs helped curb the risk of significant CVD in people living with HIV by more than one-third, potentially preventing one in five major CV events or premature deaths in this population.

Individuals living with HIV are at a much higher risk of CVD.

For the Phase III trial, REPRIEVE study researchers randomized patients in either a treatment group that administered a daily statin (pitavastatin calcium) or a control group that provided a placebo.

The researchers followed participants for about 5 years. However, the trial ended early after investigators found the treatment benefits outweighed possible risks.

Researchers found that participants who took daily pitavastatin had 35% fewer major CV events compared with placebo recipients. Patients in the treatment group were also 21% less likely than those in the placebo group to experience such CV events, and pitavastatin recipients had a 30% reduction in their LDL cholesterol levels.

"Lowering LDL cholesterol levels reduces risks for CV events, like having a heart attack and stroke, but these findings suggest there may be additional effects of statin therapy that explain these reduced risks among people living with HIV," said study chair Steven K. Grinspoon, MD, in a news release. "Ongoing research about how statin therapy may affect inflammation and increase immune activation among people with HIV may help us better understand the additional benefits we're seeing with this treatment approach." ■

AHA: Vaping harms heart and lungs

In a recent scientific statement, the American Heart Association (AHA) is urging more research about the detrimental effects of vaping on the heart and lungs.

"E-cigarettes deliver numerous substances into the body that are potentially harmful, including chemicals and other compounds that are likely not known to or understood by the user. There is research indicating that nicotine-containing e-cigarettes are associated with acute changes in several hemodynamic measures, including increases in blood pressure and heart rate," said an AHA news statement.

AHA also noted a "significant association" between e-cigarette use and the development of incident respiratory disease over 2 years, including asthma, emphysema, chronic obstructive pulmonary disease, and chronic bronchitis.

"Negative effects of e-cigarettes have been shown through in vitro studies and in studies of individuals exposed to chemicals in commercially available products," said the news release.

Vitamin E acetate is the ingredient that is likely causing e-cigarette, or vaping, product use–associated lung injury hospitalizations.

The statement noted that additional research is needed to gauge the health effects of vaping on heart attacks and strokes.

The statement also pointed out that e-cigarettes are the most commonly used tobacco product among high school and middle school–age students.

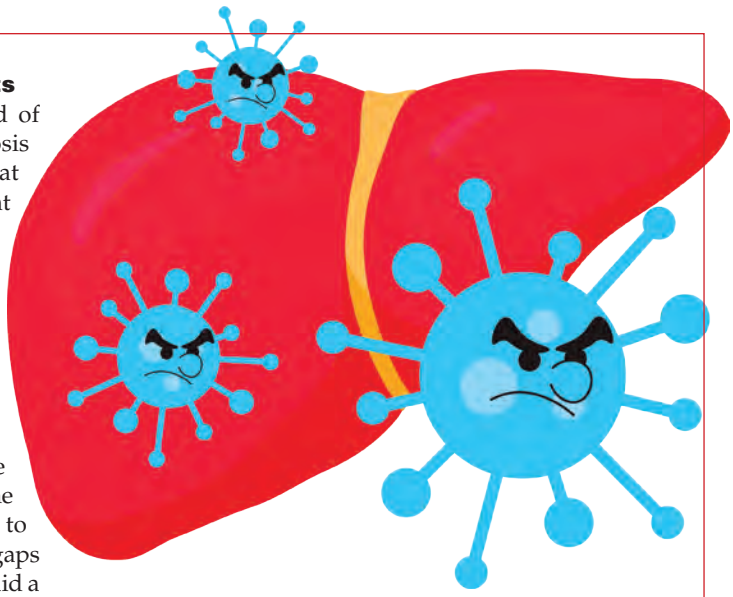
"Because e-cigarettes and other vaping systems have only been in the U.S. for about 15 years, we do not yet have enough information on their long-term health effects, so we must rely on shorter-term studies, molecular experiments, and research in animals to try to assess the true risk of using e-cigarettes," the statement said. "It is necessary for us to expand this type of research since the adoption of e-cigarettes has grown exponentially, especially in young people, many of whom may have never used combustible cigarettes." ■

State of hepatitis C cure is dismal for patients

According to a recent CDC report, only one-third of individuals with a documented hepatitis C diagnosis were cured over the past decade. Based on data that spanned from 2013 to 2022, the report also found that for patients without health insurance under the age of 40 years, only 1 in 6 have been cured.

In 2013, curative treatments known as direct-acting antiviral agents were introduced to combat hepatitis C, offering cure rates of near 100% with minimal adverse effects. The treatment is costly, however, and arduous prior authorization requirements are usually necessary.

"This alarming assessment of HCV cures in the modern treatment era underscores a stark reality: The benefits of pharmaceutical advances will only come to fruition through concerted action to rectify glaring gaps in our health care financing and delivery systems," said a press statement from the Center for Health Law & Policy Innovation of Harvard Law School and the National Viral Hepatitis Roundtable, in response to the report.



According to CDC, hepatitis C affects approximately 2.4 million Americans and is the deadliest bloodborne infectious disease in the United States. ■

Is cytisinicline effective for smoking cessation?

Researchers have found that cytisinicline effectively and safely assisted people with smoking cessation when dosed at a higher concentration than typically used in Europe. Cytisinicline is used in some European countries to aid smoking cessation, but its traditional dosing regimen and treatment duration may not be optimal.

Participants in the ORCA-2 trial received cytisinicline as a 3-mg tablet taken orally 3 times per day for 6 weeks. According to findings published in *JAMA* on July 11, 2023, this was associated with higher continuous abstinence rates for smoking during weeks 3 to 6 and weeks 3 to 24, compared to the use of a placebo.

Patients who took cytisinicline for 12 weeks demonstrated continuous abstinence rates of 32.6% versus 7.0% in the placebo group for weeks 9 to 24. All three sections of the ORCA-2 trial reported high percentages of behavioral support compliance, with 92.8% of sessions completed in the 12-week group, 89.5% in the 6-week group, and 86.8% in the placebo cohort.

"Cytisinicline reduced nicotine craving and was well tolerated by participants who adhered to the treatment schedule at a high rate, even though the trial was conducted during the early phases of the U.S. COVID-19 pandemic," wrote the study authors.

Adverse effects such as insomnia, nausea, and strange dreams occurred in less than 10% of each group but caused 2.9% of cytisinicline recipients and 1.5% of patients in the placebo group to withdraw from the trial. Serious adverse events were seen in 3.3% and 1.1% of patients, respectively, but were deemed to be unrelated to the treatment.

These results are expected to help support a request for an FDA approval for cytisinicline, which is already available as an OTC smoking cessation product in Eastern and Central Europe. ■

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CPE

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Take the Crossword Challenge

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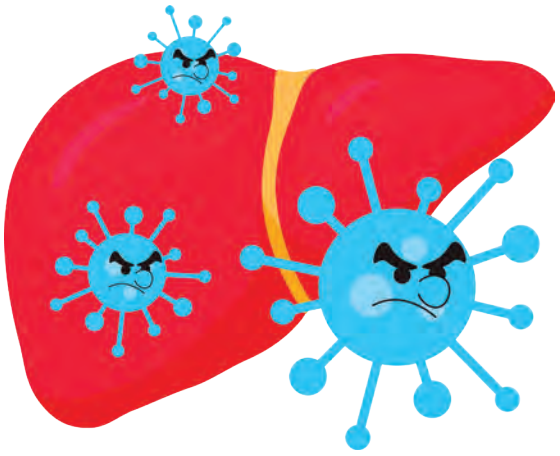

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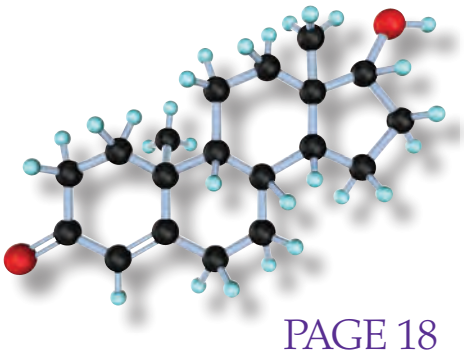
Drugs & Diseases



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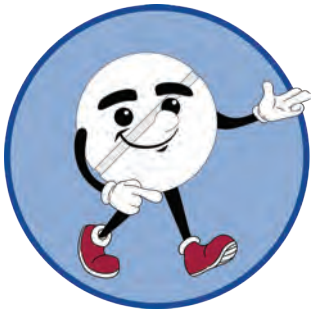

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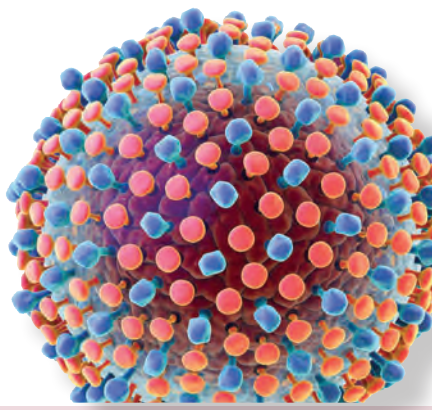


PrEPare yourselves to help patients in need

Pharmacists are increasingly instrumental in providing PrEP to patients to prevent HIV transmission.

What exactly is PrEP? There are currently two pills approved, which both contain emtricitabine combined with a form of tenofovir. An injectable form, capotegravir, is also available. Although indicated in different populations, both pills are taken once daily, with the injection administered every other month. PrEP reduces the risk of getting HIV from sex by about 99% when taken as prescribed.

Why is it important for pharmacists to be knowledgeable about PrEP and the rules and regulations governing its provision by pharmacists? This month's *Pharmacy Today* cover story breaks this down. Currently, pharmacists in 17 states have some degree of authority in providing PrEP or PEP. Inserting pharmacists into the PrEP equation is a key step to meeting a tremendous gap in health care.

Only a small percentage of individuals for whom PrEP is indicated are actually taking it. According to CDC, in 2020, only about 25% of the 1.2 million people for whom PrEP is recommended were prescribed it. This disparity is especially striking in minority populations: A mere 9% of eligible Black patients and 16% of eligible Latino patients have been prescribed PrEP.

In this issue, you'll also find the latest on newly approved drugs, new treatment options for pediatric patients with T2D, and recent immunization recommendations from ACIP. Find implementation tips on test and treat programs as pharmacy's scope of practice expands and catch up on your CPE credit with this month's article on managing chronic stress to prevent burnout.

Pharmacist-owner at Mission Wellness in San Francisco, Maria Lopez, PharmD, has experience with providing PrEP to patients. According to Lopez, if it wasn't for pharmacists providing PrEP, her patients "definitely would've had a gap in their medication, their levels would go down, and then they would be at risk for HIV." Although the percentage of eligible individuals receiving PrEP is on the rise—up to 25% in 2020 from just 3% in 2015—there is clearly an important gap remaining in this area. Learn more about rules for providing PrEP in your state and how you can help your patients get access to this much-needed therapy in this issue of *Pharmacy Today*.

Have a great *Today*!

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

Put me in the game, coach!

September and October bring us into the most exciting part of baseball season. One can lament everything that happens in the major leagues through September 1st, but only what happens after September 1st really counts. Believe me, as a lifelong St. Louis Cardinals' baseball fan, we've had many September miracles lead to playoff berths. (This year isn't looking so bright, though.) As an armchair warrior for my team, I often imagine how the game could be played better or what the coach needs to do differently—Maybe you do this, too?

While baseball is a fun game, patient safety is no game at all. In fact, it's the most serious priority of our lives as pharmacists and pharmacy team members. Ensuring that the medication use process is—first and foremost—safe is the backbone of the Oath we've taken.

CDC's Medication Safety Program reports that one out of every 250 Americans ends up in an emergency department because of a medication adverse event. Older adults are three times more likely to end up seeking emergency care for a medication issue than younger adults, with nearly one million total visits to hospital emergency departments occurring each year in the United States.

The result is approximately $3.5 billion in excess spending on the medical costs of adverse drug events annually.

Yet these statistics don't fully capture the issues in patient safety. Frankly, physician office practices and hospitals are woefully understaffed, as are pharmacies.

Recently, a medical organization tried to make the argument that pharmacists shouldn't be given provider status because community pharmacies don't have enough staff to do anything other than dispense. This is like saying physicians shouldn't be allowed to do procedures in the office because they don't have enough medical assistants. It's simply ludicrous. Taking away or denying access to care isn't going to solve the problem of health care staffing. The problems are much deeper than that.

So, while organized medicine seems to be entirely focused on turf protection, pharmacy will press on addressing patient safety and access to care issues.

Health disparities exist because our current system doesn't work. Patients have been denied access to care from pharmacists for far too long. Patient safety is suffering because, in part, of protectionist policies and hyperbole.

APhA is in the game fighting for frontline pharmacists. Our efforts in advocating with large pharmacy employers and state boards of pharmacy to empower pharmacists to meet the needs of our patients is important work. While our Well-being Index is beginning to show that distress at the pharmacy counter is improving, we've still got a long way to go. And progress to solutions will not be made simply by issuing criticisms. We must have viable solutions.

APhA's Pharmacist Well-Being and Resilience Center is collecting data and collaborating with boards of pharmacy, pharmacists, and employers to address the system changes that must occur to sustain a positive, patient-centered environment across health care from the pharmacy counter to the bedside.

I have no doubt that some who read this will complain that APhA isn't doing enough, and that they feel abandoned at the counter. It's not enough to say what we are doing—you need to feel the results of change in your day-to-day. I get it. We hear you. And APhA is working on it. But we can't do this work without members like you. Your ideas and solutions are critical. We are on the same team and working to ensure an environment that supports patient safety. We are for every pharmacist, For all of pharmacy. Won't you join us? ■

Michael D. Hogue, PharmD, FAPhA, FNAP, FFIP
Executive Vice President and CEO
American Pharmacists Association

NEW DRUGS

QUIZARTINIB
(Vanflyta—Daiichi Sankyo, Inc.)

Drug class: Vanflyta is a kinase inhibitor.

Indication: Vanflyta is indicated in combination with standard cytarabine and anthracycline induction and with cytarabine consolidation, plus as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia that is FLT3 internal tandem duplication (ITD)–positive as detected by an FDA-approved test. Vanflyta is not indicated as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation.

Recommended dosage and administration: Vanflyta tablets should be taken orally once daily with or without food at approximately the same time each day. A treatment course consists of up to 2 cycles of Vanflyta in combination with induction cytarabine and anthracycline, up to 4 cycles of Vanflyta in combination with high-dose cytarabine consolidation, and up to 36 cycles of Vanflyta as maintenance therapy or until disease progression or unacceptable toxicity. The recommended dosage varies based on the phase of therapy. See the full prescribing information for recommended Vanflyta dosage regimen and dosage modifications.

Common adverse effects: The most common adverse reactions are decreased lymphocytes, decreased potassium, decreased albumin, decreased phosphorus, increased alkaline phosphatase, decreased magnesium, febrile neutropenia, diarrhea, mucositis, nausea, decreased calcium, abdominal pain, sepsis, neutropenia, headache, increased creatine phosphokinase, vomiting, and upper respiratory tract infection.

Boxed warning: Vanflyta prolongs the QT interval. Prior to administration and periodically, perform electrocardiograms, monitor for hypokalemia or hypomagnesemia, and correct deficiencies. Torsades de pointes and cardiac arrest have occurred in patients receiving Vanflyta. Do not administer Vanflyta to patients with severe hypokalemia, severe hypomagnesemia, or long QT syndrome. Do not initiate treatment with Vanflyta or escalate the Vanflyta dose if the QT interval corrected by the Fridericia formula is greater than 450 ms. Monitor electrocardiograms more frequently if concomitant use of drugs known to prolong the QT interval is required. Reduce the Vanflyta dose when used concomitantly with strong CYP3A inhibitors, as they may increase quizartinib exposure. Vanflyta is only available through a restricted program called the Vanflyta REMS.

Other warnings and precautions: Vanflyta is contraindicated in patients with severe hypokalemia, severe hypomagnesemia, or long QT syndrome, or in patients with a history of ventricular arrhythmias or torsades de pointes. Monitor electrocardiograms and levels of serum electrolytes. Reduce, interrupt, or permanently discontinue Vanflyta as appropriate. Vanflyta can cause fetal harm. Advise patients of reproductive potential and patients with partners of reproductive potential of the potential risk to a fetus and to use effective contraception. Patients should be advised not to breastfeed while using Vanflyta. If used concomitantly with strong CYP3A inhibitors, reduce the Vanflyta dose. Avoid concomitant use with strong or moderate CTP3A inducers.

LOTILANER OPHTHALMIC SOLUTION
(Xdemvy—Tarsus Pharmaceuticals, Inc.)

Drug class: Xdemvy is an ectoparasiticide.

Indication: Xdemvy is indicated for the treatment of Demodex blepharitis.

Recommended dosage and administration: The recommended dosage is one drop in each eye twice daily and approximately 12 hours apart for 6 weeks.

Common adverse effects: The most common adverse reaction is instillation site stinging and burning.

Warnings and precautions: There are no other warnings or precautions.

NEW INDICATIONS

TRIFLURIDINE AND TIPIRACIL
(Lonsurf—Taiho Oncology)

Drug class: Lonsurf is a combination of trifluridine (a nucleoside metabolic inhibitor) and tipiracil (a thymidine phosphorylase inhibitor).

Indication: Lonsurf is indicated for the treatment of adult patients with metastatic colorectal cancer as a single agent or in combination with bevacizumab who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if renin-angiotensin-system wild-type, an anti-EGFR therapy. Lonsurf is also indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate HER2/neu-targeted therapy.

Recommended dosage and administration: The recommended dosage is 35 mg/m^2/dose orally twice daily with food on days 1–5 and days 8–12 of each 28-day cycle.

Common adverse effects: The most common adverse reactions are neutropenia, anemia, thrombocytopenia, fatigue, nausea, decreased appetite, diarrhea, vomiting, abdominal pain, pyrexia, increased AST, increased ALT, increased alkaline phosphatase, and decreased appetite.

Warnings and precautions: Obtain complete blood counts prior to and on day 15 of each cycle as severe myelosuppression may occur. Withhold and resume at the next-lower Lonsurf dosage as recommended. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception. Advise patients not to breastfeed. Thrombocytopenia may be more likely to occur in patients 65 years or older. Do not initiate Lonsurf in patients with baseline moderate or severe hepatic impairment. Reduce Lonsurf dose in patients with severe renal impairment.

ROSUVASTATIN

(Ezallor Sprinkle—Sun Pharmaceutical Industries Ltd.)

Drug class: Rosuvastatin is an HMG-CoA reductase inhibitor.

Indication: Ezallor is indicated for adult patients with hypertriglyceridemia as an adjunct to diet, adult patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) as an adjunct to diet, and adult patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, and Apolipoprotein B.

RX to OTC Switch

Opill is a daily oral contraceptive that was approved by the FDA for OTC status in July 2023. Opill is a progestin-only pill that works by thickening the cervical mucus, which helps to block sperm from getting to the egg. Patients should take one tablet at the same time every day. It is not approved for use as an emergency contraceptive. Patients should not use Opill if they are allergic to any of the ingredients contained in it, including FD&C Yellow No. 5 (tartrazine). People allergic to aspirin often have a tartrazine allergy, too. Symptoms may include hives, facial swelling, asthma, shock, skin reddening, rash, and blisters. Additionally, patients should not use Opill if they have ever had breast cancer; are already pregnant; or are concomitantly using another birth control pill, vaginal ring, patch, implant, injection, or intrauterine device. Patients should be advised to use a condom, or another barrier method, every time they have sex during the first 2 days of use. It takes 48 hours for this product to begin working. ■

Ezallor has not been studied in Fredrickson Type I and V dyslipidemias.

Recommended dosage and administration: The recommended dosage is 5 mg to 40 mg once daily. Use 40 mg dose only for patients not reaching their LDL-C goal with 20 mg. For adult HoFH, the starting dose is 20 mg once daily. Ezallor can be taken with or without food at any time of day.

Common adverse effects: The most common adverse reactions are headache, myalgia, abdominal pain, asthenia, and nausea.

Warnings and precautions: Ezallor is contraindicated in known hypersensitivity to product components, active liver disease which may include unexplained persistent elevations in hepatic transaminase levels, pregnancy, and lactation. Advise patients of reproductive potential to use effective contraception during treatment with Ezallor. In severe renal impairment in patients not on hemodialysis, the starting dose is 5 mg, not to exceed 10 mg. In the Asian population, consider a 5 mg starting dose. Skeletal muscle effects may occur. The risks increase with use of a 40 mg dose; advanced age; hypothyroidism; renal impairment; and combination use with cyclosporine, atazanavir/ritonavir, lopinavir/ritonavir, or simeprevir. Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. Advise patients to promptly report to their physician unexplained and/or persistent muscle pain, tenderness, or weakness and discontinue Ezallor if signs or symptoms appear. Persistent elevations in hepatic transaminases can occur. Perform liver enzyme tests before initiating therapy and as clinically indicated thereafter. Combination use with cyclosporine increases rosuvastatin exposure, so the Ezallor dose should be limited to 5 mg once daily. Combination use with gemfibrozil should be avoided.

If used together, limit Ezallor dose to 10 mg once daily. Combination use with atazanavir/ritonavir, lopinavir/ritonavir, or simeprevir increases rosuvastatin exposure. Limit Ezallor dose to 10 mg once daily. Combination use with coumarin anticoagulants prolongs the international normalized ratio (INR). Achieve stable INR prior to starting Ezallor. Monitor INR frequently until stable upon initiation or alteration of Ezallor therapy. Use with fibrates or lipid-modifying doses of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with Ezallor. ■

Regaining those pearly whites

Mary Warner

Patient demand for tooth whitening has been on the increase for several years, bolstered by the availability of a wide variety of nonprescription whitening toothpastes and strips.

Whitening treatments include dental office bleaching procedures, dentist-supplied products for use at home, and nonprescription whiteners. All three methods use the same chemical agents: carbamide peroxide or hydrogen peroxide in various strengths.

Products used in traditional whitening in the dentist's office as well as products supplied by dentists for use at home are FDA-approved. However, nonprescription whitening products are classified as cosmetics rather than drugs because of the low levels of peroxides they contain and are not evaluated by FDA. The American Dental Association (ADA) has indicated that it has repeatedly asked FDA to regulate nonprescription whitening products, but FDA has declined to do so.

Not all stains are alike

Tooth discoloration is typically classified as extrinsic, intrinsic, or a combination of both types.

Extrinsic stains typically result from tobacco use, exposure to iron or copper, or the consumption of highly pigmented foods (e.g., dark fruits) or beverages (e.g., red wine, coffee, tea, or cola drinks).

Intrinsic stains, on the other hand, occur inside the tooth and are commonly caused by genetic disorders, fluorosis, tetracycline use in childhood, prolonged use of chlorhexidine mouthwash, or aging, during which the enamel becomes more translucent and thinner, which allows the yellower dentin to show through and the overall tooth color to darken.

Although the in-office method has the advantage of being a faster one-time treatment due to the use of a stronger bleaching agent and accelerator light, most extrinsic stains can be effectively removed using OTC whitening products over a more extended time period. Dentists can also provide professional-strength bleaching gel for use at home using custom-fitted mouth trays. These products are unable to effectively remove intrinsic stains, however, which experts consider nearly impossible to remove when using an external whitening procedure. Some intrinsic stains can be removed with a procedure that uses carbamide peroxide, hydrogen peroxide, or sodium perborate to provide internal bleaching, but results are not guaranteed.

Whitening agents

A variety of toothpastes, whitening strips, and gels painted directly on teeth or delivered in trays are available directly to patients. Bleaching compounds in these products are peroxide-based and typically contain carbamide peroxide or hydrogen peroxide at lower concentrations than those used in a dental office.

Whitening toothpastes primarily rely on abrasives such as silica or charcoal to remove extrinsic surface stains, although some have a low level of peroxide (3–5%) to lighten the color of the tooth. Most whitening strips rely primarily on peroxide to bleach the teeth, though at a lower concentration (generally 6–14%) than professional products. Whitening gel pens contain either 3% hydrogen peroxide or up to 10% carbamide peroxide, which breaks down to about the same 3% hydrogen peroxide in the mouth.

Most extrinsic stains can be effectively removed using OTC whitening products over a more extended time period.

What to tell your patients

Per ADA, patients who have tooth-colored restorations (including crowns or implants) should be aware that only natural teeth will be affected by the bleaching agent and treatment could result in color differences between natural teeth and restorations, which will not change color.

Patients may wish to choose toothpastes and whitening strips that bear the ADA Seal of Acceptance, indicating that the company has demonstrated that the product meets ADA Seal Program requirements for safety and effectiveness when used as directed. Caution patients to avoid do-it-yourself tooth whitening processes, such as using acid-containing fruits, vinegar, or swishing coconut oil in the mouth (known as oil pulling), as none of these methods has been proven to whiten teeth. Patients who suffer from temporary tooth sensitivity or gingival inflammation, the most common adverse effects of tooth whitening, should visit their dentist for professional advice. ■

Kiwifruit: It's easy being green

Mickie Cathers

Constipation is associated with reduced quality of life for about 10% of the worldwide population, and GI discomfort affects many. Patients seeking medical care through current pharmacological treatments or OTC supplements can't always tolerate fiber supplements, laxatives, or bulking agents, and most of these approaches lack robust scientific evidence supporting their efficacy. However, a recent study offers significant evidence of the beneficial effect of green kiwifruit for GI function and comfort.

Does it work?

Several studies have shown that consumption of green kiwifruit leads to improved bowel movements in constipated patients and improves measures of GI comfort, including bloating. A growing body of evidence supports consumption of certain foods such as psyllium and green kiwifruit to reduce abdominal pain and improve GI discomfort, supporting the concept that dietary interventions can have an impact beyond simple nutrition. Both green kiwifruit and psyllium are well known as beneficial treatments for constipation and bowel habit normalization.

The mechanism of action for kiwifruit and psyllium husk in improving laxation and abdominal comfort boils down to fiber. The fiber in kiwifruit cell walls has a large capacity to hold water, which can lead to stool softening and increased stool frequency. Kiwifruit also has raphides (also found in pineapple, spinach, and agave), needle-shaped crystals of calcium oxalate monohydrate that may alter mucin production and lead to improved bowel movements.

Kiwifruit improves constipation

A June 2023 international multicenter randomized controlled trial published in the *American Journal of Gastroenterology* found that consumption of kiwifruit was associated with a clinically relevant increase in complete spontaneous bowel movements (CSBM) per week. Gearry and colleagues reported that kiwifruit also significantly improved measures of GI comfort in patients with constipation with no significant adverse effects.

This prospective, single-blinded, crossover 16-week trial included three diverse adult populations. Participants from New Zealand, Italy, and Japan with irritable bowel syndrome with predominant constipation (IBS-C) or functional constipation (FC), along with healthy controls were randomized to consume either two green kiwifruits or 7.5 g of psyllium over the course of 4 weeks as bowel habit and GI comfort were measured. Study authors assessed the effect of daily consumption of two green kiwifruits on normalization of bowel habit and measures of GI comfort. Both the kiwifruits and the psyllium provided approximately 6 g of dietary fiber, and the psyllium was used as a positive control.

The fiber in kiwifruit cell walls has a large capacity to hold water, which can lead to stool softening and increased stool frequency.

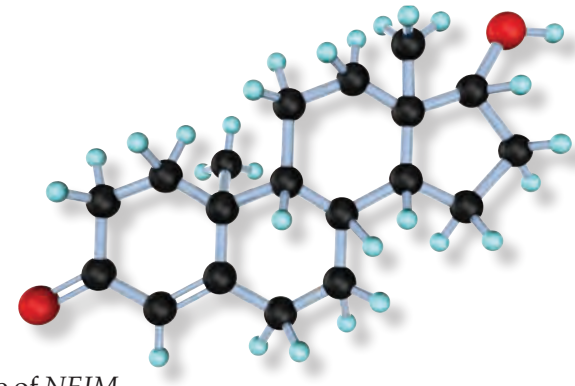
Participants were not instructed to change their habitual diet beyond the intervention over the study period or given guidance on daily time or occasion for consumption.

Primary outcome was the number of CSBMs per week; key secondary outcomes included GI comfort measured with a GI symptom rating scale, stool consistency, and degree of straining. IBS-associated quality of life was assessed by a questionnaire at the end of each study period as well as reviews to determine changes in mood.

Study results revealed that both interventions—kiwifruit and psyllium—resulted in significant and sustained increases in the weekly frequency of CSBMs in all study groups. Daily consumption of two green kiwifruits produced a significant reduction, compared to baseline, in overall GI symptoms, as determined by the total score for FC, IBS-C, and the combined FC plus IBS-C group. Consumption of psyllium was associated with a significant reduction in GI symptoms in the IBS-C group only.

What to tell your patients

Daily consumption of two green kiwifruits is considered safe, effective, and well-tolerated to increase CSBM and as a beneficial treatment for constipation and abdominal and GI discomfort. ■



Testosterone-replacement therapy unlikely to increase risk of cardiac events

Clarissa Chan, PharmD

Results of a recent trial published in the July 13, 2023, issue of *NEJM* found men 45 to 80 years old who took testosterone-replacement therapy were unlikely to experience an increased risk of major adverse cardiac events when compared to placebo.

According to Partha Sardar, MD, assistant professor of clinical medicine at Columbia University Irving Medical Center, the trial results offer vital safety information for patients and health care providers making decisions about testosterone replacement.

"Over a 2-year treatment period, testosterone-replacement therapy did not appear to increase the risk of major adverse cardiac events, and the overall incidence of adverse events was relatively low," said Sardar, who was not involved with the research. "The TRAVERSE trial was a well-executed trial that addresses the knowledge gap concerning testosterone supplementation in older men with hypogonadism at high risk for cardiovascular events."

Study design

The Phase 4, double-blind, placebo-controlled, noninferiority trial included 5,246 consenting older men with hypogonadism who had pre-existing CVD or were at high risk for it.

They were randomized 1:1 to receive either testosterone 1.62% or a placebo gel transdermally at 316 clinical trial sites in the United States. The testosterone group received doses to maintain testosterone levels between 350 ng/dL and 750 ng/dL or in response to hematocrit levels greater than 54%. The mean treatment and follow-up duration was 21.7+/−14 and 33.0+/−12.1 months, respectively.

Hypogonadism was defined as having two fasting blood serum testosterone levels of >300 ng/dL and at least one or more symptoms including decreased sexual desire or libido, decreased spontaneous erections, fatigue, depressed mood, loss of axillary or pubic body hair, decreased frequency of shaving, or hot flashes.

Patients with CVD had either coronary artery disease, cerebrovascular disease, or peripheral artery disease. Increased CV risk was defined as having three or more risk factors, including hypertension, dyslipidemia, tobacco use, Stage 3 chronic kidney disease, diabetes, elevated high-sensitivity C-reactive protein level, age of 65 years or older, or a poor Agatston coronary calcium score.

Participants with congenital or acquired severe hypogonadism, history of prostate cancer or nodules, an elevated screening prostate-specific antigen level, thrombophilia, and uncontrolled heart failure were excluded from the study. Other exclusion criteria included patients who experienced acute coronary syndrome, stroke, or revascularization within 4 months or treatment with testosterone within 6 months.

Findings

The primary CV safety endpoint—the initial occurrence of any major adverse cardiac event, death from CV causes, nonfatal myocardial infarction or nonfatal stroke, assessed in a time-to-event analysis—occurred in 182 testosterone group patients (7%) and 190 placebo group patients (7.3%). Other endpoints showed similar findings between both groups.

Notably, a higher incidence of nonfatal arrhythmias (134 testosterone patients [5.2%] and 87 placebo patients [3.3%]), AFib (91 testosterone patients [3.5%] and 63 placebo patients [2.4%]), acute kidney injury (60 testosterone patients [2.3%] and 40 placebo patients [1.5%]), and pulmonary embolism (0.9% testosterone patients and 0.5% placebo patients) was found in testosterone group patients.

Discontinuation rates in the testosterone and placebo groups were similar at 61.4% and 61.7%, respectively.

Study limitations

"The mean follow-up period was 33 months, which may not be sufficient to observe the development of atherosclerotic vascular diseases, known to take longer to manifest," said Sardar. "Longer follow-up would be beneficial to better understand the effects of testosterone therapy."

The study also included subjects with pre-existing CV risk factors such as obesity and diabetes, which might have contributed to the observed CV outcomes, he said.

Future studies could benefit from more rigorous control over confounding variables, according to Sardar.

Pharmacists' role

"Pharmacists can confidently inform patients that the TRAVERSE trial provides strong evidence that testosterone-replacement therapy over a 2-year period does not increase the risk of major adverse cardiac events in older men," said Sardar. "However, patients should be cautioned that this therapy may slightly elevate the risk of pulmonary embolism, nonfatal arrhythmias warranting intervention, AFib, and acute kidney injury."

Pharmacists should encourage patients to have open discussions with their health care providers to make informed decisions based on their individual health needs, he said.

"This study offers valuable insights into the CV safety of testosterone therapy," said Sardar. "However, further research is needed to understand the safety implications of longer-term therapy and the potential adverse effects associated with higher testosterone levels resulting from supplementation." ■

New treatment option for pediatric T2D

Lauren Howell, PharmD

This past June, FDA approved the first new class of medicines to treat pediatric T2D since 2000. Previously limited to metformin, children 10 years or older with T2D now have another treatment option that can be used in addition to diet and exercise to improve blood glucose control.

Jardiance (empagliflozin) and Synjardy (empagliflozin and metformin hydrochloride) were originally approved in 2014 and 2015, respectively, as additions to diet and exercise to improve glucose control in adults with T2D. Since then, they have also gained approval for reducing the risk of CV-related death in adults with T2D and established CVD, and to reduce the risk of CV-related death and hospitalization for adults with heart failure.

Recommended dosage and administration

For both Jardiance and Synjardy, the dosing for the pediatric population matches that of the adult population.

The recommended dosage of Jardiance is 10 mg once daily in the morning, taken with or without food. For additional glycemic control, the dosage may be increased to 25 mg in patients tolerating Jardiance. In patients with an eGFR of <30 mL/min/1.73 m^2, Jardiance is not recommended.

For Synjardy, the starting dose should be individualized based on the patient's current regimen and renal function. The maximum recommended dosage is 25 mg/day of empagliflozin and 2,000 mg/day of metformin. Initiation of Synjardy is not recommended is patients with an eGFR of <45 mL/min/1.73 m^2.

Synjardy is also available as an extended-release formulation, Synjardy XR, which is not approved for use in pediatric patients with T2D. For both medications, renal function should be assessed, and volume depletion should be corrected prior to initiation of therapy.

Children 10 years or older with T2D now have an additional treatment option.

Efficacy and safety

The safety and efficacy of empagliflozin in children were studied in a double-blind, randomized, placebo-controlled trial. This trial included 157 patients between the ages of 10 years and 17 years with inadequately controlled T2D. Participants were assigned to one of three treatment arms and received either empagliflozin, a DPP-4 inhibitor (linagliptin), or a placebo.

Prior to beginning treatment for the trial, 51% of participants were taking metformin alone, 40% of participants were taking a combination of metformin and insulin, 3% of participants were taking insulin alone, and 6% of participants were not taking medication for diabetes. At week 26, the trial found that treatment with empagliflozin was superior in reducing hemoglobin A1C compared to a placebo. The patients treated with empagliflozin had an average 0.2% decrease in hemoglobin A1C compared with an average 0.7% increase in the participants taking a placebo. Additionally, patients treated with empagliflozin had reductions in fasting plasma glucose as compared to patients taking the placebo.

Overall, adverse effects in children treated with empagliflozin are similar to those seen in adults. However, one difference seen in the pediatric population is a higher risk of hypoglycemia among patients 10 years and older who are taking empagliflozin compared to placebo, regardless of whether they were taking other therapies for diabetes.

Other common adverse effects in those taking empagliflozin include UTIs and female fungal infections. The most common adverse effects in patients treated with metformin include diarrhea, nausea, and upset stomach.

Due to an increased risk of diabetic ketoacidosis, Jardiance and Synjardy are not recommended in patients with T1D. They are also not recommended to improve blood glucose control in patients with severe kidney problems. If patients had a previous serious allergic reaction to the medications, they should not continue to use them. Synjardy must not be used in patients with metabolic acidosis or diabetic ketoacidosis. ■

PHARMACISTS EXPAND ACCESS TO PrEP IN 17 STATES

SONYA COLLINS

PrEP for HIV has made a significant impact in HIV prevention over the last decade. Since the combination of antiretrovirals tenofovir and emtricitabine (Truvada) earned FDA approval for the prevention of HIV in 2012, uptake among those for whom it is recommended has risen by an estimated 56% each year, according to data from Emory University's Rollins School of Public Health. But major gaps remain between the number of people who could benefit from PrEP and the number who take it.

Just one in four of the people for whom PrEP is indicated take the prophylactic drugs. The gap between "could" and "does" is even wider in marginalized communities and among those hit hardest by the HIV epidemic.

To help close these gaps, the National HIV/AIDS Strategy for the United States (2022–2025) called for expansion of pharmacists' prescribing authority and providing reimbursement to allow them to administer PrEP.

"Pharmacists can help address known barriers to HIV, particularly in PrEP underutilization," said LCDR Neelam "Nelly" Gazarian, PharmD, AAHIVP, a senior policy analyst in

the Office of Infectious Disease and HIV/AIDS Policy at HHS. "Pharmacies can be a nonstigmatizing venue. Pharmacists can also increase overall access to health care services, as 9 in 10 Americans live within 5 miles of a pharmacy and they may be open at different times than traditional health care settings."

In 17 states, pharmacists have some degree of expanded authority to provide PrEP or PEP to their patients at community pharmacies or clinics and, in some cases, receive reimbursement for these services. These programs provide a model for what might be possible across the country if pharmacists in all settings had the necessary authority and were able to bill for the clinical care they provide.

"The goal is to end the HIV epidemic by 2030," said Michael Murphy, PharmD, MBA, advisor for state government affairs at APhA. "Right now, we are not on track to meet that goal. Ensuring that there are more access points for patients to get into preventive medication is a way that we can help ensure we meet that goal."

Significant gap in care

Individuals who take PrEP represent a small minority of those for whom it is indicated, and the disparities are starkest in the communities that may need the drug therapy the most. Most people for whom PrEP is recommended are Black or Latino, yet only 9% of eligible Blacks and 16% of eligible Latinos have been prescribed the antiretrovirals. Among whites for whom the drugs would be beneficial, 66% take them.

Young people ages 16 to 24 years are the least likely to take PrEP. Only 16% of those for whom it is recommended had a prescription in 2020. However, this percentage increases with age.

Zeroing in further, while nearly 90% of HIV-negative men who have sex with men were aware of PrEP, according to a 2021 CDC survey, only 42% used it.

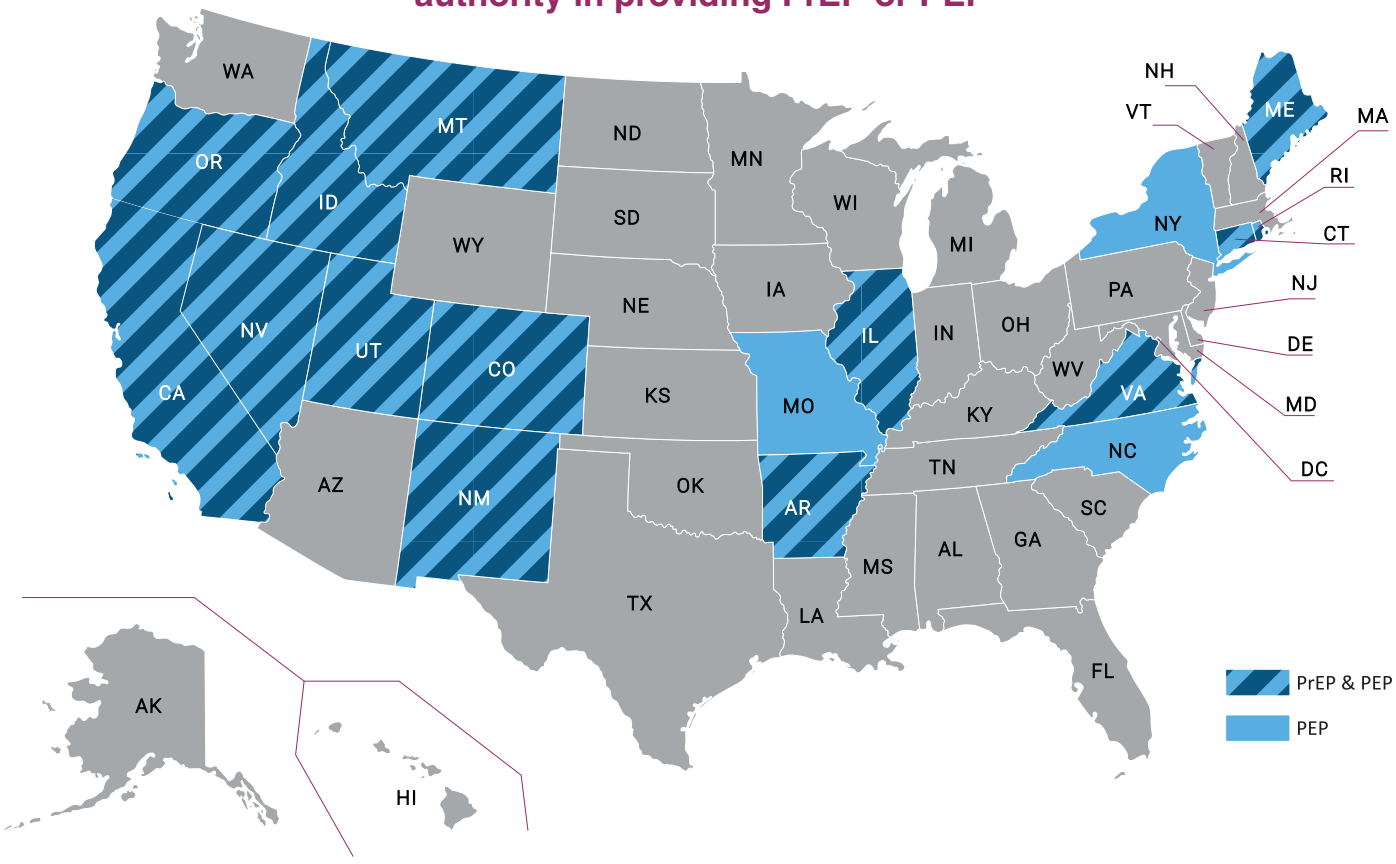
Women are even less likely to use PrEP. Just one in ten cisgender women for whom it is recommended have been prescribed the pills. Among transgender women, 92% know about PrEP, while just over 30% of them take it.

Sexual minorities, such as gay, bisexual, and transgender people, are less likely to have access to health care than their heterosexual counterparts—especially Black, Latino, and younger members of these groups. Even those who do have a regular physician might not be offered PrEP. As of 2021, it was estimated that only one in five physicians had ever prescribed PrEP.

"Pharmacists can serve as another point of access to get patients into HIV preventive care," Murphy said, "not

"During visits with patients, we've identified a lot of gaps in vaccines—[like with] TDAP, we've helped people hear about flu shots if they don't have a primary care provider."

States in which pharmacists have some degree of authority in providing PrEP or PEP



necessarily to replace a specific health care professional, but to be another open door into longitudinal preventive care for patients."

access to PrEP not only by virtue of their ubiquitousness, but also in their ability to provide same-day PrEP, which may increase retention.

"Pharmacists can help address known barriers to HIV, particularly in PrEP underutilization."

States that allow pharmacists to prescribe hormonal contraception illustrate how pharmacists increase access without necessarily supplanting other health professionals. According to a 2019 study by Anderson and colleagues in *Obstetrics & Gynecology*, in the first 2 years that Oregon pharmacists were authorized to prescribe oral and transdermal contraception, 10% of new prescriptions among Medicaid enrollees for these medications originated with pharmacists—the vast majority of which were community pharmacists.

Community pharmacies can increase

Ground zero for PrEP

Pharmacist-owner at Mission Wellness in San Francisco Maria Lopez, PharmD, prides herself on offering same-day PrEP to her patients. "We do the rapid HIV test so the patient can start that day because there's some data to support same-day PrEP," Lopez said.

California pharmacists were the first in the nation to be authorized to provide PrEP or PEP without a prescription. In 2019, SB 159 permitted pharmacists to prescribe up to a 60-day supply of PrEP in a 2-year period or a full 28-day regimen. Under this law, patients with lower incomes receive pharmacist-prescribed PrEP and PEP at little or no cost to them, and private insurance is required to cover up to a 60-day supply of this medication when initiated by a pharmacist.

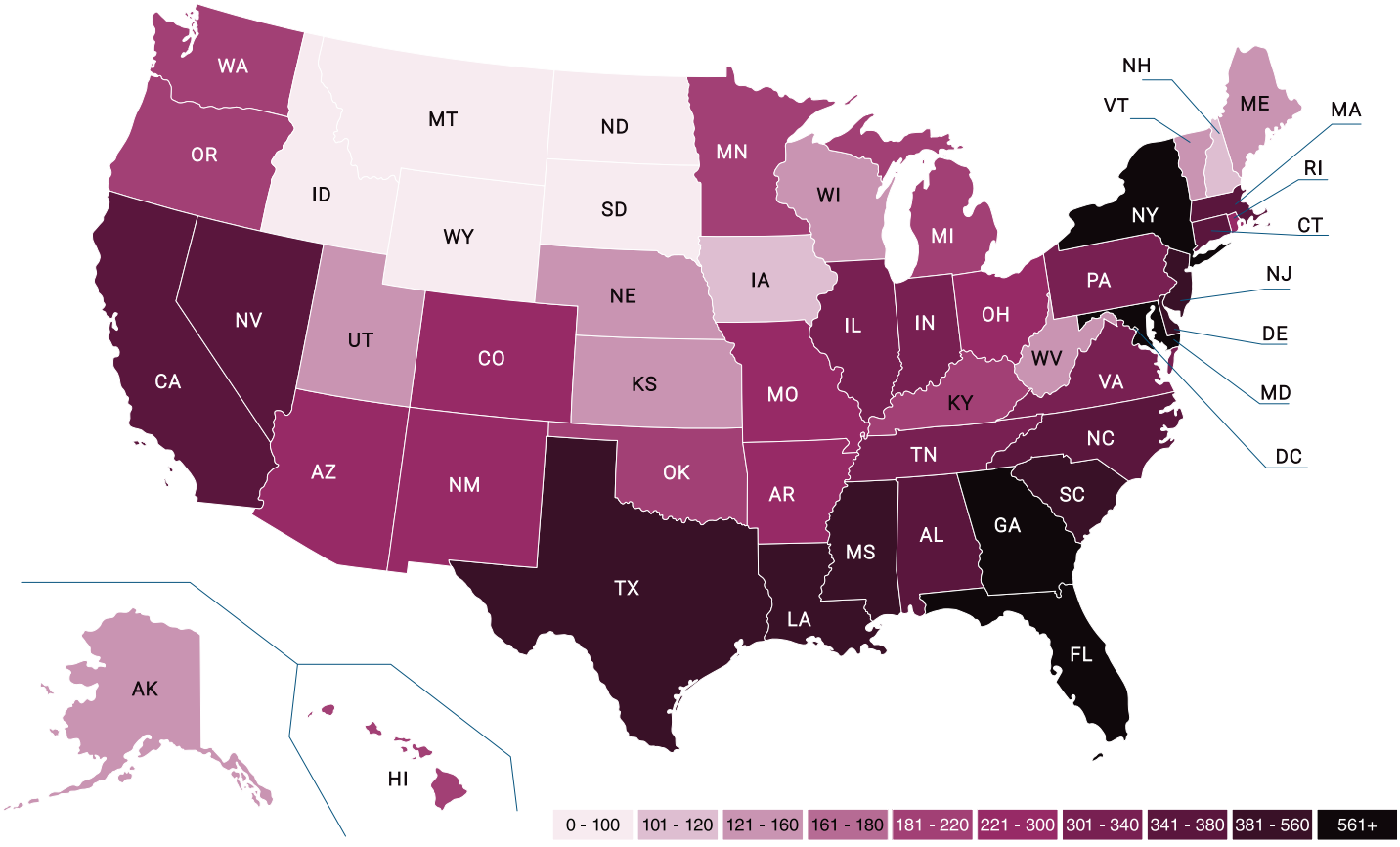
SB 339, a so-called "fix-it" bill that has not yet become law, will authorize pharmacists to prescribe up to a 90-day supply of PrEP and require commercial health insurance to reimburse pharmacists for the patient care services provided in association with PrEP.

Under this law, Mission Wellness has served some of those in greatest need.

"I would say our patients have primarily been uninsured or patients who can't get in to see a provider," Lopez said. For example, they can help patients who could not get in to see a local physician when they lost their pills while visiting San Francisco or after just moving to town.

If not for pharmacists providing

Rates of persons living with HIV per 100,000 people (2020)



PrEP, Lopez said, "they definitely would've had a gap in their medication, their levels would go down, and then they would be at risk for HIV."

The risks associated with a break in PrEP are analogous to those of a break in hormonal contraception coverage. A 2022 study in *Obstetrics & Gynecology* by Rodriguez and colleagues found that pharmacist prescription of hormonal contraception is associated with increased odds of 12-month continuation rates compared to physician prescriptions.

"It's not the same thing as PrEP, but it showcases the impact that pharmacists can have in this area," Murphy said.

PrEP patients at Mission Wellness are also predominantly Latino, which addresses a national and local need. "Overall, the number of Latinos in the city has gone down, but HIV rates among them have gone up," Lopez said. In San Francisco County, Latinos accounted for 38% of new infections in the most recent data—up from 25% in 2012.

Expanding pharmacists' reach

While California was the first state to pass laws allowing pharmacists to provide and be reimbursed for PrEP services, other states have since implemented laws that go further to expand pharmacists' scope and reimbursement in this area.

Individuals who take PrEP represent a small minority of those for whom it is indicated, and the disparities are starkest in the communities that may need the drug therapy the most.

Colorado law, according to pharmacy advocates, may be the most thorough in this respect. In Colorado, a statewide protocol allows pharmacists to provide PrEP to all eligible patients after the appropriate testing and requires that Medicaid and commercial health plans cover the service.

"The policy in Colorado addresses the two primary barriers to pharmacists being able to deliver HIV PrEP and PEP to their patients: scope of practice and reimbursement," said Murphy.

"This sets up an efficient way for pharmacists to provide these services and increase access with minimal policy barriers and within a sustainable business model," Murphy said.

In Oregon, pharmacists have been authorized since 2017 to prescribe PrEP and PEP after completing relevant con-

tinuing education. A more recent law, added to the books in 2021, ensures that pharmacists get reimbursed for PrEP and PEP services at the same rate as other health care providers.

The law expands pharmacists' reach. That gives them the ability to offer PrEP preemptively to those who may benefit from it.

"If someone is picking up a prescription for another STI medication, we can talk about PrEP and see if they'd be interested," said Jared Gallegos, PharmD, a clinical pharmacist at Central City Concern, a federally qualified health center in Portland. "If the patient wants to know why we're asking, we just say 'We think everyone's sexual health is important, so we wanted to give you this option.'"

Adding the pharmacy as a point of access, he said, has helped reach patients who might not otherwise have started PrEP. "We've had patients who only got started on it because they saw the flyers here in the pharmacy," Gallegos said.

"Any adult who wants to be on PrEP should be able to be on PrEP," Gallegos said. "They don't have to meet requirements about how much sex they are having or anything like that. If they request it, they should be able to be on it."

Greater public health impact

Adding the pharmacy as an access point may also provide what many potential patients see as a less stigmatizing setting.

"Many of our patients haven't wanted to see a primary care provider because there is some stigma in approaching a doctor about PrEP," said Elizabeth Camper, PharmD, AAHIVP, pharmacy manager at AIDS Healthcare Foundation in Seattle. "Taking the stigma out of it is key. Hopefully pharmacists can do that and make it more accessible so they can approach us about these things."

Camper and her colleague Jessi Truelove, PharmD, AAHIVP, a pharmacist on the strategic response team at AIDS Healthcare Foundation, run a pharmacist-operated PrEP clinic in a pharmacy in Seattle. The two also participated in the statewide demonstration project PIPAR (Pharmacy Integration Into PrEP and ART Provision and Retention).

While Washington is not among the 17 states where pharmacists have expanded scope of practice to provide PrEP, it is considered a pioneer in pharmacist-led PrEP services because of Seattle-based Kelley-Ross Pharmacy's work in this area. Shortly after national guidelines for PrEP provision were made available in 2014, Kelley-Ross Pharmacy created its community pharmacist–managed HIV PrEP clinic. From March 2015 to February 2018, a total of 695 patients started PrEP at the clinic—most of them on the same day as their initial appointment. All patients who stayed in care throughout the pilot program, after a 25% dropout rate, remained HIV-negative until the end.

Community pharmacies increase access to PrEP not only by virtue of their ubiquitousness, but also in their ability to provide same-day PrEP, which may increase retention

Through a collaborative drug therapy agreement, Camper and Truelove can prescribe same-day PrEP for HIV prevention. They also prescribe and administer routine vaccinations and treatment for STIs and order and monitor labs. Through a phlebotomy license, they perform venous blood draws through which they assess hepatitis B immunity, HIV status, syphilis exposure, and kidney function under serum creatinine levels.

If patients do not have a primary care provider and want one, pharmacists assist them in finding one. They also refer patients to other community resources such as charities providing clothing, food, and case management, if needed.

As the state of Washington recognizes pharmacists as health care providers, the law requires that they are reimbursed for the patient care services they provide, including PrEP therapy.

The program, Truelove said, has more far-reaching public health effects than on HIV prevention alone.

"During visits with patients, we've identified a lot of gaps in vaccines—[like with] TDAP, we've helped people hear about flu shots if they don't have a primary care provider. We've gotten a lot of people their COVID boosters. I would say we are filling a vaccine need with our patients, and we are very proud of that," she said.

Pharmacist-led PrEP programs underscore the impact pharmacists, when given the opportunity, can have on public health—an impact that was made clear during the COVID-19 pandemic. But advocates must get the message to policymakers that there is a role for pharmacists to play here.

"It comes down to policymaker education," Murphy said. "Unfortunately, pharmacies are not the first place that people think of for getting PrEP and PEP prescriptions, but once that education happens—and a lot of it has come from seeing pharmacists provide increased access to COVID-19 testing, immunizations, and oral antivirals—more and more state and federal policymakers are understanding that this is where we should be looking." ■

ACIP provides updates to several vaccinations

Lauren Howell, PharmD

ACIP gathered to discuss several vaccine recommendations in June 2023. As a result of the meeting, recommendations surrounding the influenza virus vaccine, adult respiratory syncytial virus (RSV) vaccine, polio virus vaccine, and pneumococcal vaccine for children, among others, were all updated.

ACIP meets approximately three times per year to make new recommendations for existing vaccines and discuss vaccines that may be on the horizon. CDC uses the recommendations made by ACIP to set the U.S. adult and childhood vaccination schedules. While FDA evaluates the safety and efficacy of vaccines before they come to market, ACIP bases their recommendations on the severity of the disease, the number of people who get the disease if there is no vaccine, how well a vaccine works for people of different ages, and how practical the recommendations are to put into practice.

Influenza vaccination updates

ACIP continues to recommend an annual influenza virus vaccination for all people who are 6 months or older and do not have contraindications. Additionally, no changes were made to the recommendations regarding timing of vaccination from the 2022–2023 influenza season. Most people who need only one dose of influenza vaccine should receive the vaccination in September or October. Vaccination during July and August are not recommended for most individuals, but can be considered in some circumstances. For most adults and for pregnant people in the first or second trimester, vaccination during July and August should be avoided unless there is concern that vaccination later in the season will not be possible.

For children who require two doses, the first dose should be given as early as possible, including in July or August, to allow the second dose to be administered prior to the end of October. For children who only require one dose of influenza vaccine, vaccination during July and August can be considered. During the third trimester of pregnancy, vaccination during July and August can be considered in an effort to reduce risk for illness in infants during the first months after birth, before they can receive the vaccine themselves. Influenza vaccination should continue throughout the flu season as long as viruses are circulating and unexpired vaccine is available.

In a change from previous recommendations, ACIP now recommends that all persons 6 months or older with an egg allergy should receive the influenza vaccine and any vaccine—egg-based or non–egg-based—that is otherwise appropriate for the patient can be used.

RSV adult vaccine

Both Pfizer's bivalent RSV prefusion F (RSVpreF) and GSK's adjuvanted prefusion RSV F glycoprotein antigen (RSVPreF3) vaccines have demonstrated efficacy against lower respiratory tract illness caused by RSV among older adults over at least two seasons.

However, ACIP determined that the trials used to determine efficacy were underpowered to show efficacy in adults 75 years and older and in adults who are frail. Additionally, the trials were underpowered to show efficacy against RSV hospitalization. Therefore, efficacy against symptomatic illness may indicate that the vaccine is also efficacious against more severe disease.

Cases of inflammatory neurologic events were reported within 42 days after vaccination with both vaccines; however, the clinical trials were not sufficiently powered to determine whether the small number of these cases occurred due to random chance. Because of this, ACIP decided that whether there is an increased risk of inflammatory neurologic events from RSV vaccination is not known at this time.

With changes to the COVID-19 vaccine, flu season, and the new RSV vaccines all coming this fall, pharmacists may be extra busy.

ACIP recommends that adults 60 years and older may receive a single dose of RSV vaccine using shared clinical decision-making. Factors that should be considered during shared clinical decision-making include chronic lung diseases, chronic CV diseases, immune compromise, hematologic disorders, neurologic disorders, endocrine disorders, kidney and liver disorders, other underlying conditions that may increase the risk of severe respiratory illness, and whether the patient is a resident of a nursing home or other long-term care facility.

Optimally, RSV vaccination should occur before the onset of increased RSV activity in the community. For the 2023–2024 season, ACIP recommends that RSV vaccination is offered as soon as the vaccine is available. Coadministration with other vaccines is acceptable; however, it should be considered that simultaneous administration of multiple vaccines could increase reactogenicity. Additionally, it should be considered that the recombinant zoster vaccine, GSK's Shingrix, contains the same adjuvant as the RSVPreF3 vaccine, GSK's Arexvy.

Polio virus

ACIP recommends that adults 18 years and older who are known or suspected to be unvaccinated or incompletely vaccinated against polio should complete a primary vaccination series with inactivated polio vaccine (IPV). Adults who have received a primary series of IPV or trivalent oral polio vaccine (tOPV) in any combination and who are at increased risk of poliovirus exposure may receive another dose of IPV. Available data do not indicate the need for more than a single lifetime booster dose with IPV for adults.

Pneumococcal vaccine for children

Use of either PCV15 or PCV20 is recommended for all children ages 2 months to 23 months, according to the currently recommended pneumococcal conjugate vaccine dosing and schedules.

Based on this, all children under the age of 2 years have the same pneumococcal vaccine recommendations. A primary series of vaccines should be given at 2 months, 4 months, and 6 months followed by a booster at between 12 months and 15 months old. For healthy children ages 24 months to 59 months with an incomplete PCV vaccination status and children with specified risk conditions aged 24 months to 71 months with an incomplete PCV vaccination status, use of either PCV15 or PCV20 according to currently recommended PCV dosing and schedules is recommended.

ACIP recommends that for children ages 2 years to 18 years with any risk condition who have received all recommended doses before 6 years using at least one dose of PCV20, no additional doses of pneumococcal vaccine are indicated.

For children ages 2 years to 18 years with any risk condition who have received all recommended doses before 6 years using PCV13 or PCV15, a dose of PCV20 or PPSV23 using previously recommended doses and schedule is recommended. For children ages 6 years to 18 years with any risk conditions who have not received any dose of PCV13, PCV15, or PCV20, a single dose of PCV15 or PCV20 is recommended. When PCV15 is used, it should be followed up by a dose of PPSV23 at least 8 weeks later if it was not previously given.

COVID-19 vaccine updates

It is anticipated that COVID-19 vaccines and treatments will transition to the commercial marketplace in the fall of 2023. Many Americans with insurance coverage will continue to receive the vaccine for no charge out-of-pocket. However, individuals without insurance may begin to have to pay for COVID-19 vaccination.

A temporary measure has been put into place to prevent the loss of access to COVID-19 vaccines and treatments for these patients. The Bridge Access Program for COVID-19 Vaccines and Treatments is a public–private partnership that will work to provide COVID-19 vaccines and treatments at no-cost after commercialization later this year.

Implications for pharmacists

With changes to the COVID-19 vaccine, flu season, and the new RSV vaccines all coming this fall, pharmacists may be extra busy. Pharmacists should be prepared to answer questions about new vaccines and stay up to date on current recommendations. Additionally, pharmacists should be prepared to participate in shared clinical decision-making to help patients make the best possible choice for their health. ■

As other states expand scope of practice, Arkansas' test-and-treat program offers takeaways

Loren Bonner

Could point of care testing (POCT) services become as common as immunization services in pharmacies? Megan Smith, PharmD, lead author of a new study in *JAPhA*, thinks so. In a new research paper, she and PharmD candidate Elma Abdullah highlight strategies for pharmacy leadership to put in place as pharmacy scope of practice expands in many states.

Smith and Abdullah honed in on the state of Arkansas to understand pharmacists' perceived impact of POCT services in the state and their preferred implementation strategies for expanding scope of practice.

"The data reveal that the journey toward implementing POCT services need not be all-or-nothing," said Smith, who is an associate professor in the Department of Pharmacy Practice at the University of Arkansas for Medical Sciences. "It can be tailored to suit individual practice settings."

Useful results

Arkansas Act 503 allows pharmacists to prescribe based on CLIA-waived tests using a statewide protocol. However, protocols were not developed by the time of its passage.

To actively contribute to guiding the development of these protocols, researchers conducted a cross-sectional survey of CLIA-waived pharmacies in Arkansas. A sample of 81 pharmacists representing 238 chain, regional, or multi-independent pharmacies participated in the survey. Survey questions assessed perceptions of Act 503 on POCT services and preferred implementation strategies.

After analyzing the results, they found that 37.9% of pharmacies reported that they are certain or almost certain they would prescribe using the protocol. More pharmacies (63%) reported the youngest age they would prescribe treatment is 6 years to 12 years. Most pharmacies (82.2%) said they do not anticipate or are unsure about increasing their fee once the protocol is adopted. And more than 95% of responding pharmacies reported virtual training, online modules, central contact, and a one-page resource with key protocol information would be most helpful in putting the new statewide protocols in place.

"The strategic decision-making process involved in determining when to use the protocol versus collaborating with providers highlights the importance of maintaining these valuable connections."

A particularly intriguing result, according to Smith, was whether pharmacists planned to continue their current method of obtaining treatment by working with providers or referrals, or if they intended to leverage the newly established protocol to prescribe independently. Roughly half of the respondents indicated a complete transition to the protocol, while the other half opted for a dual approach.

"The strategic decision-making process involved in determining when to use the protocol versus collaborating with providers highlights the importance of maintaining these valuable connections," said Smith.

Lots of advice

Smith said she has learned the importance of using self-paced, on-demand educational resources for general education, and clinical updates. For more intricate aspects such as workflow, legal considerations, and billing, she said virtual or live workshops have been the most beneficial.

"My most valuable advice for others embarking on scope expansion is to establish a central point of reference for all resources and webinars," said Smith. Then, dividing the information into distinct chunks—clinical, legal, billing—makes it easier to digest and understand, according to Smith.

An endorsement by the largest payer in the state of Arkansas made it possible for these services in pharmacies to be covered under the medical benefit.

As pharmacists start up services at their pharmacy, Smith advises choosing one or two services based on the population the pharmacy serves as well as existing relationships. She said it's also important to decide on a start date and create a timeline that includes key steps for planning, preparation, and the launch of the service. And, of course, pharmacies should apply for a CLIA Certificate of Waiver if they haven't already obtained one.

"Create your operating procedures around scheduling, intake, patient assessment and evaluation, billing, and documentation," Smith said. "I've seen an increase in pharmacies using online appointment scheduling and electronic intake forms to increase efficiency for patients and proactive planning of their appointments. Finally, train your staff on new services offered—all staff should be able to describe and answer general questions regarding the service."

One final piece of advice from Smith is for pharmacists to become preceptors for student pharmacists and incorporate launching a service as part of the rotation. "Students can help research supplies, organize the workspace, create staff supports—like binders, scripts, flow charts—to help your service get off the ground," said Smith. ■

APhA offers a Test and Treat Certificate Training Program that prepares pharmacists to provide point of care services. It's available at apha.us/TestAndTreat. Also, visit apha.us/Paxlovid for more information about implementing testing and treatment services for Paxlovid (Pfizer).

Pharmacy-based herpes zoster vaccinations boost rates, are more cost-effective

Jonathan Little, PharmD

Health benefits of the herpes zoster vaccine are well-documented, but lesser known are the economic impacts of a community pharmacy–based herpes zoster vaccination service in the United States.

According to findings of a research study published May 16, 2023, in *JAPhA*, 11,586 additional individuals were vaccinated for herpes zoster compared to a hypothetical scenario without community pharmacy–based vaccination services. The modeling study revealed that 706 cases of shingles were averted as well as 143 cases of postherpetic neuralgia, an unfortunate and serious consequence of shingles.

"Our study showed that community pharmacy–based herpes zoster vaccination was less costly (–$131,894), gained more quality-adjusted life years (52.5), and was associated with improved other clinical outcomes in the state of Utah," said lead author Nathorn Chaiyakunapruk, PharmD, PhD, professor at the University of Utah College of Pharmacy.

Chaiyakunapruk said their goal for the research was to create a model that could be used to address access and underutilization of vaccines and hopefully incentivize new initiatives to improve access to vaccines through community pharmacy services.

"There remains a strong need to assess the economic impact of other community pharmacy–based vaccination programs," said Chaiyakunapruk.

Broader implications

The researchers analyzed data from patients ages 50 years and older who were eligible for herpes zoster vaccination in Utah between 2010 and 2020, a cohort of 853,550 people. A comparison was then made between community pharmacy–based vaccination and a hypothetical scenario in which no community pharmacy–based vaccination programs were available.

Not only shingles, but also postherpetic neuralgia was shown to be averted through the modeling of the study.

The findings support the positive impact of pharmacist involvement in vaccination programs on both clinical and economic outcomes, according to Chaiyakunapruk. He said the key strength of the study is that it's the first to demonstrate public health and economic benefits of community pharmacy–based vaccination strategy in the United States.

The major limitation of the study is that it's only specific to the state of Utah. "Further research in other states or nationwide is needed," said Chaiyakunapruk. "The estimated effect of pharmacists on the vaccine uptake used in this model was based on an observational study assessing changes in influenza vaccination rates. Despite not being the best estimate, it can still be justified as reasonable considering the lack of research on the impact of pharmacists on the rate of herpes zoster vaccination."

Although the research focused on herpes zoster in particular, pharmacists are able to similarly make recommendations for several other vaccines.

Pharmacists, patients, policymakers

Overall, findings from the study confirm the vital role of pharmacists by demonstrating the potential public health benefits of community pharmacy–based herpes zoster vaccination programs.

Other researchers may find this model and findings helpful as evidence to build upon for future evaluations of other community pharmacy–based vaccination programs, according to Chaiyakunapruk. He believes the findings are relevant to pharmacists, patients, and policymakers alike. ■

Cough, cold, and allergy

Approximately 1 billion cases of the common cold occur annually, making it one of the top five illnesses diagnosed in the United States. Bothersome symptoms lead patients to self-medicate, with an estimated $8 billion spent annually on nonprescription cold and cough products.

Cough, cold, and allergy

Adult allergic reaction treatment
Benadryl 1

Adult seasonal allergy relief
Zyrtec 1
Claritin 2
Allegra 3

Cough lozenges
Halls 1
Cepacol 2
Ricola 2

Cough, cold, and flu multisymptom relief
Vicks Dayquil/Nyquil 1
Mucinex 2
Robitussin 2
Tylenol 2

Liquid cough expectorant
Robitussin 1
Mucinex 2

Liquid cough suppressant
Delsym 1
Robitussin 2

Nasal decongestant spray
Afrin 1
Flonase 2

Natural cold remedy
Zicam 1

Sinus rinse
NeilMed 1

Sore throat lozenges
Cepacol 1
Halls 2
Chloraseptic 3

Vapor therapy
Vicks Vapo 1

Self-care survey redux

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

The current survey was conducted by BrandSpark/Newsweek International using a scientifically valid methodology, and lists those nonprescription products most often recommended by pharmacists in the United States to consumers.

The winners were selected based on a survey of 1,716 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, then a tie was declared.

Please also see APhA's *Handbook of Nonprescription Drugs*, the definitive source of professional information about OTC products. The *Handbook* is available online at PharmacyLibrary.com.

Court rules pharmacy entitled to recover signing bonus

David B. Brushwood, BSPharm, JD

Pharmacies in some areas face challenges recruiting pharmacists to staff their practice sites. As an incentive for pharmacists to accept employment, pharmacies may offer a signing bonus. Signing bonuses can be conditional, and one common condition is that a pharmacist must complete a specified period of employment at the pharmacy following the receipt of a signing bonus. A California court recently ruled that a pharmacy was entitled to the return of a signing bonus it had paid to a pharmacist who was terminated from employment prior to completion of the specified period.

Background

A pharmacist was hired by a community pharmacy in May 2016. She was paid a signing bonus of $35,000. An agreement between the pharmacy and the pharmacist stated that "to avoid any repayment obligation with respect to the incentive payment, the pharmacist must remain continuously employed by [the pharmacy] for a period of 3 full years of service." The pharmacist electronically signed the agreement and checked a box attesting that she "accepts and agrees to all of the terms and conditions set forth" in the agreement.

The pharmacist was terminated after 21 months of employment. The court did not explain the basis of the termination. The pharmacy sent the pharmacist an invoice requesting repayment of the signing bonus. When the pharmacist failed to pay the invoice in full, the pharmacy filed a lawsuit for breach of contract, demanding return of the bonus as specified in terms of the agreement.

The trial court ruled in favor of the pharmacy, and the pharmacist appealed.

Rationale

The pharmacist represented herself during the legal proceedings. She contended that the trial court's ruling was in error. The appellate court noted that, despite her lack of legal representation, the pharmacist was required to "present meaningful legal analysis supported by citations to authority and citations to facts in the record that support the claim of error." According to the court, most of the claims of error raised by the pharmacist failed to meet this requirement.

The court then evaluated the pharmacist's claims that had been properly made. The court first noted that "written incentive payment plans that are contingent on an employee remaining with an employer for a specified amount of time are generally enforceable."

The pharmacist contended that all contracts contain a covenant of good faith and fair dealing "which requires that neither party do anything to deprive the other of the benefits of the agreement." The court ruled that this argument was inapplicable to the case, because "there is a presumption that employment is at will, and may be terminated by either party, at any time, for any or no reason."

The pharmacist maintained that since the pharmacy terminated her employment, the pharmacy had caused or initiated a breach of the agreement; thus, the pharmacy should not be able to recoup the signing bonus because the agreement had been nullified. The court disagreed, citing language of the agreement stating that the pharmacist was "obligated to repay the entire incentive payment amount if she leaves for any reason." The court concluded that "leaving because she was terminated by [the pharmacy] is 'any reason.'"

Judgment in favor of the pharmacy and against the pharmacist was affirmed.

The pharmacist maintained that since the pharmacy terminated her employment, the pharmacy had caused or initiated a breach of the agreement.

Takeaways

There are several key lessons to be learned from this case:

- Clicking through with signatures on an electronic document may not fully inform the signatory of the content of the document.
- Provisions in an employment agreement are subject to negotiation and can be modified if they seem disadvantageous or one-sided.
- The amount of money being contested in a signing bonus controversy is likely not sufficient to justify hiring legal representation.
- It may be financially advantageous to endure a challenging employment situation rather than to resign or be fired when the repayment of a signing bonus has been specified in an agreement. ■

Unrecognized need to refrigerate etoposide capsules leads to wasted drug

Institute for Safe Medication Practices, Horsham, PA

Etoposide capsules are a cold-chain medication used for small cell lung cancer that must be stored under refrigeration between 2°C and 8°C (36°F–46°F). A specialty pharmacy reported an error that resulted in a carton of etoposide 50 mg capsules being left out at room temperature overnight for about 12 hours.

This error happened during the packing phase of the pharmacy workflow, which comes after production and pharmacist verification. This was the first time the pharmacy had dispensed etoposide capsules, and the packing technician did not realize they needed to be stored at refrigerated temperatures. The technician packed it for shipment as a room-temperature medication without a cooler box or an appropriate number of cold packs.

When the pharmacist discovered the etoposide carton at room temperature the next morning, they researched temperature stability and excursion data to see if the medication was still stable. They called the manufacturer, but additional temperature stability data were not available at that time. The pharmacist then sequestered the medication for disposal since they could not confirm its stability.

Unfortunately, the product was on backorder, and the other pharmacies within the same company did not have this medication in stock. The pharmacy transferred the prescription to an outside pharmacy to prevent the patient from being late with their dose.

The storage information is printed on a narrower side panel, so it may not be immediately apparent that this product should always be stored in the refrigerator.

Standard process

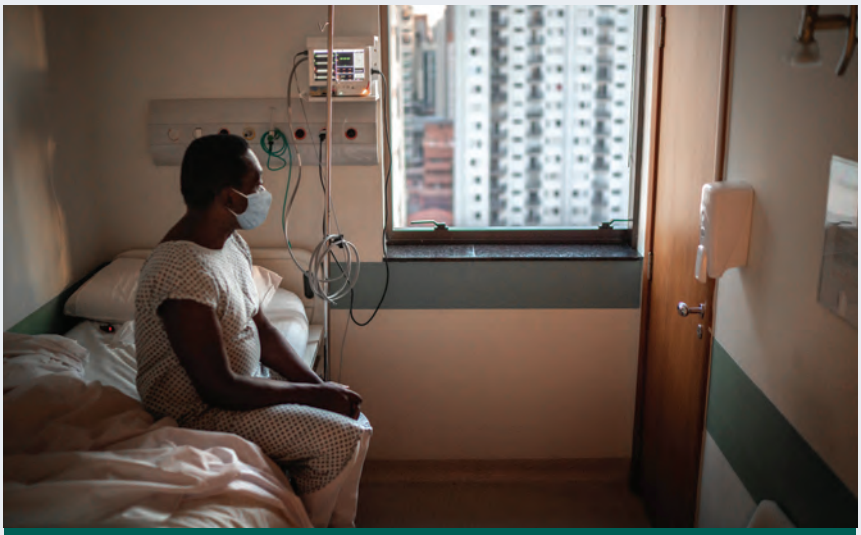
Many oral capsules are stored at room temperature, but this specific medication should be stored in the refrigerator. Etoposide 50 mg capsules are packaged in cartons with 20 unit dose capsules.

While the name of the drug and strength are prominently displayed on the carton's primary display panel, the storage information is printed on a narrower side panel, so it may not be immediately apparent that this product should always be stored in the refrigerator.

This pharmacy does have a process in which, when each cold-chain item is removed from the refrigerator, pharmacy staff place a blue laminated card in the medication tote that follows it through the entire filling and packing process until it is packed into a cooler box for shipping or returned to the refrigerator. The staff person then uses a dry-erase pen to write the time they removed the medication from the refrigerator on the blue card. This timestamp is visible during filling, product verification, and packing to help ensure that the medication is not out of the refrigerator for longer than designated in the pharmacy's drug cold-chain protocol (e.g., 30 minutes).

The pharmacy has also employed technology to remind staff they are working with a cold-chain medication. For example, the packing station computer screen says "cold," and the packing label prints automatically with an "R" (for refrigerate) as another reminder. It is unclear why all these indicators were missed in this case. ■

Inpatient*Insights*



How does hospitalization for COVID-19 affect the risk of developing other conditions post discharge?

Patients who survive hospitalization for influenza, sepsis, or other serious illnesses are known to have an increased risk for developing CV, neurological, and other conditions after discharge, but it has been difficult to determine the extent to which patients who were hospitalized for severe COVID-19 have this type of risk. The authors of a recent study published in the August 2023 issue of *JAMA Internal Medicine* attempted to determine the risk of newly developed medical and mental health conditions within 1 year following hospitalization for severe COVID-19 compared with flu or sepsis.

The researchers, led by Kieran L. Quinn, MD, PhD, of the Sinai Health and University Health Network in Toronto conducted a population-based cohort study to compare risks of incident CV, neurological, and mental health conditions and rheumatoid arthritis in 1 year following COVID-19 hospitalization against three comparator groups: prepandemic hospitalization for influenza, and hospitalization for sepsis before and during the COVID-19 pandemic. The study results indicated that hospitalization for COVID-19 was associated with an increased 1-year risk of venous thromboembolic disease compared with flu but with no increased risks of developing selected ischemic and nonischemic cerebrovascular and CV disorders, neurological disorders, rheumatoid arthritis, or mental health conditions.

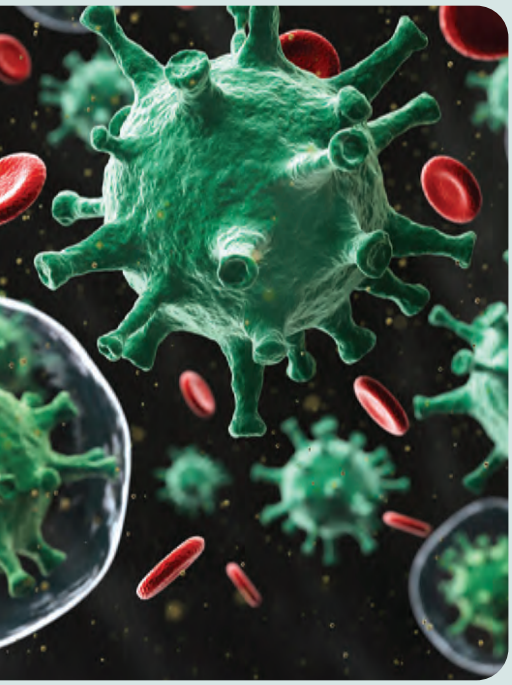
The authors suggest that many of the postacute consequences of COVID-19 may be related to the severity of infectious illness necessitating hospitalization rather than being direct consequences of infection with SARS-CoV-2. ■

Evaluating antimicrobial duration for Gram-negative bacteremia in patients with neutropenia

Short courses of antimicrobials have been increasingly demonstrated as noninferior to prolonged therapy for management of Gram-negative bloodstream infections (BSIs) given the lower risk of *Clostridioides difficile* infection and emergence of multidrug-resistant organisms. Clinical data have not been available on the effectiveness of short courses of antimicrobials on immunocompromised patients. A recent study published online on June 6, 2023, in *Transplant Infectious Disease* sought to close this gap through a retrospective cohort study involving patients with neutropenia as a result of hematopoietic stem cell transplantation or hematologic malignancy.

The study involved about 200 patients at the Mayo Clinic (Rochester) between July 2018 and April 2022 with monomicrobial Gram-negative BSIs involving *E. coli*, *P. aeruginosa*, or *Klebsiella* species. Patients were classified as having received short (<10 days), intermediate (11–14 days), or prolonged (>14 days) treatment with cefepime or carbapenem. The effect of the treatment duration on outcomes was evaluated, with a primary outcome of a composite of all-cause mortality and microbiologic relapse within 90 days after therapy completion.

No significant difference in the primary composite endpoint was observed for either intermediate or prolonged course treatment versus short course treatment. The authors suggest that their data support the use of short course treatment for Gram-negative BSIs among immunocompromised patients with neutropenia. ■

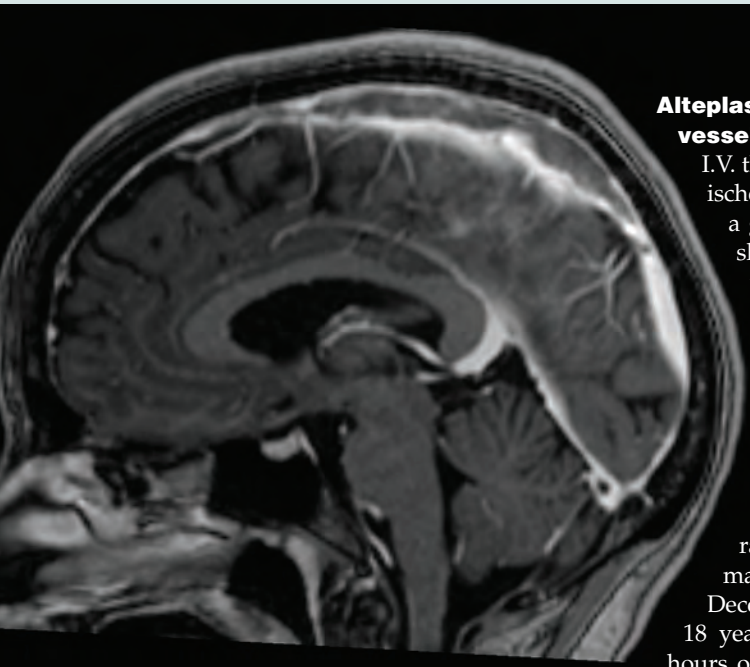


Is procalcitonin testing effective for detecting BSI at admission?

Serum procalcitonin is often ordered at admission for patients with suspected sepsis and bloodstream infections (BSIs), but its performance characteristics have been unclear. A recent study published in *Critical Care Medicine* on July 3, 2023, used a retrospective cohort study to evaluate use patterns and performance characteristics of procalcitonin-on-admission testing in patients with suspected BSI with or without sepsis.

Almost 75,000 adult inpatients at 65 hospitals who had blood cultures and procalcitonin drawn within 24 hours of admission were included in the study. Results of the study indicated that median procalcitonin levels varied considerably by pathogen, BSI source, and acute illness severity. At a ≥0.5 ng/mL cutoff, sensitivity for BSI detection was 68.2% overall, ranging between 58.0% for enterococcal BSI without sepsis and 96.4% for pneumococcal sepsis. Procalcitonin-on-admission testing displayed moderate discrimination for overall BSI and showed no additional utility in key subgroups. Empiric antibiotic use proportions were not different between blood culture–sampled patients with a positive procalcitonin (39.7%) and negative procalcitonin (38.4%) at admission.

The authors concluded that procalcitonin-on-admission testing demonstrated poor sensitivity in ruling out BSI and moderate to poor discrimination for both bacteremic sepsis and occult BSI and did not appear to meaningfully alter empiric antibiotic usage. They urge diagnostic stewardship of procalcitonin-on-admission testing and risk assessment of admission procalcitonin-guided clinical decisions. ■



Alteplase could be alternative to tenecteplase for large vessel occlusion stroke

I.V. thrombolysis is the standard of care for the treatment of acute ischemic stroke within 4.5 hours of symptom onset. Tenecteplase, a genetically modified variant of alteplase, has recently been shown to be a safe and effective alternative to alteplase for treatment of large vessel occlusion (LVO) stroke. The question remained, however, as to whether I.V. tenecteplase is as safe and efficacious as I.V. alteplase in patients with LVO stroke and whether the treatment effect differs by occlusion site. A group of researchers led by Mohammed Almekhlafi, MD, of the Cumming School of Medicine at the University of Calgary (Canada), sought to answer this question through a study published online in *JAMA Neurology* on July 10, 2023.

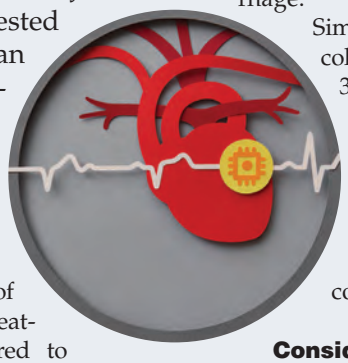
The study involved a prespecified analysis of the ACT randomized clinical trial that enrolled patients from 22 primary and comprehensive stroke centers across Canada between December 10, 2019, and January 25, 2022. A total of 1,600 patients 18 years and older with a disabling ischemic stroke within 4.5 hours of symptom onset were randomly assigned to receive either I.V. tenecteplase or alteplase and were monitored for up to 120 days. The primary outcome was the proportion of modified Rankin scale (mRS) score of 0–1 at 90 days.

Among 520 patients with LVO, an mRS score of 0–1 at 90 days was achieved in 86 participants (32.7%) in the tenecteplase group versus 76 (29.6%) in the alteplase group. These findings indicate that I.V. tenecteplase conferred similar reperfusion, safety, and functional outcomes compared to alteplase among patients with LVO. Given the ease of administration of tenecteplase (which can be administered via bolus) versus alteplase and the comparable safety and efficacy between both thrombolytics, the authors conclude that tenecteplase could be used as a first-line thrombolytic agent for patients with LVO stroke. ■

Study provides insights on ideal DOAC timing for patients with AFib post stroke

Corey Diamond, PharmD

The optimum time to resume or initiate direct oral anticoagulants (DOAC) after an acute ischemic stroke in patients with AFib remains unclear. Starting too soon may risk bleeding complications, while starting too late may risk a recurrent stroke. Currently, guidance is derived solely from expert consensus rather than from clinical data. However, findings from a new study published in the June 29, 2023, issue of *NEJM* by Fischer and colleagues suggested that it may be safe to resume DOACs earlier rather than later for select patients with AFib after an acute ischemic stroke.



Comparing timing

The ELAN trial was a randomized controlled trial that included data from over 2,000 patients who had experienced an acute ischemic stroke and AFib. Patients in the comparator groups received either early anticoagulation with a DOAC—defined as 48 hours after a minor or moderate stroke—or late DOAC anticoagulation, which was defined at day 6 or 7 after a major stroke.

The study found no significant difference between the treatment outcomes of the early DOAC treatment group compared to the late DOAC treatment group in the primary composite outcome or its individual component outcomes.

Notably, findings revealed a trend toward a slight benefit of early DOAC initiation for both the composite primary outcomes and the rates of recurrent stroke at 30 and 90 days.

An additional comparator group received DOAC anticoagulation that was consistent with the expert consensus opinion "1-3-6-12–day rule" from the European Heart Rhythm Association's (EHRA) 2013 guidelines (i.e., receiving DOAC therapy on day 1, 3, 6, or 12 after a transient ischemic attack or after a minor, moderate, or severe stroke, respectively).

The study's primary outcome was a composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death within 30 days after randomization. Additionally, secondary outcomes included the individual components of the composite outcome within 30 and 90 days after randomization.

Practice comparisons

Current clinical practice entails delaying the initiation or resumption of DOAC therapy for patients with AFib following an acute ischemic stroke.

This recommendation comes from multiple guidelines that are based on expert opinion. For instance, EHRA recommends delayed DOAC initiation based on their "1-3-6-12–day rule." Conversely, the American Heart Association makes a general recommendation of delaying DOAC initiation to 14 days after an ischemic stroke if there is a "high risk" of hemorrhagic transformation, versus 2 to 14 days if there is a "low risk."

Two other notable studies have investigated the timing of DOAC initiation after a cardioembolic stroke in AFib. Results of the TIMING trial, published in *Circulation* in 2022, suggested noninferiority of early DOAC therapy following ischemic stroke in addition to demonstrating no cases of symptomatic intracranial hemorrhage.

Similarly, findings from a cohort study using a "1-2-3-4–day rule" published in *Stroke* in 2022 found data supporting earlier initiation of DOACs for AFib following an ischemic stroke.

Regardless, clear outcome data remain elusive.

Considerations for clinicians

According to the study authors, the ELAN trial was "designed to estimate the treatment effects of early initiation and later initiation of DOACs and the degree of precision of this estimate." However, no definitive conclusions regarding the safety and efficacy of early DOAC treatment after a cardioembolic ischemic stroke can be made regarding the results.

"No statistical hypothesis was tested for superiority or noninferiority, and the results are intended to provide qualitative data that may be of use to clinicians," the authors stated in the article.

They continued, "the components of the primary outcome that are probably of most interest to clinicians are recurrent ischemic strokes, systemic embolism, and symptomatic intracranial hemorrhage.

"By day 30, recurrent ischemic strokes had occurred in 1.4% of the participants in the early-treatment group and 2.5% of the participants in the later-treatment group; systemic embolism had occurred in 0.4% and 0.9%, respectively; and the incidence of symptomatic intracranial hemorrhage was low, approximately 0.2% in both treatment groups." ■

Pharmacogenomics in the ambulatory care setting bodes well for patients, providers

Loren Bonner

New research continues to support the integration of pharmacogenomics into clinical practice.

"Pharmacogenomics is the lowest hanging fruit in medicine today," said Burns C. Blaxall, PhD, senior author of a paper in *JAPhA* about implementing comprehensive pharmacogenomics in a community hospital–associated primary care setting.

"Implementation science matters," said Blaxall, who is executive director of Precision Health at the Christ Hospital Health Network in Cincinnati.

Although many drug–gene interactions are known today, they are not yet routinely addressed in clinical practice.

A pharmacist can take a broader and all-encompassing look at a patient's medication list, acting as the central person of the health care team to help optimize all the patient's medications.

According to the research, which was published in September 2022, pharmacogenomics-certified ambulatory care pharmacists embedded within primary care offices recommended a change in medication 82% of the time when an intervention was actionable.

Blaxall and his team at Christ Hospital wanted to determine the impact of pharmacogenomic services within their primary care offices using embedded, board certified, pharmacogenomics-certified ambulatory care pharmacists; a pharmacogenomics risk evaluation tool; a comprehensive pharmacogenomics gene panel; and a clinical decision support tool integrated in the electronic medical record.

They found that the underlying reasons for recommending therapy alterations were ineffective therapy (43%), prevention of adverse drug reactions (34%), or observation of an adverse drug reaction (13%).

Frontlines of pharmacogenomics

The first pharmacist was embedded in primary care offices within the Christ Hospital Health Network in 2019. Today, there are 11 board-certified, pharmacogenomics-certified ambulatory care pharmacists—likely more than any other health system, according to Blaxall.

Each pharmacist is embedded directly into the primacy care clinic, physically located in the offices, and assisting with chronic disease management, medication therapy manage-

ment, and pharmacogenomics. The pharmacists serve as medication and pharmacogenomic experts. They recommend pharmacogenomic testing when appropriate, interpret results, and provide subsequent therapy recommendations to prescribers within and beyond primary care.

"We knew that training every doctor in our health network to do pharmacogenomics was a fantasy, and we also know that individual gene–drug practice alerts in the electronic medical record are marginally effective, but a specialized group of ambulatory care pharmacists were really the front lines for our success," Blaxall said.

Another reason to have pharmacists lead this effort is that primary care physicians or specialists may only be prescribing a small number of the many medications a patient is taking. A pharmacist can take a broader and all-encompassing look at a patient's medication list, acting as the central person of the health care team to help optimize all the patient's medications.

Pharmacogenomics-certified pharmacists

In order to have a successful pharmacogenomics program, Blaxall said pharmacists need to be board-certified in their practice area with additional training and certification in pharmacogenomics.

Board certification is administered through the Board of Pharmacy Specialties, the only board-certifying body for pharmacists in the United States. Pharmacogenomic certification for Christ Hospital pharmacists was administered through the American College of Clinical Pharmacy or the American Society of Hospital Pharmacists, two of several bodies offering such certification.

Blaxall said it's also imperative to test with the broadest pharmacogenomics panel possible. Research supports this, too. A vast majority of pharmacogenomic-guided treatment recommendations can be missed if only a single-gene or disease-specific panel is used.

"How unfortunate would it be if you had tried to optimize a patient's antidepressant medication, but they remained depressed because of another poorly treated chronic disease?" Blaxall said. A recent study published in *The Lancet* further validates a panel-based approach with a multicenter trial in seven countries showing a 30% reduction in clinically significant adverse drug events in just 12 weeks.

Pharmacogenomics testing doesn't always need to have big implications either.

"Sometimes it's the simple cases," Blaxall said. For example, he recalled how one patient of theirs had suffered from acid reflux for 12 years while trying various treatments that were not working. "This patient saw three specialists, was scoped four times, tried six medications, with no relief of symptoms. Fortunately, she was randomized to our clinical trial. Two days after her pharmacogenomic testing results came back, the patient was prescribed the right medication and remains entirely symptom-free over a year later."

Blaxall hopes their research can highlight to others that a pharmacogenomics program within primary care is not only possible, but can be highly effective.

"Four years ago, we had nothing," Blaxall said. "The path to success is C-suite support, robust IT-level integration, and of course, board-certified, pharmacogenomics-certified pharmacists embedded in primary care offices." ■

The Clinical Pharmacogenetics Implementation Consortium

One barrier to putting pharmacogenetic testing into practice in the clinic setting is the difficulty translating genetic laboratory test results into actionable prescribing decisions for affected drugs.

The Clinical Pharmacogenetics Implementation Consortium, or CPIC, is an international consortium of individual volunteers and a small dedicated staff who are facilitating use of pharmacogenetic tests for patient care.

CPIC's goal is to address this barrier to clinical implementation of pharmacogenetic tests by creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines.

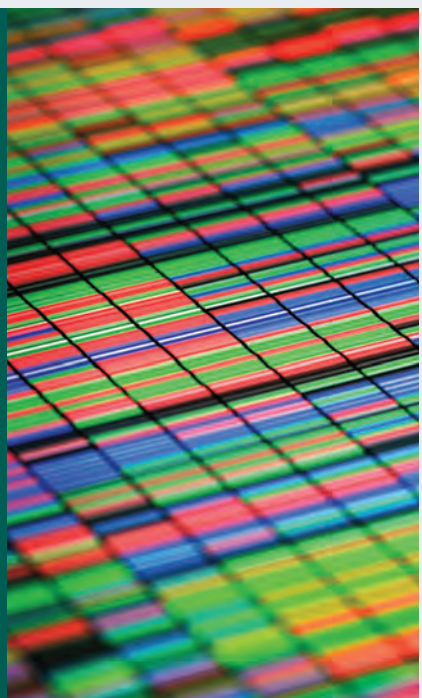
More can be found at cpicpgx.org ■

What is PGx?

Pharmacogenomics (PGx) refers to genetic determinants of drug response and uses candidate genes to study gene–drug interactions. PGx studies how germline (i.e., inherited) mutations affect response to drugs.

Virtually all of us carry a clinically relevant variant of one or more pharmacogenes. The pharmacokinetic, pharmacodynamic, and human leukocyte antigen genetic variants are associated with variability in drug response.

The field of PGx is fueled by the latest advances in artificial intelligence that combine pharmacology, genetics, and psychiatry for greater precision in diagnosis and treatment, allowing individualized drug selection and clinical practice. ■

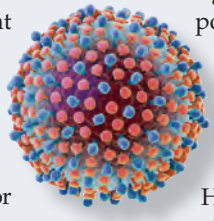


National infectious disease organizations update guidance on hepatitis C

Olivia C. Welter, PharmD

The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America recently released updated guidance on testing, treating, and managing hepatitis C.

The updated guidance, published online in *Clinical Infectious Disease* on July 23, 2023, is focused on recommendations for addressing nonadherence; treatment options for children as young as 3 years old; hepatitis C virus (HCV)–positive organ donation; eligibility changes for a simplified treatment approach; and therapy in vulnerable populations, including incarcerated persons.



The panel's updated recommendations for treating chronic HCV infection expands patient eligibility, reduces clinician intervention, and simplifies the process overall.

Treatment nonadherence

HCV can be treated with direct acting antivirals (DAA). Though the course of therapy is considered to be complete at 8 or 12 weeks, the guidance specifies that up to 40% of patients do not adhere to their treatment regimen.

To address this, the guidance panel developed a new treatment algorithm for patients that considers the timing and duration of nonadherence. The algorithm is broken down into two categories: interruptions prior to receiving 28 days of DAA therapy and interruptions after receiving 28 or more days of DAA therapy.

For all patients who are first nonadherent to their DAA therapy before 28 days, the panel recommends immediately restarting the course of treatment. If a patient misses 7 or fewer days, no other action is needed. If a patient misses 8 or more days, they should immediately receive an HCV RNA test after restarting therapy. If the test returns a negative reading, the patient should complete the medication for the full duration. If positive, the treatment should be extended by 4 weeks.

For patients whose nonadherence occurs after 28 days of treatment and who miss 7 or fewer days, they can immediately restart DAA and continue for the full duration. If a patient misses 8 to 20 consecutive days, they should immediately restart therapy and receive an HCV RNA test.

A negative test indicates that a patient should complete the full duration of therapy, which can be extended in certain circumstances. A positive test indicates stopping treatment and instead following a separate set of recommendations that is laid out in the retreatment section of the guidance document. Patients who miss 21 consecutive days of therapy or more should follow the same steps as a patient with a positive HCV RNA test.

Simplified treatment eligibility

The panel's updated recommendations for treating chronic HCV infection expands patient eligibility, reduces clinician intervention, and simplifies the process overall. Studies on minimal monitoring have shown that patients who are coinfected with HIV can safely follow a simplified HCV treatment algorithm, meaning no laboratory monitoring is needed while taking DAAs.

The guidance now states that patients who are treatment-naïve and HIV/HCV coinfected are newly eligible for simplified treatment because of these findings.

In recent years, more data have been published that show DAA therapy is both safe and effective in transplant patients. Because of this, the guidance document notes that solid organs from donors with HCV can be used effectively in patients who are HCV-negative. This strategy increases the pool of available organs and expands access to transplantation, ultimately reducing wait-list times.

HCV treatment in children and vulnerable populations

Historically, adults have been the target population for treating HCV and related diseases. However, recent studies have shown that children as young as 3 years old can safely use DAAs to treat HCV. The guidance recommends that any child 3 years or older should be treated with DAAs regardless of disease severity.

The guidance also offers recommendations on HCV treatment among vulnerable populations, including people who inject drugs (PWID), men who have sex with men (MSM), and incarcerated people.

PWID should receive annual HCV testing if injectable drug use is ongoing. The guidance notes that substance use disorder treatment programs and needle/syringe exchange programs should facilitate routine, opt-out HCV antibody testing, and subsequent linkage to care.

Initiation appointments for PrEP for MSM are an important touchpoint for testing for HCV. Sites that prescribe PrEP should offer testing at initiation appointments and annually thereafter for their MSM patients.

Because incarcerated people have a higher prevalence of HCV than the general population, jails and prisons should implement universal opt-out testing for HCV. The guidance states that DAA treatment is feasible for incarcerated peeople whether the therapy is initiated in the correctional system, a continuation of established treatment, or a continuation of treatment upon release. ■

A minute with ...

Gretchen K. Garofoli, PharmD, BCACP, CTTS, FAPhA
Clinical Associate Professor and Managing Network Facilitator, CPESN WV, West Virginia University School of Pharmacy, Morgantown, WV
Member since 2005

"I've been involved with APhA since I was a first-year student pharmacist at the University of Pittsburgh School of Pharmacy and have gained a lot through my involvement. As a community pharmacy practice resident, I spent 2 weeks on rotation at APhA headquarters and learned so much about association management and made connections with many leaders in our profession. I even had the honor and privilege of staffing the 2010 APhA Annual Meeting & Exposition in Washington, DC. It was amazing to see all that goes into planning and executing a successful annual meeting! Through my continued involvement with the New Practitioner Advisory Committee and then the Academy of Pharmacy Practice and Management, I've met and learned from many amazing pharmacists in APhA–APPM who are working tirelessly to advance our profession and inspire me every day."

How has APhA helped you establish meaningful connections?

I've met so many innovators in the profession of pharmacy through my involvement with APhA. Annual meetings provide a wonderful opportunity to interact with pharmacists and student pharmacists from across the country and even the world, so I would encourage all pharmacists and student pharmacists at APhA meetings to introduce themselves to someone they've never met before to learn their story and potentially make a lifelong connection in the profession. I've served in leadership roles through APhA and have met amazing pharmacists with whom I've continued to collaborate on projects within and outside APhA that have helped benefit our fellow pharmacists, student pharmacists, and the patients we serve.

How does APhA help you thrive in your everyday practice?

APhA provides many excellent resources that have helped me throughout my career, from *Peripheral Brain for the Pharmacist* while on rotation to the NAPLEX prep book to study for my exam to the amazing COVID-19 resources that have helped me immensely over the course of the past 3 years. APhA's resources are easy to use, which is extremely valuable in our fast-paced profession.

What excites you about the profession of pharmacy?

I'm very excited about the evolution of our profession. I think the COVID-19 pandemic has really shown all that pharmacists can do to help our communities. It's extremely important to get payors on board so pharmacists can get properly reimbursed and be engaged to our fullest potential taking care of patients.

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?

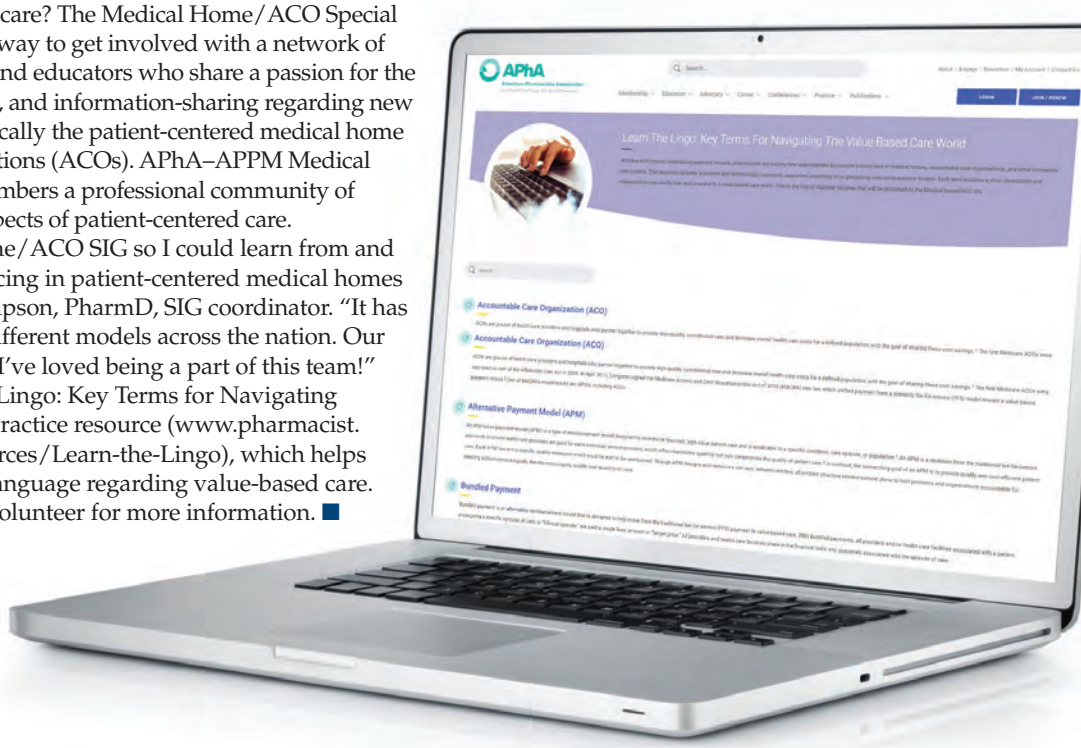
One patient, who suffers from a severe neurological condition, was due for his COVID-19 booster, but could not find a location that would administer the booster curbside, and his wife was concerned with his instability and having to get him into and out of a pharmacy location. I told his wife that I would be happy to administer the vaccine and set up a time that was convenient for them. I met the patient and his wife outside when they arrived and administered the vaccine to him while he was comfortably and safely seated in the car. His wife was extremely appreciative and thanked me multiple times for ensuring that her husband was fully protected. ■

Get involved

Interested in patient-centered care? The Medical Home/ACO Special Interest Group (SIG) offers a way to get involved with a network of practitioners, administrators, and educators who share a passion for the development, implementation, and information-sharing regarding new models for patient care, specifically the patient-centered medical home and accountable care organizations (ACOs). APhA–APPM Medical Home/ACO SIG provides members a professional community of pharmacists involved in all aspects of patient-centered care.

"I joined the Medical Home/ACO SIG so I could learn from and with other pharmacists practicing in patient-centered medical homes or ACOs," said Amy N. Thompson, PharmD, SIG coordinator. "It has been so great to learn about different models across the nation. Our SIG is an amazing group and I've loved being a part of this team!"

Don't miss the Learn The Lingo: Key Terms for Navigating the Value-Based Care World practice resource (www.pharmacist.com/Practice/Practice-Resources/Learn-the-Lingo), which helps pharmacists speak the same language regarding value-based care. Visit www.pharmacist.com/volunteer for more information. ■



Get published

APhA annually publishes between 10 and 15 professional references for pharmacists, pharmacy technicians, and student pharmacists in print and digital formats. 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*
- Trissel, *Trissel's Stability of Compounded Formulations*

APhA Books and Digital Publishing has an open call for proposals. Whether you are a veteran published author or an aspiring writer, you are invited to submit a book proposal.

Visit our book publishing website at www.pharmacist.com/Publications/Books to learn more and to download the book proposal form. ■

Left to right: Doug Hoey, NCPA CEO; Paul Abramowitz, ASHP CEO; Michael Hogue, APhA CEO; and Steve Anderson, NACDS CEO.

Pharmacists are stronger together

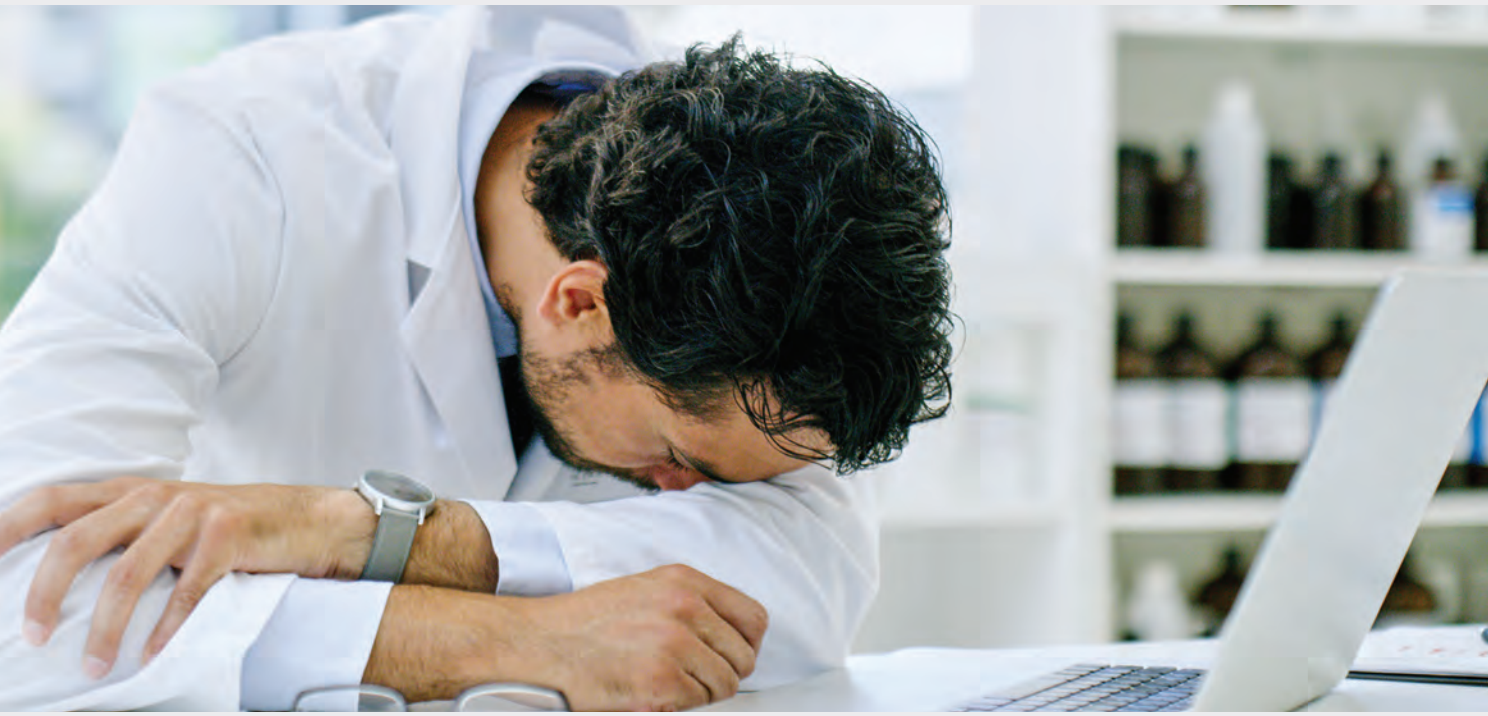
On July 18, 2023, Michael D. Hogue, PharmD, FAPhA, FNAP, FFIP, executive vice president and CEO of APhA, met with senior officials from the Biden Administration and HHS at the White House on the key role our nation's pharmacists play in helping patients understand their new prescription drug benefits and how those medicines can improve patient health. APhA collaborated with leaders from several health care partners—including the American Society of Health-System Pharmacists, the National Community Pharmacists Association, and the National Association of Chain Drug Stores—at a roundtable discussion about how pharmacies and the government can educate consumers about the new Medicare prescription drug benefits under the Inflation Reduction Act (IRA).

The administration is looking to the pharmacy community to educate and help patients take advantage of the new benefits, including caps on insulin copays and out-of-pocket drug costs for seniors and eliminating out-of-pocket costs for Medicare vaccines.

"Pharmacists are essential to achieving access to care and health care equity as part of our public health infrastructure," said Hogue. "We've found the most effective strategy for educating patients is person-to-person discussions—particularly in underserved communities. That's where the administration should focus. We are hopeful the administration will provide consumer education on drug costs so that pharmacists can continue to keep their focus on patient care."

APhA has created flyers, available at apha.us/nocopay, to help patients 65 years and older understand the vaccines they are eligible to receive with no copay.

"The IRA is a great start to improving patients' access to medications. However, further reforms are urgently needed. APhA urges HHS to use its authorities to provide coverage for pharmacist-provided care under Medicare Part B. Affordability plus patient care equals positive outcomes," said Hogue. ■



For your health: Managing chronic stress to prevent burnout

Cynthia Knapp Dlugosz, BSPharm, NBC-HWC, Artemis Health Care Communications, Ann Arbor, MI

Job-related stress and burnout are at all-time highs across professions. In the 2023 American Psychological Association (APA) Work in America Survey, 77% of workers reported experiencing work-related stress in the last month, and 57% reported experiencing negative impacts because of work-related stress.[1]

Pharmacists are no exception to this troubling trend. In a recent systematic review of 19 articles involving 11,306 pharmacist participants across eight countries, burnout prevalence estimates ranged from 5% to 75%, with an overall prevalence estimate of 51%.[2]

Everyone experiences stress to some degree. Stress is an inevitable part of life, and it is not always negative or harmful. It is the way we respond to stress that makes a big difference to our overall well-being.

What do we mean by "stress" and "burnout"?

One challenge in discussing stress and burnout is the lack of universally accepted definitions. The terms are often used casually, inappropriately, or interchangeably, which can lead to misuse and misunderstanding.[3]

Stress defined and explained

Stress can be defined broadly and simply as a physiological or psychological response to an internal or external stressor.

The classic stress response begins with an event or situation. Our brain—the central mediator of the stress response—makes an appraisal of the event or situation based on sensory input and processing (e.g., things we see and hear) and stored memories (i.e., what happened the last time we encountered a similar event or situation).[4] If danger is detected—that is, if the event or situation is appraised as a real or potential threat—the amygdala sends a distress signal to the hypothalamus, which activates both the sympathetic–adreno–medullar axis and the hypothalamic–pituitary–adrenal (HPA) axis.[5] Once these axes are activated, they generate a coordinated response involving the CV, respiratory, endocrine, GI, nervous, muscular, and reproductive systems.[5,6] These collective effects mediate physiological and behavioral changes that enable adaptation and survival (e.g., fight–flight–freeze responses).[5,6]

The classic stress response assumes that the stressor—the threatening event or situation—is short-lived, with a relatively clear start and end point.[4] On a graph, this classic stress response resembles an inverted "V" with an onset, peak, and recovery.[4] Once the immediate threat passes, the parasympathetic nervous system takes control and brings the body back into a balanced state by lowering cortisol levels and normalizing the physiologic responses (e.g., BP, heart rate).[6] Although the body remains on alert for a time during this recovery phase until the stressful event is no longer an issue, homeostasis is restored relatively quickly.[6]

Learning objectives

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

- Discuss the self-perpetuating cycle of chronic stress.
- Identify the key dimensions and primary causes of burnout.
- Differentiate between the experiences of chronic stress and burnout.
- Identify at least three evidence-based approaches to managing the physical manifestations of chronic stress.
- Identify at least three evidence-based practices that target the cognitive and emotional aspects of chronic stress.

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 is most characteristic of a chronic stress cycle?**
   a. We do not react as quickly as needed to perceived stressors.
   b. We habituate to chronic stressors because we experience them so frequently.
   c. The hypothalamic–pituitary–adrenal axis remains activated.
   d. The peak of the stress response becomes blunted.

2. **When are we most likely to interpret a potential stressor as a threat?**
   a. When it is a situation known to be inherently stressful
   b. When the perceived demands of the stressor exceed our perceived ability to cope
   c. When we are exposed to the stressor repeatedly
   d. When the personal resources available to us are equivalent to or greater than the demands of the stressor

3. **Burnout is characterized by overwhelming exhaustion, cynicism, and inefficacy. How many of these dimensions must be present for a worker to experience burnout?**
   a. At least one dimension
   b. At least two dimensions
   c. At least the two specific dimensions of exhaustion and cynicism
   d. All three dimensions

Acute stress continues to be a part of our lives. But our days are more likely to be characterized by chronic, low-level stress. As renowned stress researcher Elisa Epel, PhD, explains, stress "is the ocean we swim in"[7]:

"From the moment our eyes open in the morning to when they drift closed at night, we are flooded with constant stress triggers: demands and deadlines, logistics, to-do lists, unexpected crises both small and large, thorny conversations. There are so many triggers that can set off your body's stress response…[e]ven our own thoughts become stressors that our bodies respond to."[7]

Ideally, our stress response follows a "not too" pattern: not too low, not too high, and not too long.[8] Repeated exposure to stressors large and small results in a maladaptive stress response.[4,9] In such situations, the stress response kicks in sooner or more frequently than normal. It doesn't turn off, so we never fully recover; the HPA axis remains activated, like a motor that is idling too high.[9] There may be heightened and prolonged anticipation of future events, with accompanying worry and vigilance.[4] There also may be a heightened reactivity to an event and prolonged recovery after the event is over.[4] We may also overreact repeatedly to the same minor stressor (known as lack of habituation).[4]

A relatively new concept is that of microstresses—small difficult moments that seem manageable on their own, but accumulate relentlessly over time.[10] Microstresses fall into three broad categories:[10]

- Microstresses that drain your capacity to get things done (e.g., uncertainty about others' reliability)
- Microstresses that deplete your emotional reserves (e.g., confrontational conversations)
- Microstresses that challenge your identity (e.g., pressure to pursue goals out of sync with your personal values)

We may not even view microstresses as stressors because we accept them as a normal part of daily life and are conditioned to just work through them.[10] We may not register them, but they still take a significant toll on our well-being.[10] Behavioral neurologist Joel Salinas, MD, MBA, compares the effect of microstresses to that of wind eroding a mountain: "over time—if the wind never stops—it has the potential to slowly wear an entire mountain down to a nub."[10]

It is important to understand that there is great interindividual variability in responses to potential stressors.[4] Events or situations are not inherently stressful; instead, it is the interpretation and reaction to an event or situation that produces the cognitive, emotional, and biological manifestations of stress.[4,8] For example, it is possible for a stressor to be viewed as a "positive" challenge (something that engages and energizes) rather than as a "negative" threat.[4,11] Whether a stressor is appraised as a challenge or a threat depends on the relative ratio between the perceived demands of the stressor (e.g., the degree of physical or psychological danger present, uncertainty or novelty of a situation, required effort) and the perceived personal resources to cope (i.e., the skills, abilities, talents, and social support required to meet, mitigate, or alter the demands of the stressor).[4,12]

As a general rule, we will view a stressor as a threat if we believe the demands of a situation exceed our ability to cope and a challenge when our resources meet or exceed demands.[4]

Table 1. Six areas of mismatch between workers and workplaces

Job dimension	Mismatch	Examples
Capability	Work overload	• Unclear or overly demanding job expectations • Inadequate resources (e.g., time, tools, support) to meet job demands • Chaotic or high-pressure work environment
	Lack of control	• Insufficient autonomy over when, where, and how work is completed • Inability to muster the resources needed to meet job demands
Social	Insufficient rewards	• Insufficient financial rewards • Insufficient recognition or other social rewards • Insufficient intrinsic rewards (e.g., pride in doing something of importance and doing it well)
	Breakdown of community	• Lack of positive connection with others in the workplace • Chronic and unresolved conflict with others on the job
Moral	Absence of fairness	• Perceived inequity regarding workload, pay, promotions • Inconsistent rules • Lack of respect
	Value conflicts	• Feeling constrained by the job to do things that are unethical or otherwise not in accord with personal values • Mismatch between personal career aspirations and organizational values

Source: Adapted from Reference 22.

Unfortunately, being under chronic stress initiates a self-perpetuating cycle. When we are in a state of chronic stress, we are more likely to report a greater number of daily stressors and more frequent episodes of acute stress. We experience greater general perceived stress at any given moment and greater peak reactivity during acute stress.[4] Frequent stressors deplete our personal resources more quickly, increasing the likelihood that we will not have the resources needed to cope efficiently with additional stressors or microstresses.[4,10]

Burnout defined and explained

Burnout is a syndrome of physical, emotional, or mental exhaustion accompanied by depersonalization and reduced personal accomplishment.[13] It is a type of prolonged response to chronic stress.[13] Burnout does not happen suddenly; it evolves over time.

Burnout was first described in a pair of scientific articles in 1974.[14,15] Although the author of one of those articles, Herbert Freudenberger, PhD, is considered to be the "founding father" of burnout, he did not invent the term.[16] In fact, he adopted the term his work colleagues used—"burned out"—to describe a condition they all were experiencing.[16]

Because Freudenberger believed that burnout was attributable mostly to organizational factors, he proposed preventive interventions at the organizational level that included shorter working hours, regular job rotation, and frequent supervision and staff training.[16] Thus, from the beginning burnout has been viewed as an occupational phenomenon resulting from chronic workplace stress.

The currently accepted definition is included in the 11th Revision of the International Classification of Diseases.[17] Burnout is a syndrome conceptualized as resulting from chronic workplace stress that has not been successfully managed.[17] It is characterized by three dimensions[17]:

1. Feelings of energy depletion or exhaustion
2. Increased mental distance from one's job, or feelings of negativism or cynicism related to one's job
3. A sense of ineffectiveness and lack of accomplishment.

Burnout refers specifically to phenomena in the occupational context and should not be applied to describe experiences in other areas of life.[17]

Burnout is not classified as an illness or medical condition, nor is it considered to be a distinct mental disorder.[16,18] There is some controversy as to whether burnout is possible in other areas of life (e.g., parental burnout).[17,19]

Job burnout has been characterized and discussed extensively by the organizational psychologists Christina Maslach, PhD, and Michael P. Leiter, PhD. They have elaborated on the three key dimensions of burnout[20,21]:

- Overwhelming exhaustion—These are feelings of being overextended and depleted of one's emotional and physical resources. This is the individual stress dimension of burnout.
- Cynicism—This is a negative, callous, or excessively detached response to various aspects of the job (e.g., having a "take this job and shove it" feeling about the workplace). This is the interpersonal context dimension of burnout.
- Inefficacy—These are feelings of incompetence and a lack of achievement and productivity at work. A person may begin to feel negative about themselves, instead of just about their workplace (with thoughts such as "What's wrong with me?" "Why did I go into this job?" "Why can't I handle it?") This is the self-evaluation dimension of burnout.

Importantly, burnout is defined by the ongoing presence of all three dimensions. Maslach and Leiter view burnout as one end of a continuum, with engagement as the opposite end.[23] People who are engaged with their work have the energy to do the job, are deeply involved in their work tasks, and feel effective and successful in their accomplishments.[23]

Maslach and Leiter describe three intermediate states between the endpoints of engagement and burnout, depending on which of the three dimensions of burnout is most prominent[23]:

- People in the overextended state primarily report experiencing frequent exhaustion. Their main workplace problem is a very heavy workload, usually with high demands and long hours. People who are overextended may believe in themselves and their work, but they are always worn out.
- People in the disengaged state are primarily and consistently cynical about their jobs. Although they usually are able to manage their workload and might think they are doing a good job, they no longer have the motivation that originally attracted them to their line of work. They may feel constrained from doing the right thing in their jobs, suggesting moral distress. People who are disengaged are closest to full-blown burnout—not people who are overextended, which is the usual assumption.
- People in the ineffective state primarily have a negative sense of their own professional accomplishments. They may have the energy to do their work, and they may believe in their work. But they may not see their work as intrinsically rewarding, or they do not see themselves making any progress.

What causes burnout?

Maslach and Leiter believe that burnout arises from the increasing mismatch between workers and workplaces.[23] They have identified six forms of mismatch that can exist between a job and the person holding it (Table 1). The more that any (or all) of these six conditions depart from an employee's aspirations or preferred ways of working, the more the employee is vulnerable to burnout.

Note the use of "aspirations" and "preferred ways of working" in the previous sentence. Just as stress can be viewed as the feeling of not having sufficient personal resources to meet the demands being made on us, burnout can be viewed as the experience of being pulled between expectation and reality at work—of having to stretch across the gap between your ideals about your job and the reality of your job.[24]

Like chronic stress, burnout can be self-perpetuating. Exhaustion, cynicism, and inefficacy all have the potential to aggravate each other.[23] For example, exhaustion diminishes our capacity to take on anything new—even something that might help us be more rested. Meanwhile, cynicism may cause us to question the intentions behind offers of assistance, and inefficacy reduces our confidence in our ability to change our situation.

Table 2. Differences between stress and burnout

When you are stressed…	When you are burned out…
Your emotions are heightened. *"My work makes me feel really tense and under pressure."*	Your emotions are blunted. *"I feel numb and detached at work."*
You become more active. *"There is so much that I need to do!"*	You become more withdrawn. *"I can't bring myself to do my work."*
You feel anxious. *"I worry about how much work I have to get done."*	You feel low. *"Work leaves me feeling depressed and hopeless."*
Your work seems meaningful. *"It's important that I get these things done."*	Your work seems meaningless. *"I don't feel like my work matters anymore."*

Source: Adapted from Reference 25.

The difference between stress and burnout

How can you tell if what you are experiencing is chronic stress or burnout? We actually experience these two conditions very differently. We typically experience stress as "too much"—we have too much on our plate, or we are too "full" of tension, pressure, or worry.[25,26] On the other hand, we experience burnout as "too little"—like we have nothing left to give, or we are too "empty" of energy, motivation, or hope.[25,26] Additional examples are provided in Table 2.

Strategies for managing chronic stress to prevent burnout

It has been nearly 50 years since Freudenberger proposed that burnout was mostly attributable to organizational factors. Researchers and experts continue to emphasize that burnout is a problem that begins and ends with organizational change.[23,27,28] Maslach often uses the analogy of the canary in the coal mine: Throughout much of the 20th century, coal miners would carry canaries in cages down into the mines with them to detect carbon monoxide and other toxic gases before they could hurt humans. What would be the best long-term approach, Maslach asks, if a canary started swaying on its perch or even collapsed?[23] "Should we try fixing the canary to make it stronger and more resilient—a tough old bird that could take whatever conditions it faced? Or should we fix the mine, clearing the toxic fumes and doing whatever else necessary to make it safe for canaries (and miners) to do their work?"[23]

Or, as author Jennifer Moss puts it in *The Burnout Epidemic: The Rise of Chronic Stress and How We Can Fix It*, we need to

be asking "How do we create a better, healthier workplace for people, so they don't burn out?"[27]

While we wait for organizational change to happen, there are a number of things we can personally do to improve our ability to manage and cope with chronic job and personal stressors, bolster our well-being, and hopefully stop the inexorable march toward burnout. A simple Internet search would yield countless suggestions. But as with all behavioral change, the challenge lies in the implementation.

Keep in mind that stress is personal and subjective; we all respond to different stressors in different ways. There is no "magic bullet" for addressing chronic stress or burnout. Ideally, we have access to a broad repertoire of positive coping strategies to help us navigate the chronic stress that can lead to burnout. The strategies and practices outlined in this section are offered as examples of small, evidence-based practices and approaches that could be implemented relatively easily by pharmacists in any practice setting.

The suggestions in this section assume that the reader is experiencing chronic stress or one of the intermediate states before burnout, in which intervention is possible. Once burnout syndrome is present, the recommended best approach is to consult a mental health professional or health care provider.

Prioritize sleep

If you can prioritize only one thing to improve your ability to manage chronic stress, prioritize getting sufficient restorative sleep. It is a vicious cycle that chronic stress interferes with our ability to sleep, while sleep impairment—for example, difficulty in falling asleep, insufficient good-quality sleep, or consequent tiredness on waking—exacerbates a maladaptive stress response.[29–31] When we are in this cycle, we react to small stressors even more readily and experience even higher peak stress responses, which further reduces our psychological coping capacity.[31]

In the 2013 Stress in America survey, 21% of adult respondents reported feeling more stressed when they did not get enough sleep.[32] Among respondents with the greatest perceived levels of stress (a score of 8, 9, or 10 on a 10-point scale), nearly half (45%) reported feeling more stressed if they did not get enough sleep.[32] Adults with lower reported stress levels reported sleeping more hours per night (average 7.1 hours) than adults with higher reported stress levels (6.2 hours).[32]

A consensus recommendation from the American Academy of Sleep Medicine (AASM) and Sleep Research Society states that most adults should sleep ≥7 hours per night on a regular basis to promote optimal health.[33] Regrettably, as sleep scientist Aric Prather, PhD, notes in *The Sleep Prescription: 7 Days to Unlocking Your Best Rest*, sleep often ends up being the last thing on our to-do list when it should be the first.[34]

Better sleep begins with good sleep hygiene. Examples of good sleep hygiene habits include[35]

- Going to bed at the same time each night and getting up at the same time each morning, including on weekends
- Making sure your bedroom is quiet, dark, relaxing, and at a comfortable temperature
- Removing electronic devices (e.g., televisions, computers, smart phones) from the bedroom
- Avoiding large meals, caffeine, and alcohol before bedtime

However, good sleep hygiene may not be sufficient. The next steps are to keep a sleep diary (like the one available via AASM) and either follow a self-help program like the one outlined in The Sleep Prescription or consult a health care provider or sleep specialist.[34,36]

Breathe for calm

Stress and breathing are interrelated. During the stress response, our breathing becomes shallow and rapid to increase the supply of oxygen to muscles and prepare our bodies for action. We may also breathe through our mouth instead of our nose. Breathing in this manner also can initiate a stress response by activating the sympathetic nervous system.[7]

When we experience chronic stress, this shallow, rapid breathing pattern tends to become our default. One simple way to combat stress is to intentionally reverse this pattern of breathing.

Breathing deeply and slowly activates the parasympathetic nervous system by stimulating the vagal nerve.[37,38] Breathing deeply and slowly also lowers heart rate and BP, which reduces sympathetic activity and decreases both physiological and psychological stress.[38]

Breathing for calm has two components: diaphragmatic breathing (also called belly breathing or abdominal breathing) and prolonged exhalation. During diaphragmatic breathing, the diaphragm pulls downward, the lungs expand, and the abdomen rises (moves out) on the inhalation; the diaphragm then returns upward and the abdomen falls on the exhalation.[38] The exhalation should be at least twice as long as the inhalation.[39]

Here's how to breathe for calm:

1. Place one hand on the upper part of your chest and the other hand on your belly.
2. Breathe in slowly and deeply through your nose to a count of four. Imagine filling your lungs with air and breathing all the way down into your belly. You should feel your diaphragm moving down and your ribs widening to the sides. The hand on your belly should move as the abdomen rises, but the hand on your chest should not.
3. Pause briefly, then breathe out slowly to a count of eight.
4. Repeat.

Breathing for calm can be done anywhere and at any time. A few rounds of breathing in this manner may be all you need to help manage brief episodes of stress.

Move as much as you can

In their book *Burnout: The Secret to Unlocking the Stress Cycle*, authors Emily Nagoski, PhD, and Amelia Nagoski introduced the concept of "completing the stress cycle."[40] The idea is that because the physiologic manifestations of our stress response primarily prepare us to fight or flee in the face of life-threatening danger, we need to dissipate the energy produced by chronic activation of the stress response, ideally through physical activity.

In fact, there is emerging evidence that physically active adults have healthier acute stress responses than adults who are sedentary.[4]

According to the current physical activity guidelines for Americans, adults should be engaging in at least 150 minutes of moderate-intensity physical activity and 2 days per week of muscle strengthening activity.[41]

For anyone who is experiencing chronic stress or feeling overextended, these recommendations may seem wildly unattainable and lead to conscious or unconscious all-or-none thinking; for example, "I can't possibly manage this much activity, so I won't do anything at all." But some activity is better than none, and there is value to smaller—much smaller—bouts of activity. The Nagoskis suggest "just standing up from your chair, taking a deep breath, and tensing all your muscles for 20 seconds, then shaking it out with a big exhale" as an excellent start.[40]

Let go of muscular tension

The APA describes muscle tension as "almost a reflex reaction to stress"—the body's way of guarding against injury and pain.[42] During an acute stress response, the muscles tense up all at once, then release their tension when the stress passes. With chronic stress, muscles can remain tensed in a relatively constant state of guardedness.

Progressive muscle relaxation, which involves systematically tensing and relaxing muscle groups in a certain order, is a widely used technique that was originally developed by physician Edmund Jacobson, PhD, MD, in the early 1920s as a treatment for anxiety. Progressive muscle relaxation has been shown to be useful in reducing stress by producing both psychological and physiological relaxation.[43]

There are a number of different protocols for progressive muscle relaxation, involving as many as 16 muscle groups. Many guided audio and video practices are available online and in popular apps. Ideally, you would become familiar with the full sequence before switching to a shorter sequence. With practice, you can learn to relax specific muscles at the first signs of stress-induced tension.

Soothe yourself with supportive touch

Supportive touch (also known as self-soothing touch) may be best known as a component of the Mindful Self-Compassion program developed by Christopher Germer, PhD, and Kristin Neff, PhD.[44] Touch activates the parasympathetic nervous system and stimulates the release of oxytocin.[44] Supportive touch has been shown to have a buffering effect on the stress response, with both a calming function toward anticipatory stress and a protective function toward future stress.[45]

Supportive touch is a simple and easy practice to try any time you notice you are under stress. The classic gesture is hand on heart:

1. Gently place your hand over your heart. (If you wish, can place both hands on your chest, one hand on top of the other.) Feel the gentle pressure and warmth of your hand(s).
2. Feel the natural and subtle rising and falling of your chest as you breathe in and out for at least 20 seconds.
3. Allow the sensation of soothing to linger for as long as possible.

You can experiment with other options, such as placing one hand on your cheek or the inner part of your

forearm. You also can cross your arms and touch opposite shoulders to give yourself a gentle hug.

Check in with yourself daily

A growing body of evidence supports the theory that present-moment awareness, a key component of mindfulness, can enhance a person's response to daily stressful events and serve as a buffer against future stressful events.[46] A mindful check-in is a simple practice for tuning in to how you are feeling in the present moment and acknowledging what is there.

To perform a mindful check-in, take a few minutes each day to stop and ask yourself the following:

- How am I doing today?
- How am I feeling?

The idea is to just become aware initially, not to judge your responses or immediately try to fix anything.[47] Simply noticing feelings of stress or overwhelm can keep you from being consumed by them. You might then follow up by asking, "What is one small thing I could do right now to reduce my stress? What do I need most right now?"

Given that burnout is part of a continuum with several intermediate states, a daily check-in can give you a sense of where you are on that continuum and provide an opportunity to intervene. Chris Bailey developed the Two-Minute Burnout Checkup for this purpose based on the six areas of job–person mismatch described by Maslach and Leiter (Table 3).[48]

To do the checkup, consider how much stress you are experiencing in each area, with 0 being negligible stress and 10 being extreme stress. Your total score shows how well you are doing overall in the moment. But pay special attention to your scores in each area; these scores can help you determine if you might be in the overextended state (high scores in work overload and lack of control), the ineffective state (high scores in insufficient rewards and breakdown of community), or the disengaged state (high scores in absence of fairness and value conflicts).[23]

As mentioned earlier, people in the disengaged state are considered to be closest to full-blown burnout.

Table 3. A two-minute burnout self-checkup

Burnout factor	Level of stress (0 to 10)
Work overload	
Lack of control	
Insufficient rewards	
Breakdown of community	
Absence of fairness	
Value conflicts	
Total	

Source: Adapted from References 23 and 48.

Accentuate the positive

The human brain is hardwired with a negativity bias; that is, a universal tendency for negative events and emotions to affect us more strongly than positive ones.[49] We are more prone to interpret situations and events in a negative way and ruminate over minor frustrations, which further exacerbates our stress. Chronic stress is associated with an even greater negativity bias, particularly in women.[50]

To counteract negativity bias, we must intentionally train our brains to notice and focus on the positive. One way to do this is to practice gratitude, or the feeling of being thankful for someone or something.[51] This can be as simple as identifying three things you are grateful for each day and writing them down or saying them out loud.

Look for small things—a great cup of coffee, a shorter-than-expected commute, a kind act from another person. Be especially vigilant for things to be grateful for in the workplace.

Another way to notice and focus on the positive is the Three Good Things practice.[52] Each day for at least 1 week, write down three things that went well for you and provide an explanation for why they went well. Describe each event in as much detail as possible, including how the event made you feel at the time it happened and how it made you feel later. Try to include at least one work-related event each day.

Author Cyndie Spiegel encourages us to discover what she calls "micro-joys"—easily accessible moments of joy that exist around (and within) us regardless of our current circumstances.[53] Her examples include the joy of finding your favorite "lost" pen, the satisfaction of a fresh glass of water first thing in the morning, or the happiness you feel when you run into a friend in a seemingly random place.[53]

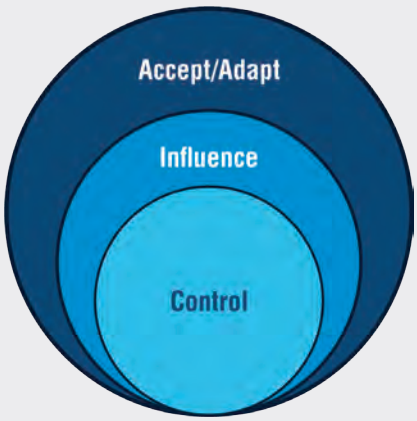
Training your brain to notice and appreciate microjoys enables you to experience moments of joy during even the most stressful times. You might consider taking photos of simple things that bring you joy, creating a catalog of beautiful moments you can turn to on difficult days to reinforce that joy is always a choice.

Focus on what you can control

A major factor in our perception of stress is whether we have control over the stressor.[4] Unfortunately, we usually have much less control over stressors in the workplace than in other life domains.[20] Because the negativity bias makes us focus disproportionately on the things that are beyond our control, we end up feeling powerless to improve our situation.

The Control–Influence–Accept (CIA) framework (Figure) is a tool that can help change your focus from the many uncontrollable aspects of life to the few controllable ones.[54]

Figure. The CIA framework



Source: Adapted from Reference 54.

It reminds us that in any difficult situation, there will be

- Things we can control
- Things we cannot control but might have some influence over (e.g., the attitudes or behavior of other people)
- Things we can neither control nor influence, and so must adapt to or accept

A simple way to put this framework into practice is to begin with control. If work stress threatens to overwhelm you, pause, take a deep breath, and ask a question such as[47]

- What one small productive action could I take to change this situation, given how things are and what is in my control?
- Is there something I can do about this situation? If so, what is one small, manageable step I can take?

Note that the "accept" part of the framework doesn't mean you approve of whatever it is you cannot change. It means that you are choosing not to make yourself more miserable by fighting it.[7] It means that you are choosing not to drain your energy by ruminating about it and trying to solve a problem that cannot be solved.[7]

Conclusion

Chronic stress is endemic in modern society; too often, burnout is its unwelcome sequela.

The good news is that burnout is not inevitable. By understanding the experiences of chronic stress and burnout and engaging in practices that address their harmful effects, we can lower our default baseline stress level and cultivate greater ease and well-being.

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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 is most characteristic of a chronic stress cycle?**
   a. We do not react as quickly as needed to perceived stressors.
   b. We habituate to chronic stressors because we experience them so frequently.
   c. The hypothalamic–pituitary–adrenal axis remains activated.
   d. The peak of the stress response becomes blunted.

2. **When are we most likely to interpret a potential stressor as a threat?**
   a. When it is a situation known to be inherently stressful
   b. When the perceived demands of the stressor exceed our perceived ability to cope
   c. When we are exposed to the stressor repeatedly
   d. When the personal resources available to us are equivalent to or greater than the demands of the stressor

3. **Burnout is characterized by overwhelming exhaustion, cynicism, and inefficacy. How many of these dimensions must be present for a worker to experience burnout?**
   a. At least one dimension
   b. At least two dimensions
   c. At least the two specific dimensions of exhaustion and cynicism
   d. All three dimensions

4. **Which of the following states that precedes burnout is closest to full-blown burnout?**
   a. Disengaged state
   b. Engaged state
   c. Ineffective state
   d. Overextended state

5. **Which of the following represents a key difference between chronic stress and burnout?**
   a. Chronic stress feels like "too much"; burnout feels like "too little."
   b. Emotions are blunted in people experiencing chronic stress.
   c. People experiencing burnout feel anxious; people experiencing chronic stress do not.
   d. There are no appreciable differences between chronic stress and burnout.

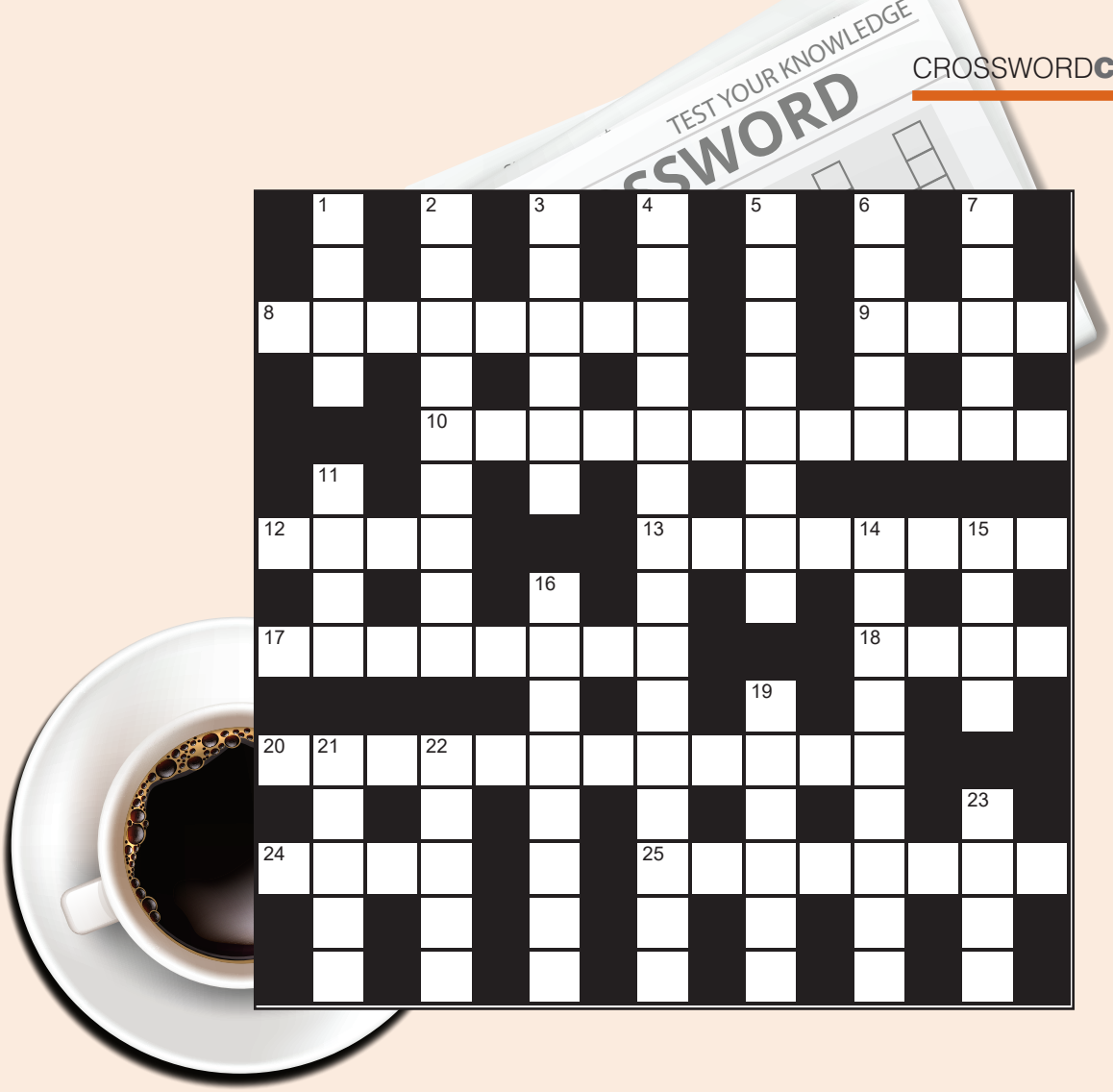
6. **If you were able to prioritize only one thing to improve your ability to manage chronic stress, that thing should be**
   a. Getting sufficient restorative sleep
   b. Getting the recommended amount of physical activity
   c. Practicing progressive muscle relaxation
   d. Soothing yourself with supportive touch

7. **A key component of breathing for calm is**
   a. Breathing from the chest rather than the abdomen
   b. Breathing in through the mouth and out through the nose
   c. Making the exhalation longer than the inhalation
   d. Making the inhalation longer than the exhalation

8. **High scores for "work overload" and "lack of control" on the Two-Minute Burnout Checkup may indicate that you are in the**
   a. Burnout state
   b. Disengaged state
   c. Ineffective state
   d. Overextended state

9. **Practicing gratitude, engaging in the Three Good Things practice, and noticing and appreciating microjoys all help to manage chronic stress by**
   a. Activating the parasympathetic nervous system
   b. Counteracting negativity bias
   c. Lowering heart rate and BP
   d. Stimulating the release of oxytocin

10. **The CIA framework is a useful tool for stress management because it**
    a. Focuses our attention on things we can control
    b. Helps us approve of and accept things we cannot change
    c. Serves as a mnemonic aid for the key stress hormones (Cortisol–Insulin–Adrenaline)
    d. Stresses the importance of influencing other people's behavior



Across

8 Disease caused by a thiamine deficiency
9 Tablet
10 Male sex hormone
12 CDC committee that recommends immunization policy
13 Patients should get a flu shot this often
17 Fast, as a rise
18 Common symptom of an allergic reaction
20 Severe allergic reaction that may be treated with 14-down
24 Medication that reduces the risk of contracting HIV
25 Asthmatic's aids

Down

1 Older adults, for example
2 Group of five
3 Gland that is the site of the most common cancer in women
4 Carbohydrates that act as a prebiotic
5 A harmful component of cigarette smoke
6 To decrease a medicine slowly
7 Longest part of the large intestine
11 Skin condition common among teens
14 Epinephrine, by another name
15 Break open, as with cells
16 Nearer to the center (trunk of the body) or to the point of attachment to the body
19 Pharmacists avoid one of these with medications
21 Common part of a test kit
22 Part of the "H" in ADHD
23 Common route of medication administration

Solution is available online at pharmacytoday.org.